Health Information and Quality Authority

An tÚdarás Um Fhaisnéis agus Cáilíocht Sláinte

Health technology assessment (HTA) of a national screening programme for atrial fibrillation in primary care

06 August 2015

About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is the independent Authority established to drive continuous improvement in Ireland's health and personal social care services, monitor the safety and quality of these services and promote person-centred care for the benefit of the public.

The Authority's mandate to date extends across the quality and safety of the public, private (within its social care function) and voluntary sectors. Reporting to the Minister for Health and the Minister for Children and Youth Affairs, the Health Information and Quality Authority has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for those health and social care services in Ireland that by law are required to be regulated by the Authority.

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- **Health Information** – Advising on the efficient and secure collection and sharing of health information, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care services.

Foreword

Atrial fibrillation (AF), the most common arrhythmia seen in general practice, is a major cause of morbidity and mortality in Ireland. Not only is it associated with a fivefold increase in the risk of stroke, but these strokes are more likely to be fatal compared with non-AF strokes, and a greater proportion of survivors are left with significant functional impairment. The overall burden of AF is increasing as our population ages, making it ever more important that the arrhythmia is detected and managed effectively to improve outcomes for patients and ensure the sustainability of health services in Ireland. Screening for atrial fibrillation has been advocated as a central component of efforts to reduce the burden of disease, by identifying those who are unaware they have the condition but remain at increased risk of stroke. However there is a high degree of uncertainty surrounding the impact of screening on stroke outcomes and on the overall cost-effectiveness of different types of screening programmes.

In this health technology assessment (HTA), we examine the long term implications of opportunistic screening in primary care, using the best available evidence on the effectiveness of screening and subsequent treatment, and the costs associated with detection, treatment and long-term care. Our analysis benefits from the considerable amount of research carried out previously on AF and stroke in Ireland, particularly the work conducted by the Health Service Executive (HSE) National Clinical Programme for Stroke, the North Dublin Stroke Study, the Cost of Stroke in Ireland study, the Irish National Audit of Stroke Care (INASC) and The Irish Longitudinal Study on Ageing (TILDA).

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate of the Authority. A multidisciplinary Expert Advisory Group was convened to advise the Authority during the conduct of this assessment.

The Authority would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the preparation of this report.

Dr Máirín Ryan

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Health Information and Quality Authority

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Acknowledgements

The Authority would like to thank all of the individuals and organisations who provided their time, advice and information in support of this assessment.

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Members of the Evaluation Team:

Members of the Authority's Evaluation Team included: Patrick Moran, Dr Conor Teljeur, Dr Patricia Harrington and Dr Máirín Ryan.

Conflicts of Interest

None reported.

List of Abbreviations

ADL	Activities of Daily Living
AF	Atrial Fibrillation
BI	Barthel Index
BIA	Budget Impact Analysis
CEAC	Cost Effectiveness Acceptability Curve
CPI	Consumer Price Index
CSO	Central Statistics Office
CUA	Cost Utility Analysis
DOAC	Direct Oral Anticoagulant (also referred to as NOAC)
EAG	Expert Advisory Group
ECG	Electrocardiogram
ESC	European Society of Cardiology
ESRI	Economic and Social Research Institute
EVPI	Expected Value of Perfect Information
HIPE	Hospital Inpatient Enquiry Database
HSE	Health Services Executive
ICD	International Classification of Diseases
ICER	Incremental Cost Effectiveness Ratio
ICGP	Irish College of General Practitioners
ILO	International Labour Organisation
INASC	Irish National Audit of Stroke Care
INR	International Normalised Ratio
NCPE	National Centre for Pharmacoeconomics
NICE	National Institute for Health and Care Excellence
NIHR	National Institute for Health Research
NIHSS	National Institute for Health Stroke Scale
NOAC	New Oral Anticoagulant (also referred to as DOAC)
NTPF	National Treatment Purchase Fund
OAC	Oral Anticoagulation
OR	Odds Ratio
PCRS	Primary Care Reimbursement Service
PICH	Primary Intracerebral Haemorrhage
QALY	Quality Adjusted Life Year
QOF	Quality and Outcomes Framework
RCSI	Royal College of Surgeons in Ireland
RCT	Randomised Controlled Trial
RR	Relative Risk
SAH	Subarachnoid Haemorrhage
TILDA	The Irish Longitudinal Study on Ageing
TTR	Time in Therapeutic Range
WTP	Willingness To Pay

Advice to the Health Service Executive

This health technology assessment (HTA) examined the clinical and cost-effectiveness of opportunistic screening for atrial fibrillation (AF) by pulse palpation followed by electrocardiogram (ECG) confirmation of an irregular pulse in the Irish primary care setting. The resource implications and budget impact of a national AF screening programme were also estimated.

The key findings, which precede and inform the Authority's advice, are as follows:

- There is good evidence from one randomised controlled trial (RCT) to show that while opportunistic and systematic screening produce comparable increases in AF detection compared with routine care, opportunistic screening does so at significantly less cost. An additional RCT of opportunistic screening for over 65s in primary care is currently in progress, the results of which could alter the conclusions drawn based on the existing evidence.
- No published studies were identified that have examined the impact of AF screening on stroke outcomes or mortality, so there is a lack of evidence on whether the additional AF cases identified through screening have the same stroke risk, and therefore the same potential to benefit from treatment, as those who present in routine care. However, international guidelines for the management of AF recommend that both symptomatic and asymptomatic AF should receive the same treatment.
- Two previous studies were identified that reported the cost-effectiveness of AF screening using pulse palpation followed by ECG confirmation in a primary care setting. Both studies concluded that screening by pulse palpation was likely to be cost-effective compared with routine care. However, the applicability of these results in an Irish setting is low.
- The primary analysis in this HTA compared the cost-effectiveness of a national AF screening programme involving annual opportunistic pulse palpation for men and women aged 65 years and over in primary care with routine practice (no screening). The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and is consistent with the best available evidence on the effectiveness of screening.
- There are approximately 8000 strokes each year in Ireland, with about a third of these being associated with underlying atrial fibrillation.
- There is a high level of uncertainty regarding a number of key parameters needed to estimate the cost-effectiveness of AF screening in Ireland. Conservative estimates of the effectiveness of screening on AF detection were used and a sensitivity analysis was conducted to estimate the impact of uncertainty in this and other parameters.

- Based on the results of the primary analysis, a strategy of annual opportunistic screening in people aged 65 years and over would result in approximately 1,944 additional AF cases being detected and 157 fewer strokes occurring in the screened cohort compared with current practice.
- Over the course of the first five years of the programme it is anticipated that screening will have been associated with a 1.9% decrease in the incidence of first ever stroke in those aged 65 to 90 years.
- Screening is associated with an incremental cost-effectiveness ratio of €20,271 per quality-adjusted life year (QALY), giving it an 83% probability of being cost-effective at a willingness-to-pay threshold of €45,000/QALY.
- The cost-effectiveness results are sensitive to changes in the start age of screening, the frequency of screening, and the baseline risk of ischaemic stroke and systemic embolism in those who would not have been diagnosed with AF through routine practice in the absence of screening.
- Changes in the proportion of AF patients who are prescribed warfarin, direct oral anticoagulants and antiplatelet therapy are unlikely to have a major impact on the cost-effectiveness of screening.
- Budget impact analysis, which did not include a separate fee for pulse palpation, showed that the total incremental cost of opportunistic AF screening to the HSE over five years is approximately €3.7 million. This includes the additional costs associated with screening ECGs and AF drug therapy in diagnosed cases, as well as cost savings as a result of a gradual decrease in stroke incidence over the five year time horizon.
- It is estimated that screening could result in approximately 2,800 additional referrals for an outpatient cardiology appointment in the first year after implementation, and approximately 550 additional referrals every year thereafter.
- There are a number of issues with regard to the implementation of a screening programme that fall outside the scope of this report that could potentially affect decision making. These include the identification of appropriate methods for flagging patient's notes in GP practices to ensure that screening is offered to everyone in the target population and ensuring that GP practices have access to ECG equipment with interpretative software.
- Consideration may also need to be given to the development of referral guidelines for GPs in advance of the introduction of screening, in view of the potential implications that a national programme has for the number of specialist referrals and requests for additional investigations.

Arising from the above findings, the Authority's advice to the Health Service Executive is as follows:

Annual opportunistic screening of men and women aged 65 years and older by pulse palpation followed by ECG confirmation of an irregular pulse in the Irish primary care setting is likely to be cost-effective using conventional willingness-to-pay thresholds, assuming that those detected through screening have a comparable stroke risk profile as those detected by routine practice. Increasing the start age of screening or the screening interval may improve the cost-effectiveness of a prospective screening programme.

Executive Summary

1. Background

Atrial fibrillation (AF) is the most common arrhythmia seen in general practice and is associated with a five-fold increase in the risk of stroke. Strokes related to atrial fibrillation are also more severe, with twice the death rate of non-AF related strokes and greater functional deficits for those who do survive. Irish data suggest that almost 40% of individuals with atrial fibrillation are unaware that they have an irregular heart rhythm. The National Cardiovascular Health Policy 2010 - 2019 recommended that a screening programme for atrial fibrillation should be established for people aged 65 and over, following formal evaluation to ensure an effective means of implementation. The HSE National Clinical Programme for Stroke recently conducted a pilot project in the west of Ireland, to assess the feasibility of a national screening programme.

Following discussions with the HSE National Clinical Programme for Stroke, the Authority undertook a health technology assessment (HTA) of screening for atrial fibrillation in primary care.

2. Objectives

The terms of reference for the HTA were:

- to review the international clinical evidence on the effectiveness and safety of screening for atrial fibrillation,
- to review the available literature on the cost-effectiveness of screening programmes for atrial fibrillation,
- to estimate the clinical benefits, cost-effectiveness, resource implications and budget impact of a national screening programme for atrial fibrillation in Ireland,
- based on this assessment, to advise on the cost-effectiveness of an Irish screening programme for atrial fibrillation.

3. Methods

This research was carried in accordance with HIQA guidelines for the conduct of health technology assessments. In summary:

- The Terms of Reference of the HTA were agreed between the Authority and the HSE National Clinical Programme for Stroke.
- An Expert Advisory Group (EAG) was convened, with representation from health policy decision makers, clinicians, patient advocates, professional

bodies and experts in health services research and economic evaluation. An evaluation team was appointed comprising internal Authority staff.

- A systematic review was carried out to summarise the available evidence on the clinical and cost-effectiveness of screening for atrial fibrillation.
- An original economic evaluation was performed to estimate the cost-effectiveness and budget impact of a prospective national AF screening programme in Ireland, with costs measured in Euro and benefits measured in quality-adjusted life years (QALYs).
- Clinical outcomes examined in the analysis included AF detection rates, incidence of ischaemic and haemorrhagic stroke, incidence of systemic embolism and gastrointestinal bleeding.
- The major costs examined in the analysis included the opportunity cost of pulse palpation, the cost of ECGs in primary care, medication costs and the cost of acute treatment and long term care associated with stroke.
- The primary analysis compared the cost-effectiveness of a national AF screening programme involving annual opportunistic pulse palpation for men and women aged 65 years and over in primary care with routine practice (no screening). The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and was consistent with the best available evidence on the effectiveness of screening.
- The primary analysis was carried out from the perspective of the publicly funded health and social care system in Ireland. The time horizon over which the costs and benefits of screening was calculated was 25 years and both costs and benefits were discounted at 5%.
- A Markov model was used to simulate costs and clinical outcomes in a hypothetical cohort of men and women with and without screening over the course of study time horizon, using a cycle length of one year.
- A budget impact analysis (BIA) was performed from the perspective of the public health system, which reports the incremental costs associated with screening over a five-year time horizon.
- The results of the analysis were also used to estimate the impact of screening on the number of specialist referrals.

4. Results

There is good quality evidence from one randomised controlled trial showing that both systematic screening by ECG and opportunistic screening by pulse palpation produce comparable increases in AF detection rates. However, opportunistic screening does so at significantly less cost. The sensitivity of pulse palpation with

confirmatory ECG is estimated to be 80%. No major safety issues associated with screening were identified. An additional randomised controlled trial (RCT) of opportunistic screening for over 65s in primary care is currently in progress, the results of which could alter the conclusions drawn based on the existing evidence. Two studies were identified that examined the cost-effectiveness of AF screening in primary care. While both of these concluded that screening was cost-effective, the applicability of the results in an Irish context is low.

Based on the results of this HTA, annual AF screening in Ireland is expected to result in the detection of 1,944 additional AF cases and prevent 157 strokes within a cohort of men and women screened from age 65 to 90 years. By the end of the fifth year of screening it is estimated that the intervention will have been associated with an overall decrease of approximately 1.9% in the incidence of first ever stroke in the screening population. From the perspective of the HSE, the incremental cost-effectiveness ratio (ICER) for AF screening in over 65s compared with routine care is €20,271/QALY, with an 83% probability of being cost-effective at a willingness to pay threshold of €45,000/QALY. The overall five year incremental budget impact of screening for the HSE is estimated to be €3.7M. It is estimated that screening could result in approximately 2,800 additional referrals for an outpatient cardiology appointment in the first year after implementation, and approximately 550 additional referrals every year thereafter.

The analysis found that if the relative risk of stroke and systemic embolism is more than 14% lower in screen-detected patients compared with symptomatic patients, then screening would not be considered cost-effective using a willingness-to-pay threshold of €45,000/QALY. There is a lack of definitive evidence on whether AF cases that are detected through screening have the same risk of stroke as symptomatic cases. Although international guidelines for the management of AF recommend that both be treated the same, some studies have suggested that the risk of stroke in asymptomatic, device-detected AF could be up to 50% lower than that of symptomatic AF. However, the relevance of results from a very narrowly defined subgroup (those with device detected rapid atrial rate) is unclear, since those diagnosed through screening will include a mix of truly asymptomatic, as well as mildly symptomatic cases. Having reviewed the available evidence, the view within the Expert Advisory Group was that screen detected AF would not be expected to be associated with a reduced risk of stroke and systemic embolism compared with AF diagnosed through routine care. This would appear to be supported by a recent analysis of data from nine European countries in the EORP-AF Pilot General Registry, which found that asymptomatic AF had a higher one-year mortality than symptomatic AF. In this analysis it was assumed that the risk of stroke and systemic embolism in those detected through screening is the same as in those who present with symptoms.

Sensitivity and scenario analyses were carried out to examine the impact of uncertainty regarding the model parameter estimates. This showed that lowering the start age of screening would tend to make any prospective screening programme less cost-effective, with a start age of 50 being associated with an ICER of €50,578/QALY compared with no screening. Conversely, increasing the screening interval beyond once a year would tend to make screening more cost-effective. If extended screening intervals of greater than one year are considered feasible in the context of an opportunistic screening programme, then screening once every three years becomes the optimal strategy at a willingness to pay threshold of €45,000/QALY. However, these results need to be interpreted with caution, as all the available evidence on the effectiveness of screening comes from studies carried out in people aged 65 years and over, and no studies have as yet compared the results of using different screening intervals. The results of the economic analysis were insensitive to changes in the incidence rate of AF and changes to the rate of warfarin and direct oral anticoagualant (DOAC) usage.

There are a number of issues with regard to the implementation of a screening programme that fall outside the scope of this report that could potentially affect decision making. These include the identification of appropriate methods for flagging patient's notes in GP practices to ensure that screening is offered to everyone in the target population and ensuring that GP practices have access to ECG equipment with interpretative software. Consideration may also need to be given to the development of referral guidelines for GPs in advance of the introduction of screening, in view of the potential implications that a national programme has for the number of specialist referrals and requests for additional investigations. The costs of screening in primary care were calculated based on current General Medical Services (GMS) remuneration rates, which may change in the future as a result of planned contract re-negotiations or potential changes to the funding model as part of the shift in policy towards effective chronic disease management in primary care. However, the results of a sensitivity analysis show that unless the fees and allowances payable under the GMS capitation agreement increase dramatically, then the conclusions of this report are unlikely to change.

5. Conclusion

Annual opportunistic screening of men and women aged 65 years and older by pulse palpation followed by ECG confirmation of an irregular pulse in the Irish primary care setting is likely to be cost-effective using conventional willingness-to-pay thresholds, assuming that those detected through screening have a comparable stroke risk profile as those detected by routine practice. Increasing the start age of screening or the screening interval may improve the cost-effectiveness of a prospective screening programme.

1 Introduction

1.1 Terms of Reference

The Terms of Reference agreed between HIQA and the HSE National Clinical Programme for Stroke were:

- to review the international clinical evidence on the effectiveness and safety of screening for atrial fibrillation,
- to review the available literature on the cost-effectiveness of screening programmes for atrial fibrillation,
- to estimate the clinical benefits, cost-effectiveness, resource implications and budget impact of a national screening programme for atrial fibrillation in Ireland,
- based on this assessment, to advise on the cost-effectiveness of an Irish screening programme for atrial fibrillation.

1.2 Overall approach

The Authority convened an Expert Advisory Group (EAG) comprising representation from relevant stakeholders. The role of the EAG was to inform and guide the process, provide expert advice and information, and to provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report. The Terms of Reference of the EAG were to:

- Contribute to the provision of high quality and considered advice by the Authority to the Health Service Executive.
- Contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate.
- Be prepared to provide expert advice on relevant issues outside of group meetings, as requested.
- Provide advice to the Authority regarding the scope of the analysis.
- Support the Evaluation Team led by the Authority during the assessment process by providing expert opinion and access to pertinent data, as appropriate.
- Review the project plan outline and advise on priorities, as required.
- Review the draft report from the Evaluation Team and recommend amendments, as appropriate.
- Contribute to the Authority's development of its approach to HTA by participating in an evaluation of the process on the conclusion of the assessment.

The Authority appointed an Evaluation Team comprising internal staff from the HTA directorate to carry out the assessment.

The Terms of Reference of the HTA were endorsed by the EAG at the initial meeting of the group.

A systematic review of the evidence on the clinical and cost effectiveness of screening for atrial fibrillation was carried out, along with an analysis of the applicability of the results in an Irish context. Following this review it was considered appropriate to conduct an original economic evaluation of a prospective national AF screening programme that combined the best available Irish data on the epidemiology of AF and stroke with published literature on the effectiveness of AF screening and subsequent management of the arrhythmia. Where possible Irish data sources were also used to inform estimates of the cost and utility weights associated with the clinical outcomes included in the analysis.

All parameter estimates used in the analysis were reviewed by the Expert Advisory Group and interim findings from the assessment were discussed at a meeting of the group. A final draft report was reviewed by the Expert Advisory Group prior to being submitted for approval by the Board of the Authority. Following its approval, the report was submitted as advice to the Minister for Health and the HSE.

2 Description of the technology

Atrial fibrillation (AF) is the most common cardiac arrhythmia encountered in general practice. It is characterised by a rapid and irregular contraction of the upper chambers of the heart, which diminishes its ability to pump blood efficiently. In some cases AF can be asymptomatic, while in others the person may experience palpitations, chest pain and shortness of breath. Different types of AF can be classified by the frequency of occurrence of the arrhythmia or by the underlying cause. The 3-P system distinguishes between paroxysmal (two or more episodes that terminate within seven days), persistent (one episode that lasts more than seven days) and permanent AF (episode lasts more than a year and cannot be terminated by cardioversion).[1] Aetiological classification distinguishes between AF cases where there is no clinical or echocardiographic (ECG) evidence of structural heart disease (lone AF), or by the presence or absence of heart valve problems such as rheumatic mitral valve disease (valvular or non-valvular AF). The overall population prevalence of AF is around 2%, rising sharply with age. The median age of AF patients is 75 years and 70% are between 65 and 85 years old.[2-4] Estimates of AF prevalence in those aged over 80 vary from around 8% to greater than 15%.[5] Men are 1.5 times more likely than women to develop the condition, but because women have a longer life expectancy, the overall number of men and women with AF in older populations is approximately equal.[6;7]

As well as reducing quality of life, non-valvular AF is associated with a fivefold increase in the risk of stroke.[2] This is due to uncoordinated atrial activity disrupting blood flow through the heart, which increases the propensity for thrombus formation, particularly in the left atrial appendage. These clots may be pumped out of the heart and cause an ischaemic stroke by blocking an artery supplying blood to the brain. Compared with non-AF strokes, AF strokes are more likely to be fatal, and result in longer hospital stays, poorer functional outcomes and a lower chance of being discharged home afterwards for those who survive.[8] It is estimated that there are approximately 8000 strokes annually in Ireland, with about a third of these being associated with underlying atrial fibrillation.[9;10]

Recommended management of AF is outlined in the (draft) AF care pathway developed by the HSE National Clinical Programme for Stroke.[11] Diagnosis of the arrhythmia is made by ECG in patients with suspected AF or those with an irregular pulse. However, pulse palpation of patients who present without symptoms indicative of AF is not routinely carried out in primary care. Once diagnosed, patients may undergo further testing to rule out structural heart disease or other problems. Most patients receive pharmacological treatment to decrease the risk of stroke in AF, with treatment decisions being guided by the CHA_2DS_2-VASc score for AF stroke risk. The two main types of anti-thrombotic treatment are antiplatelet therapy and oral anticoagulation, which have been shown to reduce the risk of stroke by

approximately 20% to 60%.[12] Risks associated with these medications include an increase in the likelihood of haemorrhagic stroke or major extracranial bleeding. A minority of patients undergo invasive procedures to treat AF, including ablative surgery to modify electrical conductivity in the atrium itself, and left atrial appendage occlusion devices to seal off the area principally associated with thrombus formation.

It is estimated that over 30% of people with AF have no obvious symptoms, but are nonetheless at increased risk of stroke and systemic embolism.[13;14] In the absence of screening, asymptomatic AF is diagnosed incidentally through routine physical examinations or after complications such as stroke or heart failure have occurred. The North Dublin Stroke Study found that 45% of strokes had underlying AF which was undiagnosed prior to the stroke.[15] AF would therefore appear to meet many of the Wilson-Junger criteria for a successful screening programme.[16] The natural history of the disease is well documented and includes a significant proportion of latent cases, a suitable test is available and effective treatments can be administered to those diagnosed, which substantially reduce the risk of serious injury or death from stroke. However there remains a great deal of uncertainty regarding the final criterion of whether the costs of case finding (including diagnosis and treatment of patients diagnosed) are economically balanced in relation to possible expenditures on medical care as a whole. Our aim is to address this issue in an Irish context, by estimating the cost-effectiveness of an opportunistic AF screening programme in primary care, which was recommended in the 2010 National Cardiovascular Health Policy and is currently being considered by the HSE National Clinical Programme for Stroke.[17]

3 Review of effectiveness and safety of screening

A systematic review of the evidence on the effectiveness of AF screening was carried out to inform the economic analysis and identify any potential safety implications associated with the intervention. Full details of the search strategy, inclusion criteria, quality appraisal and results were previously published in the Cochrane Library.[18] This section provides a summary of the most relevant findings from the 2013 review and an update of the literature search (June 2012 to June 2015).

Two randomised controlled trials of AF screening were identified. One was a three-arm cluster randomised controlled trial (RCT) that compared systematic screening (by ECG) and opportunistic screening (by pulse palpation followed by ECG confirmation) with routine care for individuals aged 65 and over in the UK general practice (SAFE study).[19] The other was an RCT of screening people aged 75 and 76 in Sweden using intermittent ECG recording over a two week period (STROKESTOP study) compared with standard of care (no screening).[20] One ongoing study examining the effectiveness of opportunistic AF screening of over 65s in primary care in Spain (DOFA-AP study) was also identified.[21]

3.1 Summary of included studies

3.1.1 The SAFE study

The Screening for Atrial Fibrillation in the Elderly (SAFE) study recruited a total of 50 general practices in the UK and used stratified randomisation by practice size and level of deprivation (Townsend score) to allocate them to either control or intervention groups.[19] All enrolled practices had to have computerised record keeping facilities in order to participate. Educational materials highlighting the importance of AF detection and available treatment options were provided to intervention practices and staff were encouraged to consider opportunistic pulse taking during routine consultation. Ten thousand patients aged 65 years or older were randomly selected from the intervention practices and allocated evenly to either systematic or opportunistic screening. In the systematic screening arm patients received a letter inviting them to attend an electrocardiogram (ECG) screening clinic. In the opportunistic arm, patients' records were flagged to prompt the general practitioner (GP) to check the pulse whenever that patient next attended the practice for any reason. Five thousand patients aged 65 years or older were randomly selected from among the control practices to act as a routine care comparator. Staff in the control practices received no training.

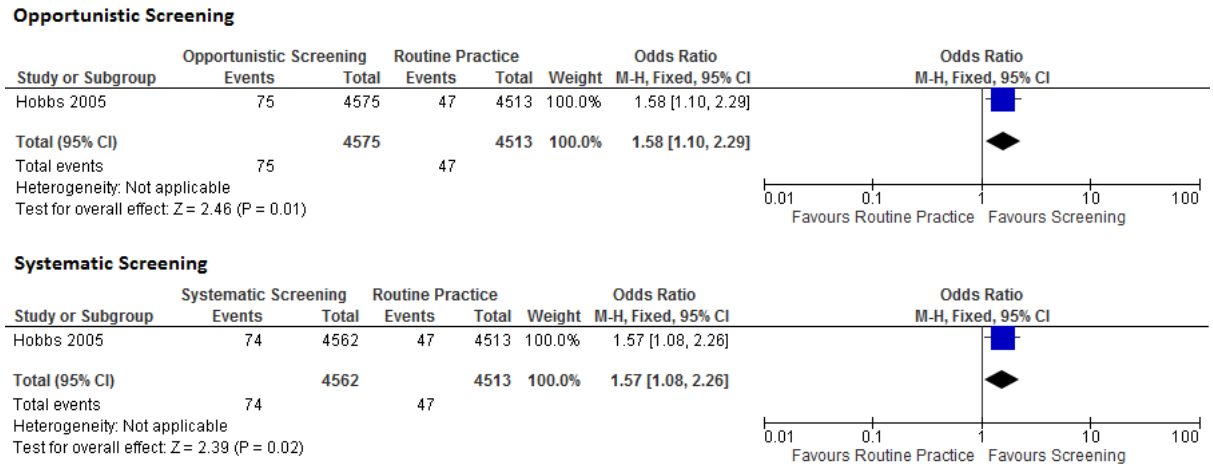
The risk of bias in the SAFE study is low. Blinding of participants was not possible given the nature of the intervention, but the clinicians who read the ECGs were blinded as to which group the tracing came from. The primary outcome of the study

was the detection of new cases of AF. The long term impact of the intervention on stroke outcomes in screened versus unscreened populations was not examined.

The study found that both systematic and opportunistic screening increased detection of new cases of AF compared with routine care. The effect size in both arms was comparable (odds ratio of being diagnosed with AF in the intervention group compared with the control group was 1.57), but systematic screening was associated with substantially higher costs. The incremental cost per additional case detected by opportunistic screening was GBP £337, compared with GBP £1,514 for systematic screening. All cost estimates were based on UK data from 2001 to 2003.

The absolute effect of screening on AF detection rates in the overall population was relatively modest (<1%). It is also noted that a greater proportion of the 75 newly identified cases in the opportunistic arm were diagnosed outside of the screening programme (44/75, 59%) than within it (31/75, 41%). Forest plots for both opportunistic and systematic screening versus routine care are shown in Figure 3.1. No major safety concerns associated with screening were reported and a patient survey completed at the end of the trial indicated that the screening process was acceptable to patients.

Figure 3.1 Forest plots of opportunistic and systematic screening versus routine care (SAFE)



3.1.2 The STROKESTOP study

The STROKESTOP study randomly assigned people aged 75 and 76 years from two separate regions within Sweden to treatment and control groups.[20] People without a history of AF in the treatment group were sent a letter inviting them to participate in an AF screening programme. Those who accepted the invitation were given handheld one-lead ECG recorders to use over the course of a two-week-period. Patients were instructed to take ECG recordings twice daily or when they experienced palpitations by placing their thumbs on the device, which then

automatically transmitted a 30-second ECG tracing to a centralised database. In the case of inconclusive tracings, participants were offered additional ECG recordings at the discretion of the investigating cardiologist.

The study ran from March 2012 to June 2014 and invited a total of 14,387 people. The overall response rate was 54% (n=7,173). New diagnoses of AF were made in 218 patients (3.0%, 95% CI 2.7 to 3.5) in the screened group. Of the 666 patients with a prior diagnosis of AF, 517 (77.6%) were using oral anticoagulation (OAC), meaning 149 patients (2.1%) of the total screened population (7,173) had diagnosed AF but were not anticoagulated. Therefore 5.1% of patients screened benefitted from the intervention by being offered OAC. Among newly identified cases, 93% accepted starting OAC, while the corresponding figure for those with previously diagnosed AF was 47%. However, the authors failed to report the rate of AF diagnosis in the control arm, so it is not possible to estimate the effect of screening on AF detection in this study. No major safety concerns associated with screening were reported.

The uptake rate of screening was relatively low (54%) so there is a risk of self-selection bias if there were inherent differences between the group that accepted screening and those that did not. The results are reported using the denominator of those who accepted the invitation and were screened, and included those with a prior diagnosis of AF, (7,173) rather than doing an intention-to-treat analysis using the overall invited population (14,387). In contrast, the SAFE study calculated the detection rate as a percentage of the total invited population without a history of AF.

STROKESTOP investigators intend to follow study participants for five years to examine the impact of screening on the incidence of ischaemic stroke. They will also use registry data at five years to measure the detection rate of AF in the control group. Therefore currently there are no data on the relative effectiveness of this type of screening on AF detection or long term stroke outcomes.

3.1.3 The DOFA-AP study

A protocol for an randomised controlled trial (RCT) currently in progress in Spain was published in 2012.[21] The authors planned to conduct a cluster randomised trial comparing opportunistic screening of over 65s in primary care with routine care. The investigators intended to recruit almost 13,000 participants over the course of 12 months and use the same screening test as the SAFE trial (pulse palpation followed by ECG confirmation). The estimated completion date for this study was March 2015. Contact with the principal investigator for this study revealed that a manuscript reporting the results of the trial is currently in preparation. Initial indications are that the authors will report that screening was not effective, with a greater number of irregular pulses having been detected in the control arm than the treatment arm.[22] The finding that opportunistic screening would decrease the number of irregular

pulses detected is counterintuitive. Of particular interest will be further details on what exactly constituted routine care in the Spanish primary care centres involved in the trial. The results of this study are not expected to be available until late 2015 or early 2016. Given the methodological quality of the UK SAFE trial and the high level of applicability in terms of the patient population, the screening intervention and the study setting, the risk that the results of the DOFA-AP trial will seriously alter the parameter estimates used in the decision analysis model is considered low.

3.2 Summary of findings

No published studies were identified that examined the impact of AF screening on stroke outcomes or mortality. Two RCTs examined the impact of screening on detection of AF, but one of these failed to report the AF detection rate in the control arm. These studies used different screening tests in different populations, so the results cannot be combined. Based on the UK trial both opportunistic and systematic screening are equally effective at improving AF detection, but systematic screening is associated with much higher costs. The magnitude of the effect of screening on observed annual AF incidence within the overall population aged 65 years and older is relatively small, with annual increases of less than 1%. Screening older age groups with intermittent ECG recordings as opposed to once-off ECG or pulse palpation during GP consultations may increase the rate of detection in those screened. However, given the relatively low uptake rates reported in the Swedish RCT, the overall impact of screening on observed AF incidence is likely to be less than 3%. As well as detecting latent AF, screening may also improve anticoagulation rates among those with an existing diagnosis. The Swedish study reported a 1% increase in anticoagulation rates within the screened group.

Challenges in evaluating the impact of AF screening include the difficulty in estimating the effect of routine care and handling differences in the background prevalence of AF between control and treatment groups. In the SAFE trial the baseline incidence of AF was higher in the control arm than in both treatment arms (7.9% versus 6.9%). This could be due to real differences in AF risk between groups, in which case randomisation failed, or as a result of better detection in the GP practices in the control group. The study authors concluded that it was probably the latter, but this then raises questions about whether higher detection rates in the treatment group were partly due to there being a higher proportion of undiagnosed AF to begin with. The interaction of the relative effects of routine care and screening is also difficult to assess. In the UK trial a significant proportion of new cases continued to be diagnosed outside of the screening programme in both the systematic and opportunistic arms of the trial.

The results of the Spanish RCT of opportunistic screening of over 65s are awaited. This will provide valuable evidence on the transferability of the UK results outside of

the UK primary care setting and hopefully give greater certainty about the impact of screening on AF detection. However it is not anticipated that this study will report the impact of screening on stroke outcomes or mortality.

The UK National Screening Committee reviewed its recommendations with regard to AF screening in 2014.[23] They concluded that although screening is likely to increase AF detection it should not be offered given current deficiencies in the management of existing AF patients and uncertainty about the clinical benefits of early diagnosis. Data from the UK indicates poor compliance with currently recommended anti-thrombotic treatments. Approximately half of those who should be on anticoagulation are not, while a third of those for whom anticoagulation is not indicated (because their risk of stroke is low) are receiving it.[24;25] They also found a lack of evidence showing that undiagnosed AF carries the same risk of stroke as diagnosed AF, citing some studies that have suggested that the relative risk of stroke in asymptomatic device-detected AF may be 33% to 50% lower than the risk of stroke for those with symptomatic AF.[23] However, the CHA_2DS_2-VASc score for AF stroke risk does not differentiate between asymptomatic and symptomatic individuals when calculating stroke risk. Also in the event of screening, not all screen-detected people will be completely asymptomatic, just as not all AF patients currently detected are symptomatic, so the evidence from pacemaker studies may not be directly applicable.

In summary, there is good evidence to show that screening improves detection rates of AF compared with routine care. No major safety concerns were identified and both opportunistic and systematic screening were reported to be acceptable to patients. An additional RCT of opportunistic screening for over 65s in primary care is currently in progress, the results of which could alter the conclusions drawn based on the existing evidence. A major limitation of the available evidence is the lack of data on the stroke risk profile of asymptomatic AF and the impact of screening on long term stroke outcomes and mortality.

3.3 Key points

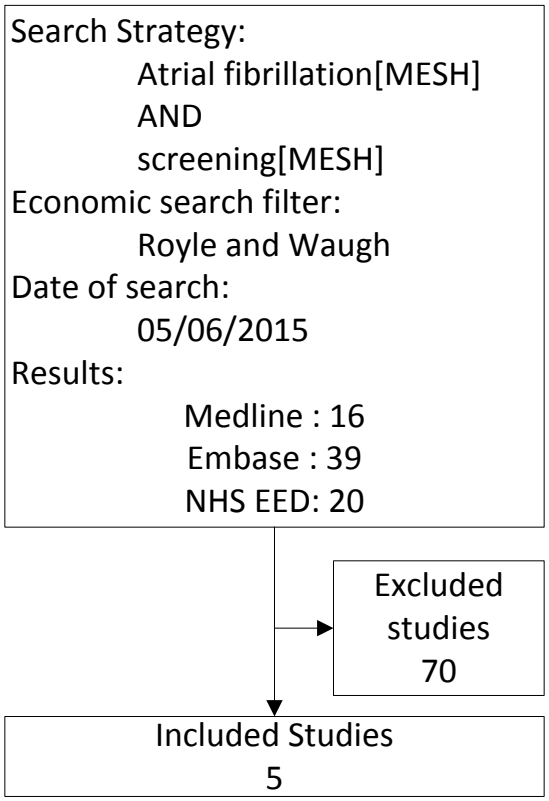
- There is good evidence from one randomised controlled trial to show that screening improves detection rates of AF compared with routine care.
- No published studies were identified that have examined the impact of AF screening on stroke outcomes or mortality so there is a lack of evidence on whether the additional AF cases identified through screening have the same stroke risk, and therefore the same potential to benefit from treatment, as those who present in routine care.
- Opportunistic and systematic screening in primary care are associated with increases in AF detection of about 1% annually compared with routine care.

- Prolonged intermittent screening may increase AF detection rates compared with a screening test carried out at a single point in time.
- No safety concerns associated with screening were identified and both opportunistic and systematic screening were reported to be acceptable to patients.
- An additional RCT of opportunistic screening for over 65s in primary care is currently in progress, the results of which could alter the conclusions drawn based on the existing evidence.

4 Review of cost-effectiveness of screening

A search for economic evaluations of screening for atrial fibrillation (AF) conducted in Medline, Embase and NHS EED identified five studies that compared any type of screening programme in the general population to usual care. Figure 4.1 shows the search strategy used and a flowchart of the results.

Figure 4.1 Search strategy and results



4.1 Summary of included studies

Five studies were identified, two from the UK, and one each from Japan, Australia and Sweden. The included studies were all published between 2004 and 2015, and examined the cost-effectiveness of both organised and opportunistic screening. Table 4.1 provides a summary of identified studies, each of which are described in more detail below.

Table 4.1 Summary of cost-effectiveness studies

Study	Setting	Perspective	Study (Costs)	Screening	Findings*
Maeda 2004[26]	Primary care Japan	Societal	Cost-utility analysis (2001 USD)	Pulse palpation and ECG	Screening by pulse palpation and screening by ECG are both cost-effective (ICERs <€17,000/QALY)
Hobbs 2005[19]	Primary care UK	Health service	Cost-utility analysis (2003 STG)	Pulse palpation and ECG	Screening by opportunistic pulse palpation has a 60% chance of being cost-effective). Systematic ECG screening is not cost-effective.
Lowres 2014[27]	Community pharmacies Australia	Health service	Cost-utility analysis (2012 AUD)	ECG	ECG screening using a mobile phone attachment is cost effective (€3,311/QALY)
Rhys 2013[28]	Flu vaccination clinics UK	Health service	Cost-effectiveness analysis (2011 STG)	Pulse palpation	Cost per new case of AF diagnosed was €292
Aronsson 2015[29]	Primary care Sweden	Societal	Cost-utility analysis (2014 EUR)	ECG	Prolonged, intermittent ECG recording was cost-effective (ICER €5,097/QALY)

* All results have been converted to 2014 Irish € using the relevant consumer price index and purchasing power parity

4.1.1 Annual pulse palpation and ECG in primary care

Maeda et al. examined the cost-effectiveness of community-based annual ECG or pulse palpation AF screening programmes compared with no screening for over 65s in Japan.[26] This was a cost-utility analysis with costs in (2001) US dollars and benefits in QALYs. They used a Markov model that differentiated between non-disabling, disabling and repeated disabling ischaemic and haemorrhagic strokes over a 25 year time horizon with costs and benefits discounted at 3%. In this analysis it was assumed that ECG and pulse palpation have sensitivities of 100% and 97%,

respectively, that the screening programme would achieve uptake rates of 100% and that all detected AF cases would be anticoagulated. The study included direct costs associated with screening and treatment (apart from the capital costs of ECG equipment), as well as the cost of the patient's time, calculated using Japanese average salary data. Results for screening in men and women were reported separately. The incremental cost-effectiveness ratio (ICER) for annual pulse palpation in males was $7,637 and $9,968 in females. The ICER for annual ECG in males was $7,830 and $10,220 in females. The authors concluded that screening was cost-effective and that both screening tests were comparable in terms of the benefits and costs.

An economic analysis was carried out as part of the Screening for Atrial Fibrillation in the Elderly (SAFE) trial of opportunistic and systematic AF screening of over 65s in a UK primary care setting.[19] This was conducted from the perspective of the National Health Service in the UK, but also included the opportunity cost of patient's time. Data on the sensitivity of pulse palpation (87%) and ECG (12-lead GP read ECG 80%) were taken directly from the trial. Long term outcomes were estimated from the literature, using an assumption that screen detected cases carry the same risk of stroke and systemic embolism as those detected through routine practice. Discrete event simulation was used to model a cohort of people from age 65 to death, differentiating between non-disabling and disabling ischaemic stroke. Costs and benefits were discounted at 3.5% annually. Results showed that the incremental benefit of opportunistic screening (in QALYs) was not significantly different from that of no screening, but was either cost neutral or marginally less costly. This resulted in a very flat cost-effectiveness acceptability curve (CEAC) indicating that opportunistic screening had approximately a 60% chance of being cost-effective at any given willingness to pay (WTP) threshold. Opportunistic screening was more cost-effective than systematic screening, which was associated with a fivefold increase in the cost of AF case detection (GBP£1,787 versus GBP£363, 2003).

4.2.2 AF screening using iPhone ECG in pharmacies

Lowres et al. reported the results of a cost-utility analysis of screening for AF in community pharmacies using an ECG taken by a specially adapted iPhone and interpreted using a software algorithm reported to have a sensitivity of 98%.[27] The analysis was conducted from the perspective of the Australian health service, based on a cohort of men and women aged 65 to 84 years. Cost data were taken from a feasibility study using the iPhone ECG device carried out by the authors previously, and data on the long term effectiveness of AF detection were taken from UK registry data. Utility data were taken from previous studies estimating that each stroke prevented by screening resulted in a gain of 5.09 QALYs. Only costs were discounted, at a rate of 5% annually. It was assumed that the uptake rate of screening would be 50% and that adherence to treatment would be 55%. Results of

this study found that screening was highly cost-effective, with an incremental cost of €3,142 per additional QALY gained through screening.

4.2.3 AF screening in flu vaccination clinics

Rhys et al. reported the results of a study examining the clinical effectiveness and costs associated with screening over 65s attending annual flu vaccination clinics in the UK using pulse palpation and ECG confirmation of an irregular pulse.[28] A total of 573 patients were screened and two new cases of AF were identified. The study was not a cost-effectiveness analysis, but did report the cost of identifying a new case (GBP£234). The cost was based on estimated ECG costs in primary care of £34 that included the cost of the time required for a nurse to perform an ECG (£12). Long term costs and benefits were not reported. The authors concluded that although acceptable to patients, screening at annual flu vaccination was ineffective.

4.2.4 AF screening using intermittent ECG recording

Aronsson et al. reported a cost-effectiveness analysis based on the STROKESTOP trial of screening of 75 and 76 year olds in Sweden using intermittent ECG recordings (see Section 3.2).[29] In this study, participants underwent an initial ECG screen and if AF was not detected they were requested to provide two 30-second ECG traces per day for two weeks from home, using a portable device that automatically transmitted the recordings to a central database. Although no information on the AF detection rate in the control group is currently available, data from the screened group indicated that this type of screening increased the known AF prevalence by 3%.The study also detected a further 2% who had a prior AF diagnosis but were not taking anticoagulant medication. Estimates of the effect of treatment were taken from the literature and cost data from 2014 were obtained from the Swedish healthcare system. It was assumed that 93% of AF patients would be anticoagulated with apixaban. QALY losses as a result of ischaemic and haemorrhagic stroke were included as QALY decrements (0.15 and 0.30, respectively) rather than as a QALY weighting based on baseline quality of life by age. A Markov model was used to estimate the costs and benefits of screening in a cohort of 1,000 patients over their entire lifetime. Results indicated that intermittent ECG screening of 75 year olds was cost-effective, with a cost per additional QALY gained of €4,313, compared with no screening.

4.2 Summary of findings

All cost-utility analyses identified in this review concluded that AF screening is cost-effective compared with no screening. However there is a high degree of heterogeneity in the type of screening programme, study population and methods used to estimate the short and long term consequences of the intervention.

An appraisal of the available evidence was carried out per the International Society For Pharmacoeconomics and Outcomes Research (ISPOR) guidelines for assessing

applicability, validity and transferability of findings.[30] The most applicable studies in terms of screening programme and population were the Japanese and UK (SAFE) studies, which were the only ones to examine pulse palpation in primary care for over 65s.[19;26] These produced conflicting results, with the Japanese evaluation finding that both annual pulse palpation and annual ECG cost approximately the same, whereas the UK study found that the costs of systematic screening by invitation to ECG were five times that of opportunistic pulse palpation. Both studies found that screening was associated with marginal increases in the number of QALYs gained. The Japanese study assumed that the sensitivity of pulse palpation and ECG were higher than the estimates used in the UK trial. As the UK estimates were based on RCT data they have greater validity. Both studies used fixed estimates of the risk of stroke over the course of the study time horizon, rather than adjusting the risk based on the age of the cohort. Neither of the studies examined the impact of changes in the proportion of patients on antiplatelet versus anticoagulant therapy, and both studies were carried out prior to the widespread use of direct oral anticoagulants (DOACs, also referred to as new oral anticoagulants [NOACs]). They also failed to examine the impact of screen-detected AF patients potentially having a lower baseline risk of ischaemic stroke.

In summary, two of the five cost-effectiveness studies identified examined the type of screening programme of interest to this health technology assessment (annual opportunistic pulse palpation in those aged 65 years and over). While both ultimately found that screening was cost-effective, there are limitations in regard to the validity of some of the clinical and cost estimates used in the analyses. The applicability of the results to the present situation in Ireland is low, given the differences in healthcare costs and advances in the available treatments to reduce the risk of stroke in AF since these studies were carried out. Therefore to estimate the cost-effectiveness of a prospective national AF screening programme in Ireland it was necessary to develop an original economic model to simulate the anticipated costs and benefits associated with screening, using the best available Irish and international data on the epidemiology of AF and AF-related stroke, the effectiveness of treatment, the impact of AF and stroke on health related quality of life and the costs associated with diagnosis, treatment and long term care.

4.3 Key points

- Five previous studies reporting the cost-effectiveness of screening for AF in a general population were identified.
- Two studies examined annual opportunistic AF screening using pulse palpation followed by ECG confirmation in a primary care setting (UK and Japan).
- Both studies found that screening was associated with moderate increases in

the number of QALYs gained, compared with routine care.

- The Japanese evaluation found that both annual pulse palpation and annual ECG cost approximately the same, whereas the UK study found that the costs of systematic screening by invitation to ECG were five times that of opportunistic pulse palpation.
- Since the UK study was based on RCT data, the validity of the estimates of the costs of screening and the sensitivity of the screening test is greater than that of the Japanese study.
- Both studies concluded that screening by pulse palpation was likely to be cost-effective compared with routine care.
- The applicability of these results to the present situation in Ireland is low, given the differences in healthcare costs between different health systems and the arrival of new AF treatments that were unavailable at the time these studies were carried out.

5 Clinical and epidemiological data

Evaluation of the cost-effectiveness of screening requires estimation of the average probability of an event occurring in members of the simulated cohort, such as developing atrial fibrillation, having a stroke, dying, or being diagnosed with AF through screening, as well as the impact of treatment on the risks of experiencing these clinical outcomes. This section outlines how each of these parameter estimates was derived.

5.1 Incidence of atrial fibrillation

Accurately measuring the incidence of atrial fibrillation by age is challenging due to the characteristics of the disease, which can be minimally symptomatic or intermittent. There is currently no AF register in Ireland that records the number of people diagnosed by age group. The Irish Longitudinal Study on Ageing (TILDA) study recorded prevalence data by asking all 8,175 participants whether or not they had ever been diagnosed with AF and also by screening 4,890 participants using 3-lead ECG. The results of this showed an overall prevalence estimate of 3% in over 50s (approx 150 individual cases in total).[31] This was of limited use in the analysis, which requires data on the risk of developing AF by year of age (incidence data).

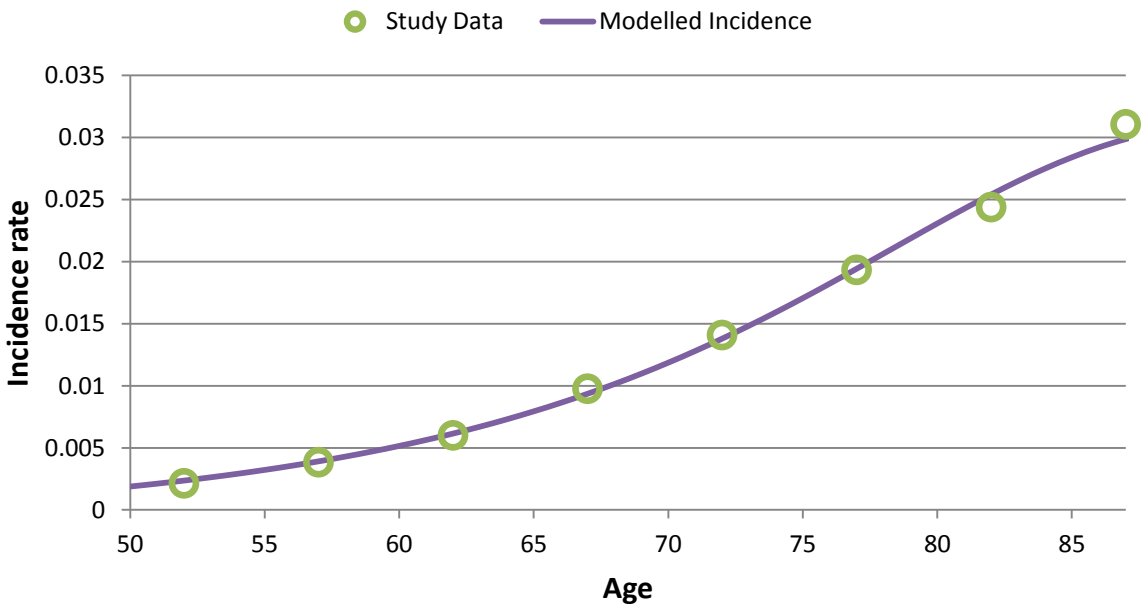
A number of international studies have estimated the incidence and prevalence of AF in the general population. One of the most recent and highly populated studies was carried out in Germany between 2006 and 2008, involving 8.3 million patients.[5] This produced relatively high estimates of AF prevalence compared with previous studies. Some of this difference is explained by the fact that the German study included any type of AF diagnosis whereas other studies only included permanent AF. It has also been suggested that AF prevalence has risen in many societies in the recent past due to an increased focus on detection, which could contribute to some of the difference between older and more recent studies.[32;33] The risk that AF prevalence is overestimated in this study by including suspected (as opposed to definite) AF cases is low, since inclusion required two outpatient AF diagnoses in two different quarters or at least one inpatient AF diagnosis. Generally in these types of studies the risk of underestimating AF prevalence is greater than the risk of overestimation, since not every case of AF is diagnosed and many patients with AF may not visit a doctor regularly.[34] Given the large numbers of participants, thorough case ascertainment and the applicability of the setting (Western Europe), the German study[5] on AF incidence by age is the best available data to use in this analysis. When prevalence in the TILDA study is calculated for those aged 50 to 84 within the group of people that were screened (N=4,849) by adding those that were screen-detected to those that reported a previous diagnosis of AF, the prevalence of AF in Ireland is consistent with the German study. The real prevalence of AF is likely to exceed both these estimates, given the difficulty in detecting all prevalent cases.

Incidence by year from this study is modelled using a rational function of the form:

$$Incidence_{AF} = \frac{\beta_0 + \beta_1 Age}{1 + \beta_2 Age + \beta_3 Age^2}$$

The study data and fitted model are shown in Figure 5.1.

Figure 5.1 AF Incidence



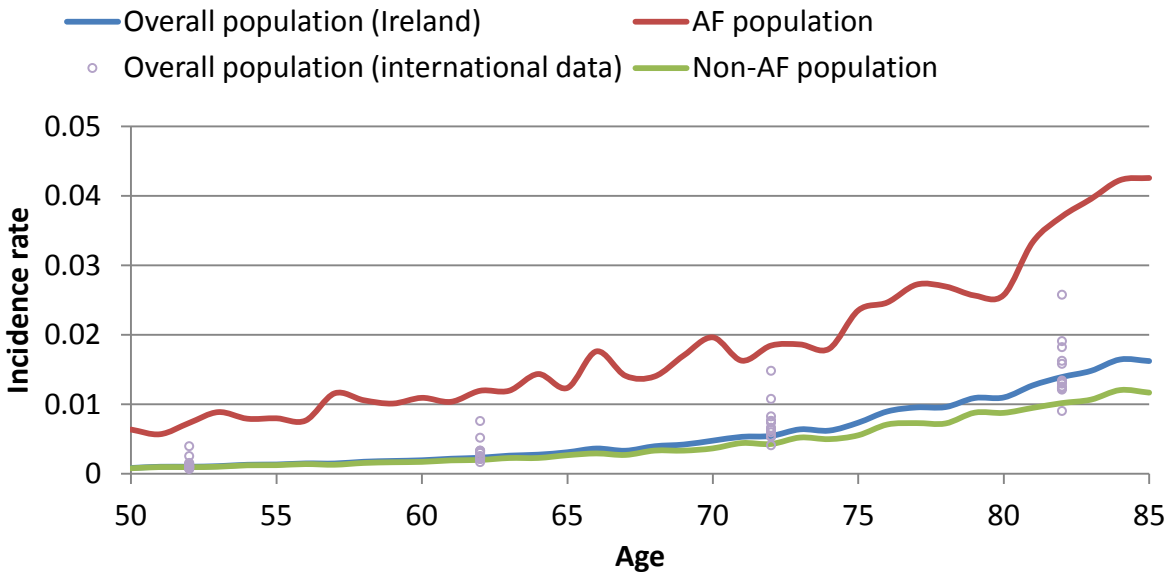
5.2 Incidence of stroke

The analysis required an estimate of the incidence of first-ever ischaemic stroke and intracranial haemorrhage by age for those without AF, those with undiagnosed and untreated AF and those with diagnosed and treated AF. Data on the percentage of ischaemic and haemorrhagic strokes that result in death and severe, moderate or mild disability within each of these three groupings was also required.

Irish data on the incidence of ischaemic (ICD I63), haemorrhagic (I60-I62) and undefined (I64) stroke by year of age for those without a diagnosis of AF (ICD I48) were obtained from the hospital in-patient enquiry (HIPE) system for the period 2010 to 2014. Population data required to calculate overall incidence rates were obtained from the Central Statistics Office (CSO). To exclude, insofar as possible, cases of recurrent stroke, only one episode was included per patient, and that episode had to be an emergency, non-readmitted case. Undefined stroke cases (I64) were divided between ischaemic and haemorrhagic strokes in the same ratio as the incidence of definite ischaemic to haemorrhagic strokes, to avoid underestimating overall incidence. HIPE data on overall stroke incidence for those with and without a diagnosis of AF are shown in Figure 5.2, which shows incidence rates consistent with those reported internationally.[35]

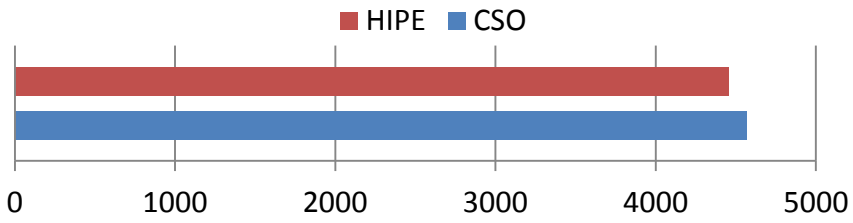
The evaluation also required an estimate of the rate of ischaemic and haemorrhagic stroke in those without a diagnosis of AF. In the analysis this baseline risk is then adjusted if the person develops AF and is diagnosed, or if they develop AF and remain undiagnosed. The evidence used to inform these parameters is discussed below. Briefly, an AF diagnosis increases the risk of ischaemic stroke, but does not alter the risk of haemorrhagic stroke, whereas antithrombotic treatment decreases the risk of ischaemic stroke, but increases the risk of haemorrhagic stroke.

Figure 5.2 Overall incidence of stroke in AF and non-AF populations



Since HIPE only includes data on hospital admissions there is a risk that it will underestimate the total number of strokes due to the exclusion of people who are pronounced dead before being brought to hospital. Specific data on the number of such cases is unavailable. The recently established National Stroke Register relies solely on HIPE data and does not collect this information. To examine the potential impact of this issue the latest five years of data from the CSO on total death certificate mortality from ischaemic and haemorrhagic stroke (I60-I64, 2008 to 2012) were compared with HIPE data on the total number of stroke deaths in hospital during the same period (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). There was only a 2% difference between the two (Figure 5.3), which indicates that using the HIPE data will not result in a major underestimate of stroke incidence. This is consistent with the results of previous work carried out by The Economic and Social Research Institute (ESRI) comparing HIPE data from Dublin hospitals with that of the North Dublin Stroke Study, which found a difference of 3% in first-ever or recurrent stroke incidence.[36]

Figure 5.3 Total deaths from stroke 2008-2012, CSO versus HIPE

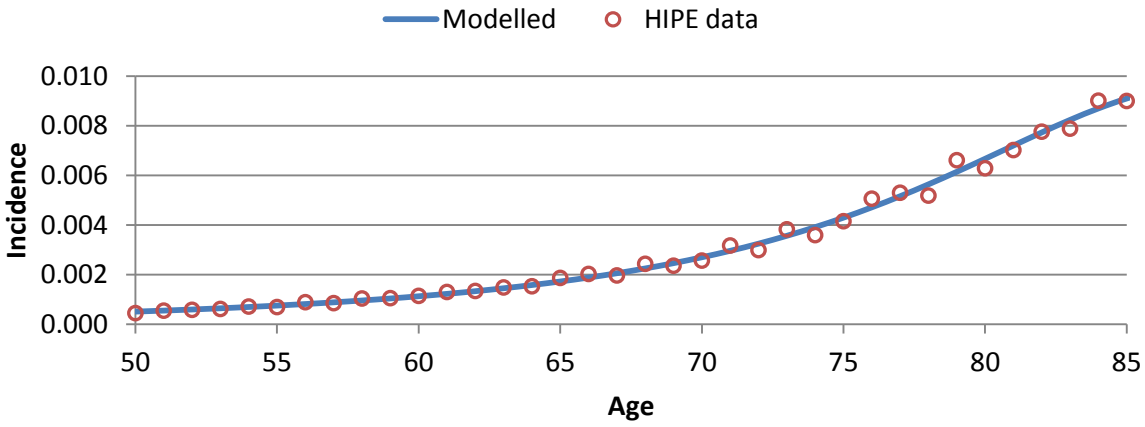


5.2.1 Incidence of ischaemic stroke in patients without AF

The estimated incidence of first ever ischaemic stroke by age for those without AF in Ireland is shown in Figure 5.4. This was modelled using a rational function of the form:

$$Incidence_{IS} = \frac{\beta_0 + \beta_1 Age}{1 + \beta_2 Age + \beta_3 Age^2}$$

Figure 5.4 Baseline incidence of ischaemic stroke by age

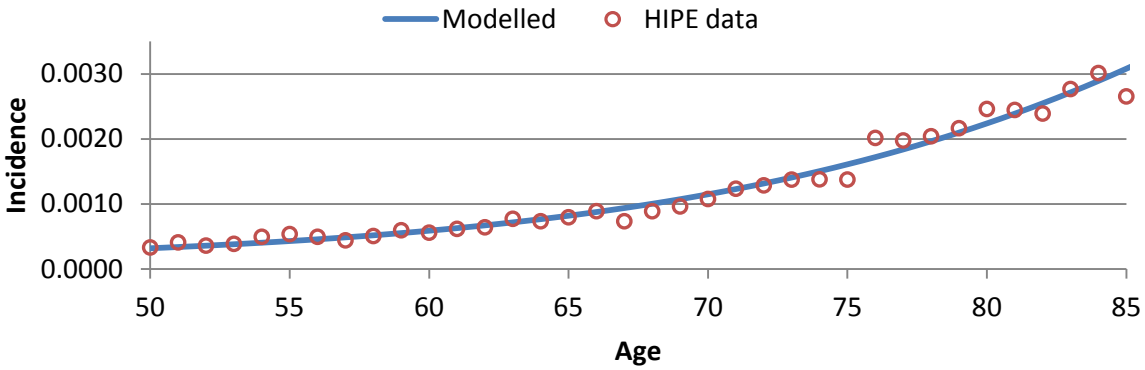


5.2.2 Incidence of haemorrhagic stroke in patients without AF

As with ischaemic stroke, the incidence of first-ever haemorrhagic stroke by age in people without AF was estimated using HIPE data and modelled as a 4th order polynomial (Figure 5.5):

$$Incidence_{HS} = \beta_0 + \beta_1 Age + \beta_2 Age^2 + \beta_3 Age^3 + \beta_4 Age^4$$

Figure 5.5 Baseline incidence of haemorrhagic stroke by age

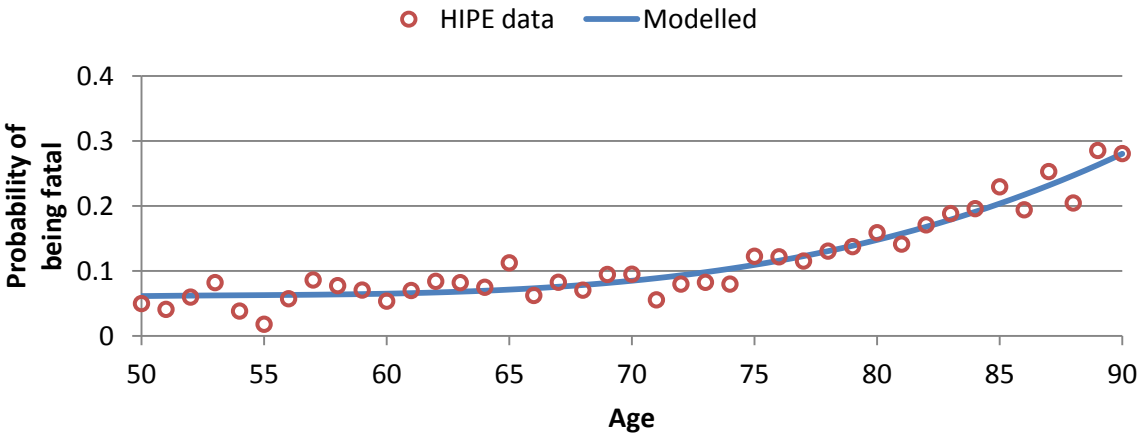


5.2.3 Probability of an ischaemic stroke being fatal in the absence of AF

Not only does AF increase the chances that a stroke will occur, but these strokes are more likely to be fatal and those who do survive are left with a greater degree of functional impairment than non-AF strokes.[18] In order to capture this, the model applied the baseline probability that a first-ever non-AF stroke is fatal to those without the arrhythmia and applied the appropriate relative risk to those with AF (the risk of stroke associated with AF is dealt with separately further on).

The probability of a first ever non-AF ischaemic stroke being fatal was estimated by age, using HIPE data on the percentage of cases that died in hospital (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). This parameter was modelled as a 3rd order polynomial (Figure 5.6).

Figure 5.6 Probability of a non-AF ischaemic stroke being fatal

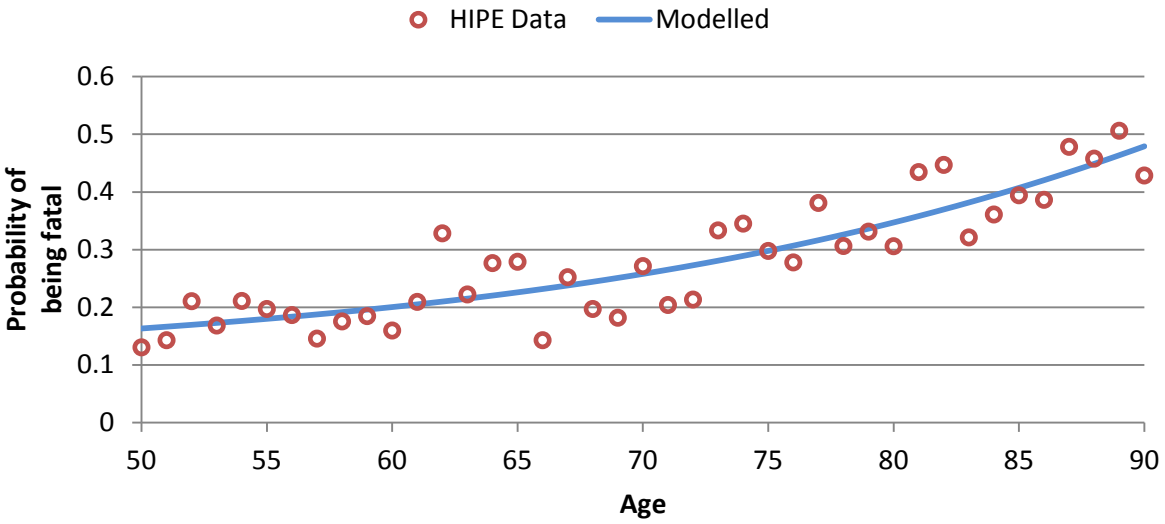


5.2.4 Probability of a haemorrhagic stroke being fatal in the absence of AF

The probability of a first ever non-AF haemorrhagic stroke being fatal, was estimated by age, using HIPE data on the percentage of non-AF haemorrhagic stroke cases

that died in hospital (discharge code of 06 [Died with post mortem] or 07 [Died no post mortem]). This parameter was modelled as a 3rd order polynomial (Figure 5.7).

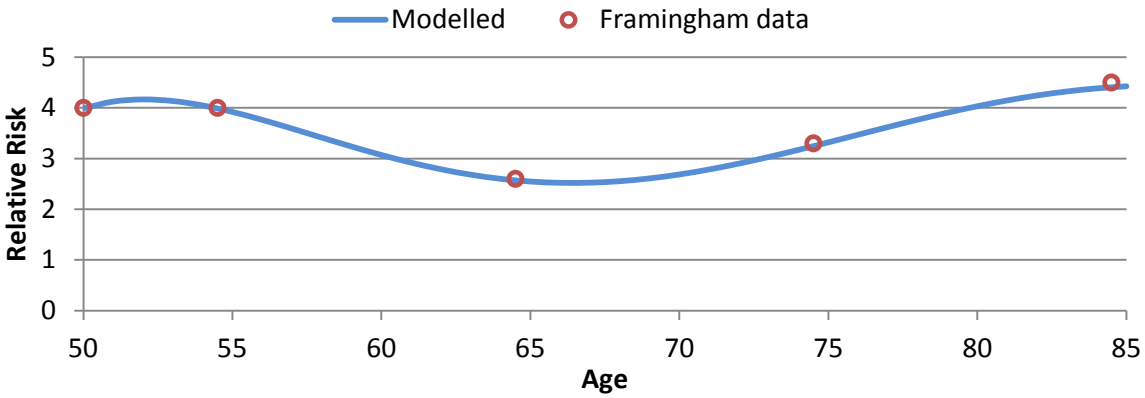
Figure 5.7 Probability of a non-AF haemorrhagic stroke being fatal



5.2.5 Relative risk of a ischaemic stoke in patients with AF

AF increases the risk of stroke. Therefore, it was necessary to estimate the relative risk of stroke by age, in those without AF (already covered above) and those with AF who are not receiving treatment. The best evidence on the relative risk of stroke associated with AF comes from the Framingham Heart Study, which examined a cohort of 5,070 men and women free of cardiovascular disease (including atrial fibrillation) at baseline every two years during a 34-year follow up period prior to the widespread use of oral anticoagulation.(2) Results of this study found that the risk of stroke is not uniform across all age groups. Relative risk of stroke associated with AF by age group (adjusted for other stroke risk factors [hypertension, coronary heart disease and cardiac failure]) is shown in Figure 5.8. This was modelled as a 5th order polynomial. The study included both ischaemic and haemorrhagic strokes, whereas ischaemic strokes are primarily of interest for this analysis. However they report that "stroke events resulting from haemorrhage accounted for only 11.6% of the total, and their exclusion would not appreciably influence the results of the analyses".(2)

Figure 5.8 Relative risk of stroke in AF versus non-AF patients, adjusted for other risk factors



Although there is some evidence to suggest that the risk of stroke varies by how long someone has had AF, insufficient data are available to reliably model stroke risk by time since onset of the arrhythmia. The relative risk used in the model was calculated based on AF patients that were diagnosed at a range of different time intervals. The limited available data suggest that the risk of stroke is as high, if not higher, than average immediately after the onset of the arrhythmia, so it is reasonable to apply the overall average risk within the population to all those with a diagnosis of AF.[37]

As outlined in the clinical effectiveness section (Chapter 3) a major limitation of the available evidence is the lack of data on whether those identified through screening have the same stroke risk profile as those diagnosed in routine care. The analysis examined the implications of screen-detected AF patients having a lower baseline risk of stroke and systemic embolism in a scenario analysis where the relative risk of stroke in undiagnosed versus diagnosed AF was varied between 0.50 and 1.[23]

5.2.6 Relative risk of a fatal ischaemic stroke in patients with AF

As well as stroke incidence, the Framingham study also examined differences in the severity of AF versus non-AF stroke using the same cohort of 5,070 people in which the link between AF and stroke was first established.[38] During the 40 years of follow-up there were 501 first-ever ischemic strokes, 103 of which were in people with a diagnosis of AF. Multivariate regression analysis of 30-day post-stroke mortality controlling for age, smoking status and coronary heart disease gave an odds ratio (OR) of 1.84 (95% CI 1.04 to 3.27). When this odds ratio is converted to a relative risk using the formula,[39]

$$Relative\ Risk\ (RR) = \frac{OR}{(1 - \rho_0 + (\rho_0 \times OR)}, where\ \rho_0 = baseline\ risk$$

the relative risk of a fatal stroke with AF is 1.70 (95% CI 1.04 to 2.67).

5.2.7 Functional outcomes in survivors of AF and non-AF ischaemic strokes

The Framingham study also reported the proportion of the 150 survivors of first-ever AF and non-AF ischaemic stroke who had mild, moderate and severe symptoms at three, six and 12 months post-stroke.[38] Severity of symptoms was classified using a modified Barthel Index (BI).[40] A score of 40 or less indicated severe dependence in activities of daily living (ADL), a score of 85 or above indicated mild to no dependence in ADL, and an intermediate score implied moderate dependence in ADL. The economic model uses a Markov cycle length of one year, so functional outcomes at 12 months are used, with an assumption that no further improvement occurs after that time. Due to the high mortality associated with stroke the number of survivors at 12 months in the study was small (10 out of 30 in the AF group and 55 out of 120 in the non-AF group), which introduces significant uncertainty in the estimates. Point estimates for the long term functional outcome for AF and non-AF stroke patients are provided in Table 5.1.

Table 5.1 Long term functional outcomes for AF and non-AF ischaemic stroke (proportion of stroke survivors in each functional category)

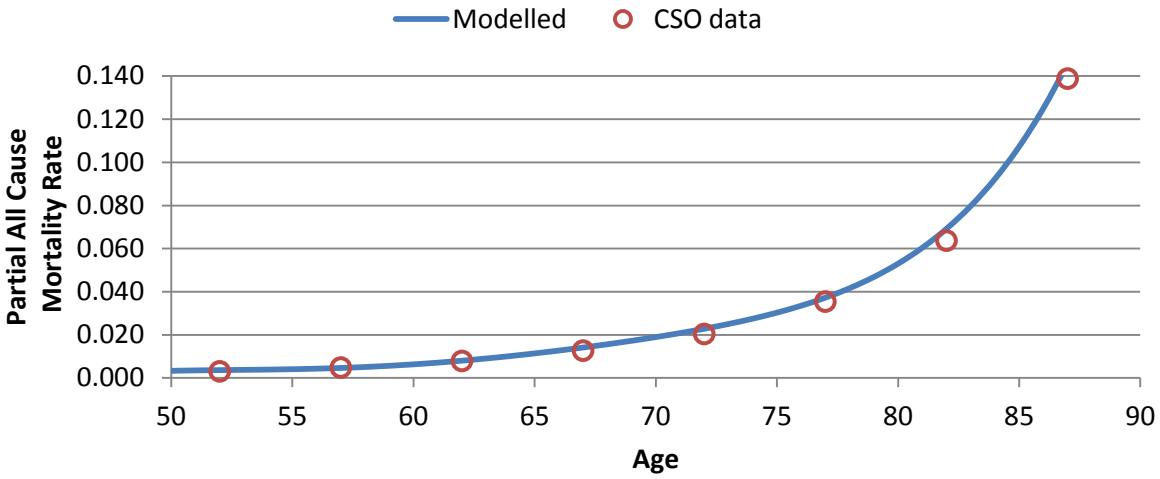
	Non-AF	AF
Mild or no dependency	0.64	0.40
Moderate dependency	0.25	0.30
Severe dependency	0.11	0.30

5.3 Deaths from other causes

The economic model simulates a cohort of individuals with and without screening in order to estimate the incremental costs and benefits associated with the intervention. The model is, by necessity, a vastly simplified representation of real life that only includes the clinical outcomes that are directly affected by the intervention. It was also necessary to take account of the fact that people within the cohort can die as a result of causes other than stroke. To do this, partial all-cause mortality was calculated, which is the overall pooled mortality rate from all causes other than stroke and associated sequelae.

Data from the most recent available five-year period (2008-2012) on the number of deaths from all causes other than stroke (I60-I69) by five-year age group was obtained from the CSO, along with the corresponding population estimates over that time period, to calculate the age-specific partial all-cause mortality rate. In the analysis this outcome was modelled as a 6^{th} order polynomial (see Figure 5.9).

Figure 5.9 Mortality rate from all causes other than stroke



5.4 Effectiveness of treatment

Having modelled the risk of stroke for those with and without AF, it was necessary to estimate the decrease in the risk and severity of stroke associated with treatment, as this is ultimately what determines the benefit associated with any change in case detection as a result of screening.

5.4.1 Effect of treatment on stroke risk

There are multiple treatment options for decreasing the risk of stroke in people with AF. Therefore the effect of treatment in the modelled cohort needs to be a composite parameter reflecting the proportion of people receiving each type of treatment and the relative effectiveness of each of these treatments in reducing the risk of stroke. Data on the current standard of care were obtained from TILDA, which recorded all medications prescribed for the 161 respondents who reported having a diagnosis of AF. The percentage of AF patients receiving each type of treatment based on this data is shown in Table 5.2, which also shows previous estimates of the standard of care derived from the North Dublin Stroke Study (NDSS, 2006 data) and the Irish National Audit of Stroke Care (INASC, 2007 data).[41;42] The more recent TILDA data (collected between 2009 and 2011) show a higher proportion of AF patients receiving oral anticoagulation (OAC). However, the TILDA data are based on a cohort of people with AF regardless of stroke status, whereas the other two datasets are derived from cohorts of stroke patients who had a previous diagnosis of AF, which one would expect to be less well managed given the fact that a stroke had occurred. A letter circulated by the HSE Medicines Management Programme reported a threefold increase in direct oral anticoagulant (DOAC) prescribing rates between 2012 and 2014, with AF accounting for 80% of all DOAC prescriptions.[43] Given the significant rise in the use of DOACs in Ireland since the first TILDA survey was completed, the applicability of these data to the present

day is questionable. The TILDA dataset has recently been linked to the Primary Care Reimbursement Service (PCRS) database, which provides more recent treatment information for those who were identified as having a history of AF. Data from a total of 68 patients indicate that there has been an increase in both the use of DOACs and the total proportion of AF patients receiving OAC (Table 5.2). However given the low number of patients and the fact that the standard of care for people diagnosed before the widespread use of DOACs may differ from that of newly diagnosed AF cases, this is probably an underestimate of the total proportion of AF patients taking DOACs. Unpublished data from the AF screening pilot carried out by the HSE Stroke Programme in the first half of 2014 shows that a significantly higher proportion of new AF cases were prescribed DOACs compared with the other data sources (Table 5.2.[44] The most recent PCRS data for overall DOAC use across all indications (October 2014) indicates that DOACs accounted for 35% of all patients taking oral anticoagulants (either DOACs or warfarin). UK data indicate that primary care centres with a sustained focus on optimal treatment for AF achieve OAC rates of around 60%.[45] This is consistent with the 2014 Irish data for warfarin and DOACs combined (59% to 66%). The UK data also show that increases in OAC rates correspond with decreases in the use of antiplatelet therapy, while the proportion of patients receiving neither treatment remains relatively constant at around 10%.

Table 5.2 Estimated current standard of care for AF patients in Ireland

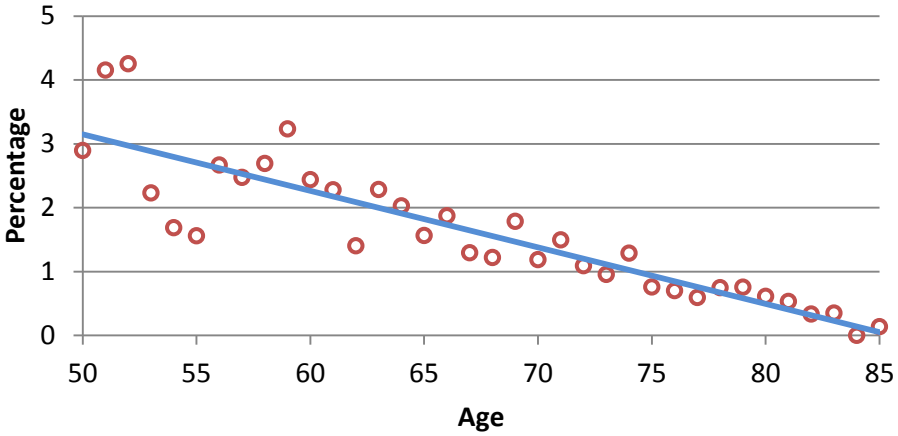
Population	Data Source	Warfarin	DOACs	Antiplatelet	None
AF population	TILDA (2009-2011, n=161)	38%	5%	47%	10%
	TILDA/PCRS (2014, n=68)	50%	9%	28%	13%
	AF Screening Pilot (2014, n=51)	26%	40%	18%	16%
Stroke population	NDSS (2006)	28%	-	55%	17%
	INASC (2007)	26%	-	52%	22%
Model estimate*	Combination of Irish and UK data	39%	21%	30%	10%

* UK primary care data from 2014 showing overall OAC rates of 60% and 2014 Irish PCRS data indicating that 35% of OAC patients are prescribed DOACs

In the primary analysis the current standard of care was estimated using an assumption that a total of 60% of newly diagnosed AF patients will receive OAC, with 35% of these being prescribed DOACs. These were modelled using a Dirichlet distribution to capture the uncertainty around these parameters. A sensitivity analysis was performed to examine the effect of varying these assumptions and to assess the potential impact of increasing rates of OAC and DOAC use.

Figure 5.10 shows HIPE data on the number of atrial ablation procedures as a percentage of incident AF cases in Ireland over five years from 2010 to 2014. This shows a marked decline by age, dropping to under 2% at age 65 to almost 0% at age 85. Due to the low numbers of cases and the fact that European guidelines state that discontinuation of warfarin therapy post-ablation is generally not recommended in patients at risk for stroke, coupled with uncertainty regarding its clinical effectiveness, surgical ablation is excluded from the analysis.[12;46]

Figure 5.10 Surgical ablation procedures as a percentage of incident AF cases by age, 2010 to 2014 (HIPE)



The relative effectiveness of warfarin, direct oral anticoagulants (DOACs) and antiplatelet therapy compared with no treatment in reducing the risk of ischaemic stroke was obtained from Cochrane reviews of warfarin and antiplatelet therapy for preventing stroke in AF patients and a meta-analysis of all pivotal phase 3 trials of the four direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and endoxaban) versus warfarin in non-valvular AF.[47-51] Estimates of the relative effectiveness of warfarin and antiplatelet therapy compared with no treatment were derived from placebo controlled trials and the relative effectiveness of DOACs compared with no treatment are estimated through indirect comparison based on data comparing DOACs and warfarin. Where only odds ratios were reported these were taken to be equivalent to relative risks, given the rarity of the outcomes being measured (baseline risk ~0.05).[39] Table 5.3 shows the relative risk of ischaemic and haemorrhagic stroke for each of the three categories of treatment compared with placebo.

Table 5.3 Clinical outcomes of warfarin, direct oral anticoagulants and antiplatelet therapy versus placebo (RR [95% CI])

	Ischaemic Stroke	Intracranial Haemorrhage
Warfarin	0.34 [0.23, 0.52]	2.38 [0.54, 10.50]
Antiplatelet Therapy	0.70 [0.46, 1.07]	1.32 [0.22, 7.80]
Direct Oral Anticoagulants	0.31 [0.19, 0.53]	1.17 [0.21, 6.72]

Suboptimal warfarin anticoagulation

Anticoagulation with warfarin requires regular testing to ensure that effective therapeutic levels are maintained in the bloodstream. This measurement is called the International Normalised Ratio (INR). An INR of between 2.0 and 3.0 is considered optimal for stroke prevention in atrial fibrillation, with a recommendation that the time in this therapeutic range (TTR) should exceed 70%.[8] Achieving this target can be difficult due to natural variability between individuals' INR levels, compliance rates, and drug, food and alcohol interactions. Well controlled clinical trials only achieved average TTR rates of 60%,[52-55] and real-life studies have estimated that some patients may achieve optimal TTR for less than 50% of the time.[12] There is a lack of national Irish data on average TTR rates for those receiving prophylactic anticoagulation for atrial fibrillation in the community. An RCT involving the anticoagulation management service in Cork University Hospital in 2007 found that TTR was 58.6% in the control group receiving usual care.[56] This is consistent with audit data from a general practice in Mallow, Co. Cork reporting a TTR point prevalence of 60.5% in 2009.[57] Since these are comparable to TTR rates achieved in the original RCTs of warfarin for non-valvular atrial fibrillation, this analysis applied the same relative risk of stroke to all patients treated with warfarin.

Suboptimal DOAC dosing

An analysis of DOAC prescribing in Ireland from January to October 2013 found that 16% of patients on rivaroxaban are on less than the recommended 20mg/day dosage for stroke prevention and approximately 66% of patients on dabigatran receive the lower dose of 110mg/day, which was found to be non-inferior to warfarin in preventing ischaemic stroke.[43] The impact of suboptimal dosing of DOACs will be examined in a scenario analysis that will apply the same therapeutic effect as warfarin in reducing the risk of ischaemic stroke, while retaining the same risk of bleeding and systemic embolism.

5.4.2 Effect of treatment on stroke severity

There is evidence to show that treatment of patients with atrial fibrillation is associated with a reduction in the proportion of fatal strokes and decreased stroke severity.[58;59] However, the evidence on severity and long term outcomes is not as strong as that for the impact of treatment on stroke incidence. The model requires

data on mortality at one year, as well as the proportion of survivors who are left with mild, moderate or severe functional deficits. Two recent systematic reviews of stroke severity in patients with atrial fibrillation who were receiving prior antithrombotic therapy identified a total of 11 relevant studies.[60;61] Of these, five reported data on the incidence of fatal stroke for those receiving no treatment, antiplatelet therapy, or therapeutic (INR≥2) and subtherapeutic (INR<2) warfarin.[58;59;61-63] Figure 5.11 shows a meta-analysis of all studies reporting short term mortality (at 30 days or prior to discharge) for patients with atrial fibrillation by type of prior treatment. Both therapeutic and subtherapeutic levels of warfarin are associated with a statistically significant decrease in the risk of fatal stroke, unlike antiplatelet therapy, which showed no difference. In the model, the estimated TTR point prevalence in Ireland of 60% was used to calculate a weighted relative risk of 0.67 (95% CI 0.54 to 0.86) of a stroke causing death for those receiving warfarin treatment. The relative risk for those receiving DOACs was assumed to be equivalent to therapeutic warfarin (RR 0.59 [95% CI 0.46 to 0.76])

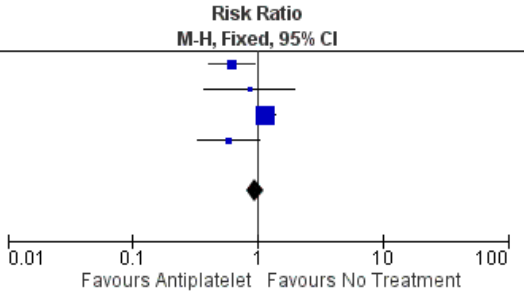
As described earlier, long term functional outcomes from AF versus non-AF stroke were taken from the Framingham Study, which used the modified Barthel Index to measure the percentage of survivors with mild, moderate and severe impairment at one year post-stoke. None of the studies examining the impact of prior treatment on stroke severity report this outcome. The best available evidence comes from a 2003 US study that reported functional outcomes at discharge as measured using the modified Rankin Scale (mRS), which classified strokes as severe (mRS=5), major (mRS = 3,4) and minor (mRS=0,1,2).[58] Although this categorisation is slightly different to the Framingham study, if it is assumed that the relative differences between each category as a result of prior treatment are broadly consistent, and that functional outcomes at discharge are directly correlated with long term outcomes then this can be used to estimate the impact of prior treatment on stroke outcomes. As before the impact of warfarin on stroke severity was calculated as a weighted average using a TTR point prevalence of 60%, and in the absence of specific data on DOACs, it was assumed they were equivalent to therapeutic warfarin (INR≥2). Figure 5.12 shows the results for non-AF strokes, as well as AF strokes with each type of prior treatment.

Figure 5.11 Relative risk of fatal stroke in patients with atrial fibrillation by type of treatment being received prior to onset of stroke

Antiplatelet Therapy

Study or Subgroup	Antiplatelet Events	Antiplatelet Total	No Treatment Events	No Treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hylek	24	160	60	248	22.1%	0.62 [0.40, 0.95]
Indredavik	12	169	9	109	5.1%	0.86 [0.37, 1.97]
O'Donnell	147	292	134	306	61.3%	1.15 [0.97, 1.36]
Schwammenthal	17	124	21	89	11.5%	0.58 [0.33, 1.04]
Total (95% CI)		**745**		**752**	**100.0%**	**0.95 [0.82, 1.11]**
Total events	200		224			

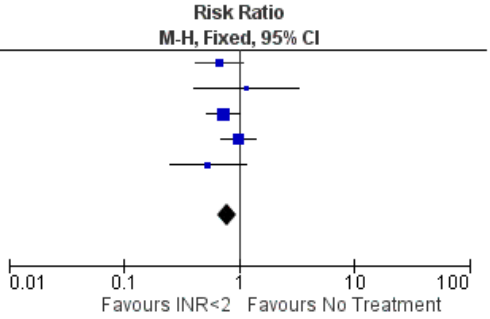
Heterogeneity: Chi² = 11.37, df = 3 (P = 0.010); I² = 74%
Test for overall effect: Z = 0.62 (P = 0.53)



Subtherapeutic Warfarin (INR<2)

Study or Subgroup	INR <2 Events	INR <2 Total	No Treatment Events	No Treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hylek	19	117	60	248	20.9%	0.67 [0.42, 1.07]
Indredavik	5	52	9	109	3.2%	1.16 [0.41, 3.30]
Johnsen	35	215	126	566	37.6%	0.73 [0.52, 1.03]
O'Donnell	47	238	61	306	28.9%	0.99 [0.70, 1.39]
Schwammenthal	8	63	21	89	9.4%	0.54 [0.25, 1.14]
Total (95% CI)		**685**		**1318**	**100.0%**	**0.79 [0.65, 0.96]**
Total events	114		277			

Heterogeneity: Chi² = 3.91, df = 4 (P = 0.42); I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)



Therapeutic Warfarin (INR≥2)

Study or Subgroup	INR >2 Events	INR >2 Total	No Treatment Events	No Treatment Total	Weight	Risk Ratio M-H, Fixed, 95% CI
Hylek	4	71	60	248	16.9%	0.23 [0.09, 0.62]
Indredavik	3	64	9	109	4.2%	0.57 [0.16, 2.02]
Johnsen	39	224	126	566	45.1%	0.78 [0.57, 1.08]
O'Donnell	11	112	184	948	24.5%	0.51 [0.28, 0.90]
Schwammenthal	6	48	21	89	9.3%	0.53 [0.23, 1.22]
Total (95% CI)		**519**		**1960**	**100.0%**	**0.59 [0.46, 0.76]**
Total events	63		400			

Heterogeneity: Chi² = 6.73, df = 4 (P = 0.15); I² = 41%
Test for overall effect: Z = 4.08 (P < 0.0001)

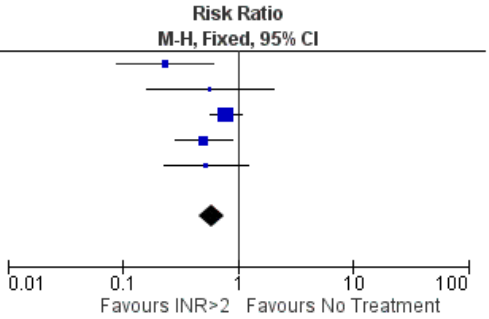
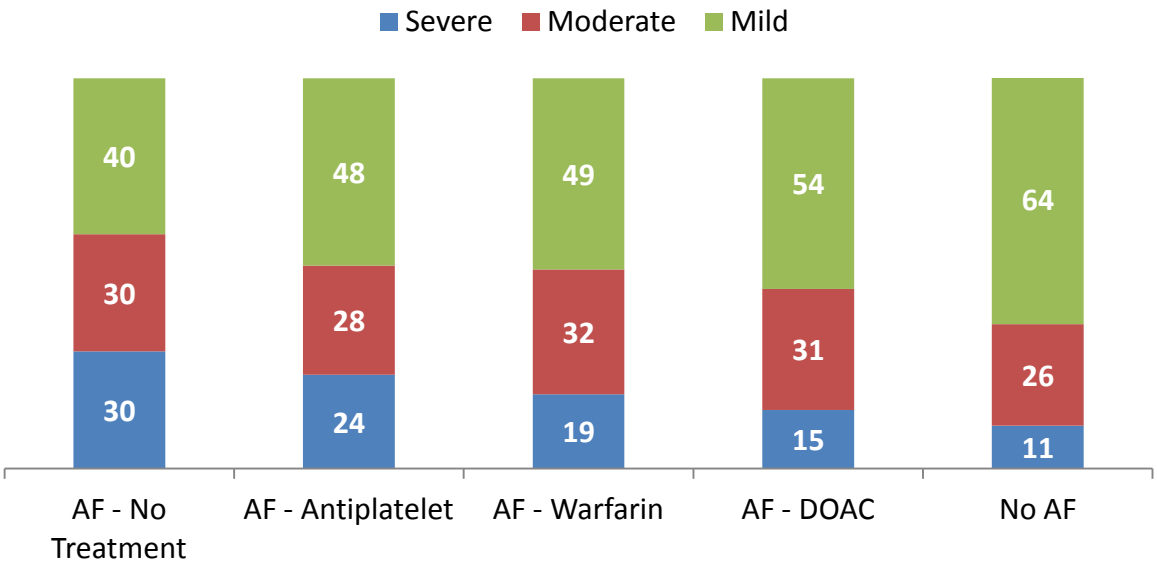


Figure 5.12 Percentage of survivors with severe, moderate or mild impairment post-stroke, by type of prior treatment



5.4.3 Other effects of treatment

As well as changing the risk of ischaemic stroke and intracranial haemorrhage, antithrombotic treatment can also affect the risk of gastrointestinal bleeding and systemic embolism. In order to include this in the model, it was necessary to estimate the baseline risk of both these events in people with atrial fibrillation, as well as the relative risk associated with the three type of treatment included in the model (antiplatelet, warfarin, DOACs).

The average baseline risk of systemic (non-central nervous system [CNS]) embolism and major extracranial bleeds in untreated AF patients without a history of stroke was obtained from randomised trials that included a placebo control arm (see Table 5.4).[47;48] Confidence intervals were approximated using the formula:

$$95\%\ CI = \frac{d}{N} \pm 1.96 \times \sqrt{\frac{\frac{d}{N} \times \left(1 - \frac{d}{N}\right)}{N}}$$

$$Where\ d = number\ of\ events\ and\ N = total\ number\ of\ cases$$

Table 5.4 Risk of systemic embolism and major extracranial bleed in patients with atrial fibrillation not receiving antithrombotic therapy

RCT	Systemic Embolism	Total	Major Extracranial Bleed	Total
AFASAK1	2	315	0	315
LASAF	0	91	NR	NR
SPAF1	4	527	8	527
BAATAF	0	201	8	201
CAFA	2	184	2	184
SPINAF	1	265	4	265
Total	9	1,583	22	1,492
Baseline Rate [95% CI]	0.006 [0.002, 0.009]		0.014 [0.009, 0.021]	

The relative risk of systemic embolism and major bleeding associated with warfarin, direct oral anticoagulants (DOACs) and antiplatelet therapy was obtained from Cochrane reviews of warfarin and antiplatelet therapy for preventing stroke in AF patients and a meta-analysis of all pivotal phase 3 trials of the four direct oral anticoagulants (dabigatran, rivaroxaban, apixaban and endoxaban) versus warfarin in non-valvular AF.[47-50] Where only odds ratios were reported these were taken to be equivalent to relative risks, given the rarity of the outcomes being measured.[39] Table 5.5 shows the relative risk of embolism and bleeds for each of the three categories of treatment versus placebo.

Table 5.5 Relative risk of systemic embolism and major bleeding associated with antithrombotic treatment in AF

	Gastrointestinal Bleeding	Systemic Embolism
Warfarin	1.07 [0.53, 2.12]	0.45 [0.13, 1.57]
Antiplatelet Therapy	1.14 [0.44, 2.98]	0.67 [0.19, 2.33]
Direct Oral Anticoagulants	1.34 [0.54, 3.29]	0.41 [0.11, 1.60]

As is evident from the wide confidence intervals around these relative risks, there is a high degree of uncertainty in relation to the relative risk of gastrointestinal bleeding and systemic embolism associated with the different antithrombotic treatment options for atrial fibrillation. There is also a lack of reliable evidence on the subsequent impact, if any, of these on mortality rates. These outcomes were therefore incorporated into the analysis using estimates of their effect on health-related quality of life and the duration of that effect. These estimates are provided in Section 6.5.

5.5 Effectiveness of screening

Estimates of the effectiveness of screening at increasing the detection of new cases of AF are taken from the Cochrane review of this topic, which was updated as part of

this project.[18] The results of this review are discussed in Chapter 3. The primary source of information is the UK SAFE trial, which compared opportunistic screening (by pulse palpation in GP practices followed by ECG if irregular) and systematic screening (by ECG) to routine care.[19] They found that both types of screening programme were equally as effective at detecting new AF cases compared with usual care (OR 1.6), but that systematic screening costs substantially more. This study also provided results for the sensitivity and specificity of pulse palpation and ECG in AF detection, which varied depending on who carried the test and what type of ECG was performed (Table 5.6).[19;64]

Table 5.6 Sensitivity and specificity of pulse palpation and ECG

Test	Sensitivity	Specificity
Pulse palpation		
GP or Nurse	87.2	81.3
ECG		
12-Lead		
CDSS	83.3	99.1
GP	79.8	91.6
Nurse	77.1	85.1
GP & CDSS	91.9	91.1
Limb lead		
GP	82.5	88.5
Nurse	72	83.4
Chest lead		
GP	84.8	86.4
Nurse	68.7	82.8

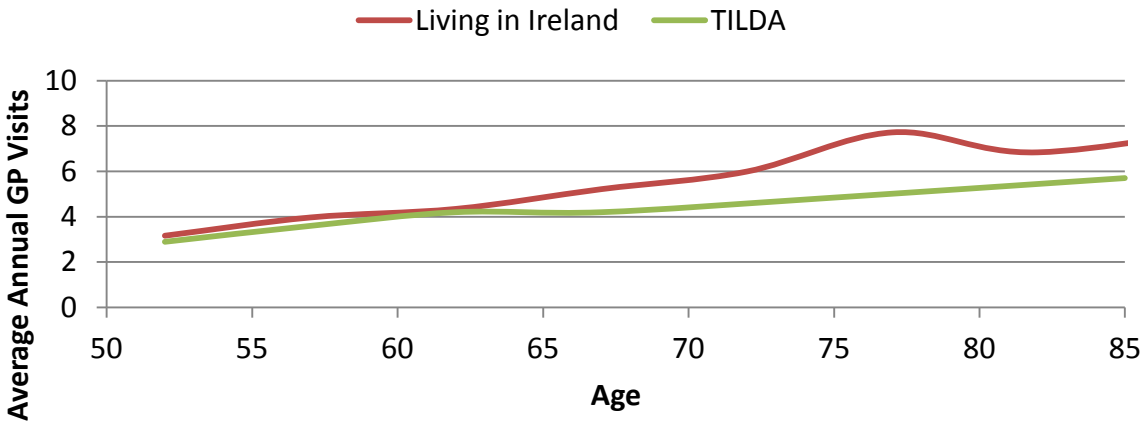
CDSS – Clinical decision support system

Evaluating the effectiveness of opportunistic screening for atrial fibrillation presents a number of unique challenges. The arrhythmia may be paroxysmal and therefore not always present when the index test is performed. This complicates any analysis based on the sensitivity and specificity of the test. There is also uncertainty relating to uptake and GP attendance rates, which influences how often the average person with undiagnosed AF will get tested. This may be especially important if there is an association between healthcare utilisation and undiagnosed AF. Detection of the arrhythmia requires that an undiagnosed person attends a GP, agrees to screening, is in atrial fibrillation when the test is performed and that the arrhythmia is successfully detected by the test. In terms of evaluating the impact of screening versus no-screening, the uncertainty regarding the baseline detection rate of atrial fibrillation in the absence of screening as a result of routine care must be considered.

5.5.1 GP attendance rates

GP attendance rates for those aged 50 to 85 were obtained from TILDA (2011) and the Living in Ireland Survey (2004).[65;66] There was some discrepancy between the two, with the earlier survey reporting higher frequency of attendance for those over 65 years (Figure 5.13). In the primary analysis, it was assumed that all those in the screening cohort attend a GP consultation at least once a year.

Figure 5.13 Annual number of GP visits by age



5.5.2 Uptake of opportunistic screening

Data on uptake rates of opportunistic screening was obtained from the SAFE study. This found that 69.2% of patients consented to having their pulse palpated and 65.9% of patients found to have an irregular pulse agreed to have an ECG. Patients are considered to have accepted an offer of screening if they complete the two stages of the screening test. This reduces the combined uptake rate to 45.6%. However, of the people who declined an ECG, 45.5% already had a diagnosis of AF. When these were excluded from both the numerator and denominator then the rate of uptake of ECG is 79.0%, and the combined uptake rate is 54.7%.

Since pulse palpation by GPs is a recognised component of routine care it is likely that acceptance rates among a prospective screening cohort in a real life setting would be greater than that observed in an RCT, which required patients to provide formal consent as trial participants. It was therefore assumed that all patients will agree to have their pulse palpated and that all those with an irregular pulse will agree to have an ECG. A sensitivity analysis was carried out to examine the impact of significant numbers of patients either failing to attend at least one GP consultation per year or declining to be screening, by varying the uptake rate between 50% and 100%.

5.5.3 AF detection rates

National UK data on AF prevalence is routinely collected in each commissioning group as part of the NHS Quality Outcomes Framework (QOF). By comparing

observed to expected cases in all GP practices, clinical commissioning groups and for the whole of the country, Public Health England recently estimated that overall diagnosis rates for AF in the absence of screening were approximately 65%.[67] In Ireland the TILDA study screened approximately 5,000 people from a nationally representative sample of over 50s and found that approximately 60% of people with AF were unaware that they had the arrhythmia.[31] This difference is assumed to be as a result of the incentives in place to promote AF diagnosis in primary care in the UK. In the model, it was assumed that approximately 60% of incident AF cases are diagnosed by routine care, and the impact of uncertainty was examined using sensitivity analysis. The primary estimate is consistent with recent data collected from nine European countries in the EORP-AF Pilot registry, which reported that 40% of AF patients were asymptomatic.[68]

In this analysis it was assumed that opportunistic screening involves pulse palpation followed by an ECG read by a GP with the support of computer software, with a diagnosis requiring a positive result in both. Therefore the overall sensitivity of this two stage test is:

$$Sn_{test} = Sn_{pulse} \times Sn_{ecg}$$

Using values from Table 5.6, this gives a sensitivity of 80.1%.

The average person will attend a GP consultation more than once a year. If they are tested each time the overall sensitivity will increase, since a diagnosis is made if the person tests positive either time:

$$Sn_{total} = Sn_{test} + Sn_{test} - (Sn_{test} \times Sn_{test})$$

For example, if a person was tested twice a year the sensitivity increases from 80% to 96% and if tested every time they attend the probability of being detected approaches 100% (average attendance rate in screening cohort is >4 per year). However, the direct application of the sensitivity of the screening test in this way risks significantly overestimating the proportion of AF patients who would be detected with screening. The data are derived from a trial that involved once-off pulse palpation during the course of one year, rather than repeat testing every time the patient attended, or annual testing over the course of multiple years. Therefore it is risky to assume that those who were not picked up in the first test have an 80% probability of being picked up in each subsequent test. Rather it is likely that factors such as whether asymptomatic AF is paroxysmal or persistent, or has atypical electrocardiographic presentation, make undetected cases more likely to remain undetected.

In this analysis it was assumed that people are opportunistically screened once a year when they attend their GP and that the sensitivity of the test in detecting

incident cases is 80%. In the primary analysis the conservative assumption was adopted that false negatives are not detected in subsequent screening tests. A scenario analysis examined the impact of a screening test that has a consistent 80% sensitivity in detecting both incidence and prevalent cases every year. The sensitivity of the test itself was also varied to estimate the impact of uncertainty in the estimate of the effectiveness of pulse palpation and GP-based ECG.

Limitations associated with the approach to estimating the impact of screening in Ireland are that it may overestimate the increase in the detection of AF due to a lack of data on the impact of paroxysmal AF on detection rates. This would tend to make screening appear more effective. Results obtained using the proposed approach show a greater increase in detection compared with directly transposing the absolute difference in the percentage of new cases detected in the treatment and control arms of the SAFE study. Using this method would mean applying a 10% increase in observed prevalence in the screened cohort (absolute increase in AF cases was 22% in screening arm compared with 10% in control arm), giving observed prevalences of 75% with screening (versus the model estimate of 80%). However, differences in the baseline prevalence of AF in the different arms of the trial, along with the fact that the majority of new AF cases in the treatment arm were detected outside of the screening programme, make such direct transposition to the absolute results problematic.

5.6 Long-term stroke survival

Screening is primarily designed to detect AF prior to the occurrence of stroke, since investigating whether not the arrhythmia is present after a stroke is standard practice for informing ongoing management of the patient. Therefore it is the incidence and severity of first-ever stroke that should differ between screened and unscreened populations, rather than the clinical outcomes after a stroke has occurred. For this reason the analysis estimates the overall average life expectancy and health-related quality of life after a stroke, by age and stroke severity. It does not separately model stroke recurrence or survival post-stroke by AF status or by type of treatment. There are some potential limitations of this approach. If screening and subsequent treatment were extremely effective then overall average survival would be improved because fewer patients with AF would have a stroke and given the association between AF strokes and worse outcomes, there would be fewer severe strokes. However given the challenges associated with detection and treatment, which mean that not all AF cases are detected and not all future strokes in detected cases are avoided through treatment, coupled with that fact that AF is implicated in a minority (~30%) of all strokes, overall population averages for stroke outcomes are unlikely to be significantly affected by screening. Another limitation is that by failing to model differences in post-stroke outcomes by treatment, the analysis will not be able to draw conclusions about the effectiveness and cost-

effectiveness of competing treatment alternatives for those who experience a stroke. However this is beyond the scope of this project and the data required to carry out such an analysis are not readily available.

5.6.1 Ischaemic stroke

Survival by severity of initial stroke was reported from the Oxford Vascular Study between 2002 and 2012.[69] Strokes were classified using the NIH stroke scale as minor (NIHSS≤3), moderate (NIHSS 4-10) or severe (NIHSS≥10). Survival to five years is shown in Figure 5.14. Their results show an initial drop in survival due to short term case fatality (at one month or hospital discharge), which was accounted for separately in this HTA as the incidence of fatal stoke. Therefore in the analysis it was necessary to adjust the UK data to estimate long-term survival by stroke severity for those who have survived to hospital discharge (Figure 5.15). The results show that for patients who survive the initial insult, survival is not linear. Rather, a steeper reduction is observed in the first year compared with years' two to five. The increase in mortality in the first year increases with stroke severity, while the mortality rate after year one is similar for all strokes.

Figure 5.14 Survival to five years by severity of ischaemic stroke

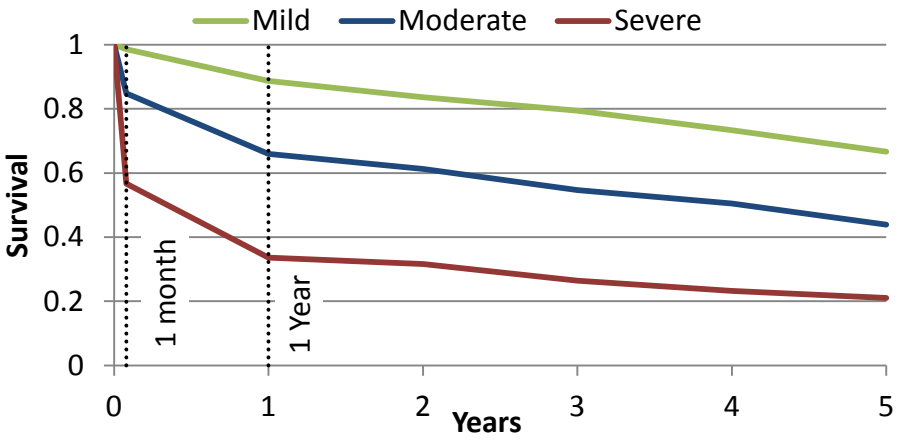
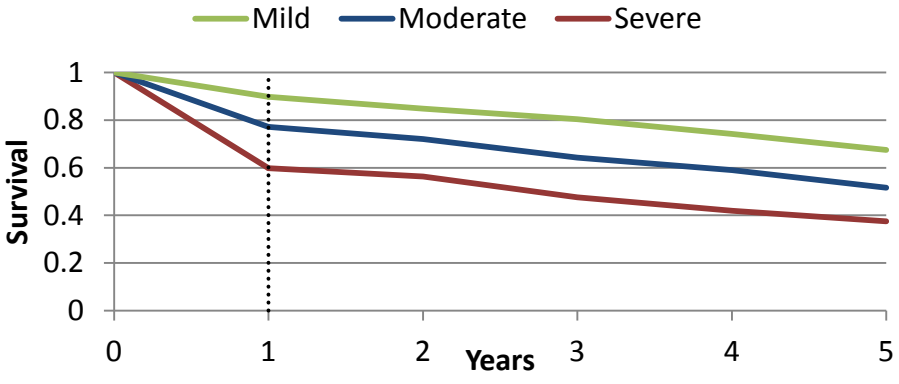


Figure 5.15 Survival to five years by severity of stroke for those who survive the initial ischaemic stroke



Using this data the annual probability of death by severity of stroke (in the first and subsequent years separately) was estimated as the slope of the survival curve (Table 5.7).

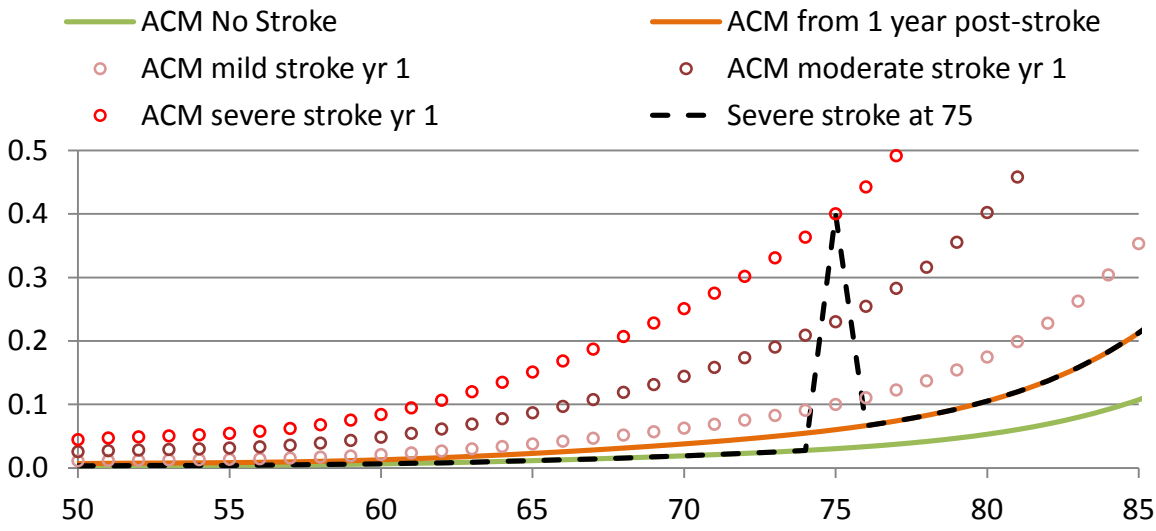
Table 5.7 Annual probability of death in year one and subsequent years by severity of ischaemic stroke

	Year 1	Subsequent years
Mild	0.10	0.06
Moderate	0.23	0.06
Severe	0.40	0.06

Care has to be taken when estimating rates from survival curves, since it is incorrect to say that the slope of the curve is equivalent to the annual mortality rate (which will vary over time with decreasing population).[70] However in the Markov model, it was necessary to estimate the annual probability of death in each of the stroke states (mild, moderate, severe) if a person has survived the previous year, so the denominator is always one, making the probability of death equal to the slope of the survival curve for the corresponding time period.

The average age of patients in the Oxford Vascular Study was 75 years. To estimate survival by age the relative risk of death in year one and subsequent years was compared with the baseline mortality rate at that age without stroke (partial all cause mortality, see Section 5.3 above). Figure 5.16 shows the annual probability of death in each stroke state by age. As an example, the dashed line shows annual mortality probabilities for a person who survives a severe stroke at age 75. They would have a normal annual risk of death prior to the stroke, which would be significantly elevated in the year following the (severe) stroke before decreasing after the first year to a level in excess of non-stroke mortality risk.

Figure 5.16 Annual risk of death by age and severity of ischaemic stroke



5.6.2 Haemorrhagic stroke

Long term survival from haemorrhagic stroke was estimated in a similar manner to ischaemic stroke. A 2014 systematic review[71] identified three studies that reported haemorrhagic stroke survival at one and five years in the same study.[72-74] One of these studies reported a combined outcome of death or stroke recurrence rather than death alone.[74] Of the remaining two, one reported outcomes in the UK for both first ever subarachnoid haemorrhage (SAH) and primary intracerebral haemorrhage (PICH) and the other reported outcomes in Finland for PICH only.[72] As shown in Figure 5.17, PICH results from both studies were similar and again a high initial drop in survival corresponding with fatal events was observed, followed by a relatively steep curve in year one when compared to subsequent years. The annual probability of death was calculated as the slope of the survival curve using the combined UK data on SAH and PICH (Figure 5.18 and Table 5.8).

Figure 5.17 Survival to five years for haemorrhagic stroke

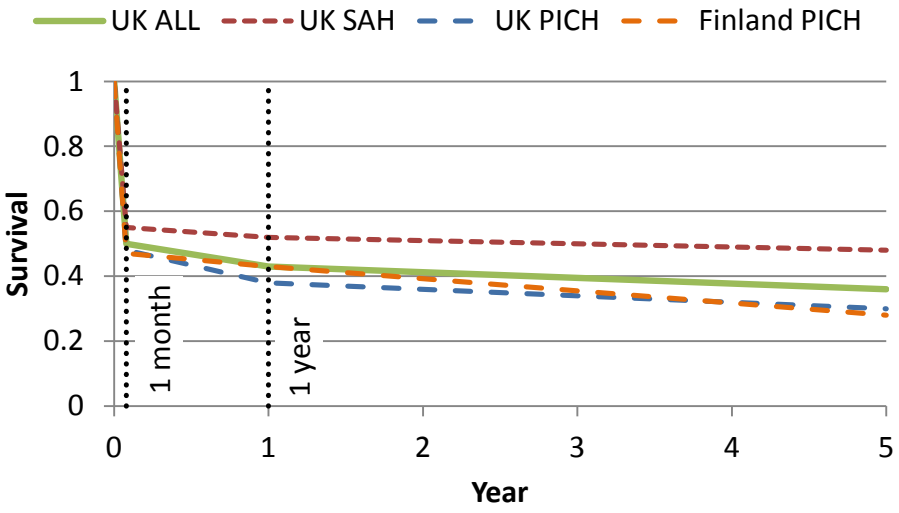


Figure 5.18 Survival to five years for those who survive the initial haemorrhagic stroke

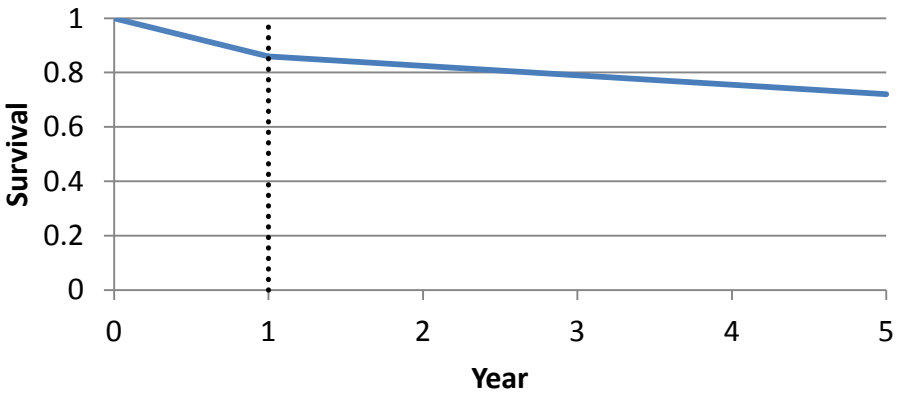
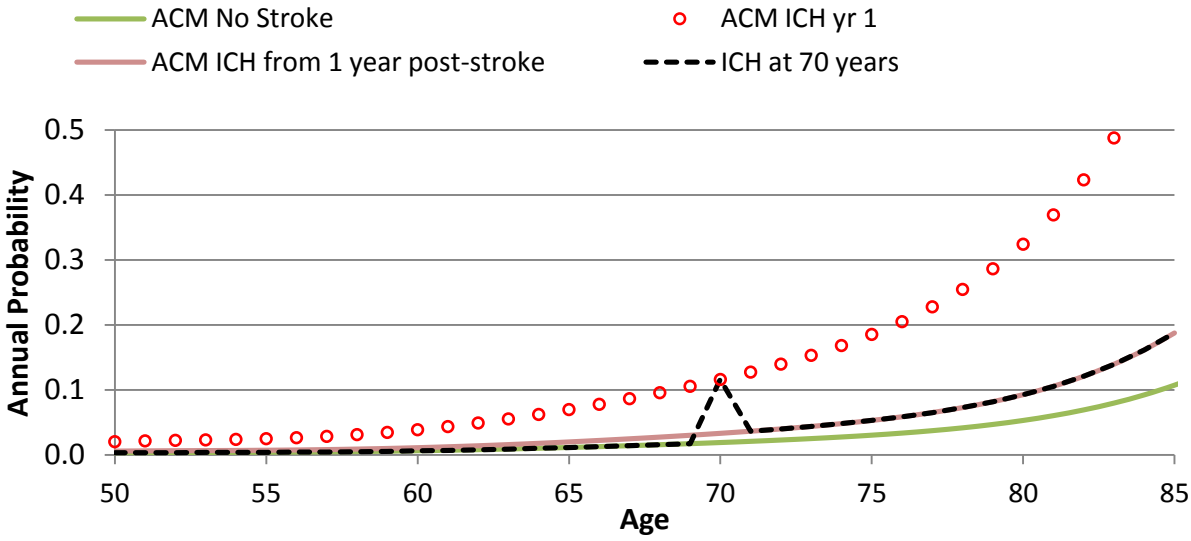


Table 5.8 Annual probability of death in year one and subsequent years by severity of stroke

	Year 1	Subsequent years
Haemorrhagic Stroke	0.14	0.04

The average age of participants in the UK study was 72 years. As before the relative risk of death in year one and subsequent years compared with the baseline mortality rate at that age without stroke (partial all cause mortality) was calculated. Figure 5.19 shows the annual probability of death for survivors of haemorrhagic stroke by age, both in the first and subsequent years. The dashed line shows annual mortality probabilities for a person who survives a haemorrhagic stroke at age 70.

Figure 5.19 Annual risk of death by age and severity for haemorrhagic stroke



5.7 Limitations of the clinical and epidemiological data

There are certain limitations to the approach adopted for estimating long term survival after stroke. While the outcomes for haemorrhagic stroke are taken exclusively from studies examining SAH and PICH, a minority (17%) of participant in the study used to estimate survival in ischaemic stroke had either SAH (5%), PICH (7%) or a stroke of unknown aetiology (5%). However, as outcomes were not reported separately the combined figure was used, which was assumed to be indicative of ischaemic stroke since these made up the majority of cases (>83%). There is also a risk that the relative risk of death calculated based on the mean age of the study cohorts may not be consistent across all age groups. However, in the absence of data on different age groups this is a better approach than directly applying results of the study to all people in the cohort, since this would produce counterintuitive results (chances of dying decreasing with advancing age) and there is evidence that mortality risk increases substantially with age.[72] It was also

assumed that stroke severity at admission (measured by NIHSS) is correlated with long term functional outcomes (measured by Barthel Index).[75-77] There may also be differences in survival from iatrogenic stroke as a result of AF treatment compared with that of the overall haemorrhagic stroke population, however the analysis models all those who survive a haemorrhagic stroke as a single group, so average survival rates are sufficient. There is also a risk that the treatment received by stroke survivors in the studies differs substantially from the current standard of care in Ireland, which would have implications for the applicability of the results. However both studies were carried out in a community setting in the UK, which has a comparable access to treatment, and results for ischaemic stroke are recent enough to justify an assumption of a comparable mix of available treatments for those who suffered a stroke (2002-2012). Finally, the analysis uses the best available Irish and international data on the detection rate of AF in routine care to estimate the proportion of cases diagnosed at any given time in the absence of screening. In the absence of any data by age group, it was assumed that the rate of undiagnosed AF is similar across all ages.

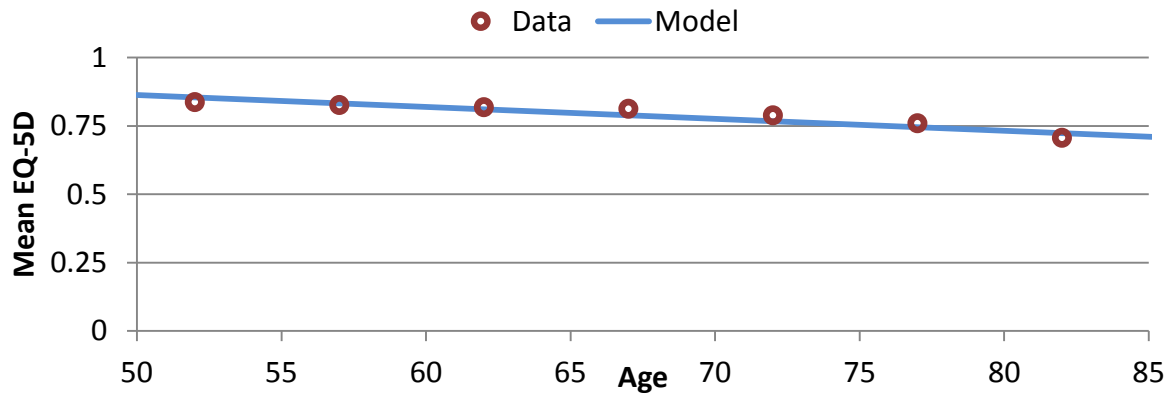
6 Utility data

The estimates of the impact of stroke on mortality enable calculation of the likely effect of screening in terms of life years lost or gained. What it does not take account for is any change in the quality of life for screened versus unscreened patients as a result of changes in functional status post-stroke, or treatment related adverse events, such as GI bleeds, that may not necessarily shorten life expectancy but are associated with significant morbidity. This information is included in the analysis using utility weights that measure the degree of impairment associated with each health state included in the model compared with full health.

6.1 Baseline quality of life by age

Baseline data on mean utility weights for people without atrial fibrillation or stroke by age were taken from a previously published analysis of data from the Health Survey for England. This analysis estimated mean EQ-5D scores for the general population, as well as for those with and without heart problems other than myocardial infarction or hypertension.[78] In the absence of comparable Irish data it is assumed that both populations are comparable. This parameter is modelled as a linear function (Figure 6.1).

Figure 6.1 Baseline utility weight estimates by age for those without atrial fibrillation or stroke



6.2 Quality of life with atrial fibrillation

The model requires an estimate of the impact on quality of life for diagnosed and undiagnosed AF patients who have not suffered a stroke. It is generally accepted that AF is associated with a reduced quality of life due to symptoms such as weakness, fatigue and palpitations, which can be managed to varying degrees with rhythm or rate control medication.[79] There is also evidence to suggest that those with undiagnosed AF experience a reduction in quality of life, despite the absence of overt symptoms, or because moderate symptoms are misattributed.[14;80]

Previous studies have estimated a utility weight of 0.81 (95% CI 0.68, 0.91) associated with diagnosed AF, which was derived using EQ-5D data from a nationally representative sample of US AF patients without a history of stroke, adjusted for age, sex and co-morbidities.[81;82] This is consistent with estimate used in the economic evaluation of the UK SAFE trial.[19] Although TILDA collected data on quality of life, the numbers of people who reported a diagnosis of AF were relatively low and quality of life was measured using the CASP-19 tool, rather than the EQ-5D, which is the tool that was used to estimate baseline utility weights for the general population in the absence of AF.

Estimating the utility loss associated with undiagnosed AF is more problematic as there is little evidence on the extent to which people in this cohort are genuinely asymptomatic, or are experiencing general symptoms such as dyspnoea or weakness, but lack a definite diagnosis. What evidence is available is derived from studies that compare diagnosed AF patients who are either asymptomatic or symptomatic.[14;68] A UK study comparing quality of life (measured using SF-36) in symptomatic and asymptomatic AF patients (mean age 58 years), and healthy controls found significantly lower scores in all domains for the symptomatic AF group, and lower scores in one domain (general health) for the asymptomatic AF group. Compared with healthy controls, the asymptomatic group had average quality of life scores that were 6% lower than healthy controls, giving a utility weight of 0.94 (95% CI 0.86, 0.98).[83] Applying this to all undiagnosed AF patients may underestimate the true utility loss, since it assumes that all undiagnosed patients are asymptomatic. However any adjustment for this risks overestimating this parameter. In the analysis the conservative estimate was used in the base case and the implications of undiagnosed AF being associated with a greater utility loss was examined in a sensitivity analysis.

Limitations regarding the use of utility data for AF include applicability issues about using US data in an Irish population and uncertainty about the level of AF symptoms in the undiagnosed cohort. There are also some recent studies that would appear to challenge the idea that AF results in poorer quality of life in non-acutely ill older patient cohorts, finding little or no reduction associated with the arrhythmia in this population.[84;85] It was also assumed that the quality of life reduction associated with undiagnosed AF does not decrease as a result of treatment after detection. This will tend to underestimate the effectiveness of screening if treatment does have a beneficial effect of the quality of life of previously undiagnosed AF patients. However in the absence of data for this group a conservative approach was adopted.

6.3 Quality of life decrease associated with treatment

There is evidence to suggest that treatment for atrial fibrillation is associated with minor reductions in quality of life, unrelated to stroke or complications, as a result of

the need for various degrees of ongoing monitoring, required changes in diet or lifestyle and the potential for adverse side effects. Warfarin, which requires regular blood tests to monitor INR levels, is associated with a greater degree of utility loss than antiplatelet or DOAC use. Estimates of the utility loss associated with each type of treatment are taken from published US survey data from patients with AF taking warfarin and aspirin, and a US physician survey of quality of life for patients on ximelagatran (Table 6.1).[86-88]

Table 6.1 Quality of life estimates for antithrombotic treatment

Treatment	Utility Weight (95% CI)
Warfarin	0.987 (0.953, 1.00)
DOAC	0.994 (0.975, 1.00)
Aspirin	0.998 (0.994, 1.00)

6.4 Quality of life after a stroke

A meta-analysis of quality of life outcomes for stroke identified 20 studies that reported outcomes for mild, moderate and severe stroke separately.[89] This found that severity of stroke and the bounds of the scale used (death or worst possible outcome to normal, excellent or perfect health) predicted quality of life weights, but the elicitation method (time trade off, standard gamble, judgement) and type of respondent (patients, communities) did not. Time trade off elicitation from community members using a scale of death to perfect health produced pooled quality-adjusted life year (QALY) weights of 0.52 for major stroke, 0.68 for moderate stroke, and 0.87 for minor stroke. The same type of respondents, using the same type of elicitation method but a scale of death to normal health produced significantly lower pooled weights of 0.28, 0.45 and 0.64 for major, moderate and minor stroke, respectively. A previous cost-effectiveness study used data from this meta-analysis to group stroke severity by functional status post stroke according to whether the person was independent (0.65), moderately dependent (0.46) or totally dependent (0.30).[81] These estimates are most closely aligned with the Framingham data on stroke severity used in the analysis, which used the modified Barthel Index to classify stroke survivors as severely dependent, moderately dependent or with mild to no dependence. The overall utility weight for haemorrhagic stroke was calculated as the average utility weight across all survivors using the same weights and functional outcomes as ischaemic stroke (average utility weight 0.57). A utility weight of zero was applied to fatal strokes.

6.5 Quality of life decrements for complications and adverse events

It is assumed that non-central nervous system (CNS) bleeding events and systemic emboli result in a temporary reduction in quality of life. They are therefore included

in the model as utility decrements that are incurred in the year that they happen. Previously published data estimated a utility decrement (calibrated to apply for one month) of 0.092 for major bleeding and 0.022 for pulmonary embolism.[90] These were applied to all major extra-cranial bleeding and systemic embolism events in the model, with a sensitivity analysis to estimate the impact of uncertainty in relation to these parameters on the overall cost-effectiveness results.

6.6 Limitations of the utility data

The main limitation in regard to utility data is the lack of published Irish data on preferences for AF and stroke-related clinical outcomes. In the absence of Irish data, international estimates from the US and the UK were used, which may differ from the utility valuation that the Irish population would assign to the various health states. There is also a high degree of heterogeneity in the published literature for utility weights associated with mild, moderate and severe stroke. The estimates used in the model were chosen based on how closely the reported health states aligned with the categorisations employed in the clinical studies included in this analysis, and are consistent with those used in cost-effectiveness analyses elsewhere.

7 Cost data

Relevant costs included in the analysis include the costs of AF case-finding and treatment, as well as costs associated with the clinical outcomes that may be impacted by AF screening. The primary analysis was carried out from the perspective of the publicly funded health and social care system. The cost-effectiveness of screening was also estimated using a societal perspective, as there are significant costs associated with informal care and lost productivity associated with stroke that are not be borne by the health service. Therefore it was necessary to distinguish between costs that fall on the health service and those covered by private health insurers or out of pocket payments. Historical and international costs were converted to 2014 Euro using the relevant purchasing power parity and inflation rate.[91]

7.1 Cost of screening

Costs of screening include the incremental cost associated with pulse palpation during routine GP consultations and the cost of ECGs carried out in primary care. There may also be additional costs generated by the screening programme for specialist referral or additional tests beyond those normally required for a diagnosis of AF, or for further testing for incidental findings. However, as these costs are not directly associated with the screening programme they are not included in the primary analysis. The impact of including the cost of blood tests and an echocardiogram for each AF case diagnosed through screening is examined in a sensitivity analysis and the number of additional specialist referrals due to a prospective Irish screening programme is estimated based on the available literature.

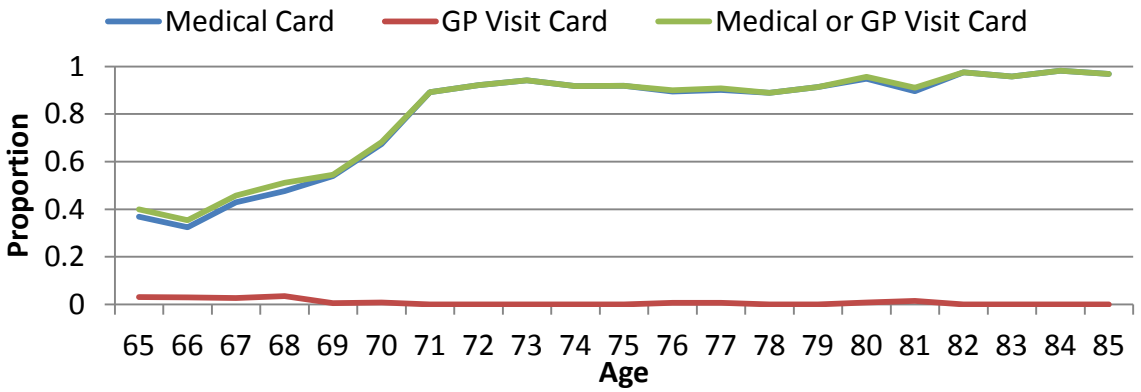
There are a number of approaches to costing opportunistic screening depending on how a prospective programme would be funded. The economic analysis carried out alongside the UK randomised controlled trial (RCT) of screening combined trial data on the average length of time it took to palpate the pulse and perform an ECG with labour costs by profession and the cost of ECG consumables to estimate average costs.[19] However, there are differences in how GP practices are funded in Ireland and the UK, which may influence how the costs of screening are calculated. In Ireland, GPs are sole traders operating on a fee-per-service basis, who set their own fees for private consultations and receive a contract price for patients who qualify for a medical card or GP visit card. An alternative approach is cost screening using a fee per service, with set costs being assigned to some or all of the services provided. This could include a separate cost for pulse palpation and ECG, or simply assigning a fee for each new case of AF detected. The incremental costs of pulse palpation alone are likely to be minimal as it is a short procedure that does not require specialised equipment. Advertised prices for a resting ECG in Ireland range from €30 to €55.[92;93] Paying a fee per new AF diagnosis would represent a departure from traditional methods of funding screening in primary care, which would have parallels

with the UK QOF system for incentivising and rewarding GP practice. This would be difficult to reliably model, given the uncertainty about how any such fee would be calculated and how the system would operate in the context of wider contractual agreements for the delivery of primary care services in Ireland.

In this analysis pulse palpation was costed based on the opportunity cost of staff time required to carry out this procedure for all patients in the screening cohort who attend a GP consultation. Staff time was calculated using the schedule of fees and allowances payable to doctors participating in the General Medical Services (GMS) scheme and other community schemes provided through the Primary Care Reimbursement Service (PCRS). The cost of an ECG for those with an irregular pulse was taken as the set fee for this test under the GMS scheme and did not include the capital costs of equipment, since it is assumed that all GP practices are equipped to perform an ECG. The rationale for this is that the majority of people in an over 65s screening cohort will have access to GP services paid for by the HSE, through either a medical card or a GP visit card, so the PCRS fees represents the best estimate of the marginal costs, as well as the opportunity cost of using that time for another purpose. However, GP care is not publicly funded for those without a medical card, apart from some tax relief on medical expenses, so a minority of people in the screening cohort will be required to pay out of pocket expenses at a higher rate to access a GP consultation. Also since screening is not part of the current GMS contract, its inclusion could put upward pressure on the existing schedule of fees and allowances. To assess the potential impact of this, a sensitivity analysis will be carried out to examine the impact of varying the cost of screening in the analysis.

Nationally representative TILDA data (n=8175) on the number of people with either a medical or GP card by age are shown in Figure 7.1.[(65)] Coverage increases sharply once people reach 70, as this is the age at which people become eligible to apply for an over 70s medical or GP visit card, subject to a means test. The total percentage of people over 65 with access to free GP services is 81%. The opportunity cost of pulse palpation was included in the cost-effectiveness analysis but not in the budget impact analysis as the cost of staff time doesn't represent an additional direct cost to the HSE.

Figure 7.1 Proportion of people over 65 with access to free GP services, by age



7.1.1 Pulse palpation and ECG

The SAFE RCT of opportunistic screening reported that the total time taken to perform pulse palpation during a GP consultation for some other reason was one minute.[19] The annual GMS capitation fee for patients over 70 years is €271.62 (as of July 2013).[94] Using TILDA data on the average number of visits per year for this group (4.83, SD 0.85) and estimated average consultation times of approximately 10 to 15 minutes, the cost per minute of a HSE funded GP consultation in an older population was calculated to be approximately €4.50 (range €2.79 to €8.82). Many GP surgeries employ practice nurses, who can also perform pulse palpation in patients in the screening cohort. The subsidy paid to GPs through the PCRS towards the cost of employing practice nurses ranges from €30,945.86 to €37,822.72.[94] Assuming a 39 hour working week and an annual leave entitlement of 24 days, this equates to a subsidy of €19.93 per hour, or €0.33 per minute (range €0.30 to €0.37).[94] The UK trial of opportunistic screening in general practice reported that 62% of patients had their pulse palpated by a GP.[19] If similar rates can be expected in Ireland than the weighted average for the cost to the health service for opportunistic pulse palpation as part of routine GP consultations in older patients would be approximately €2.88 (range €1.81 to €5.57). This is lower than the estimate obtained in the 2005 SAFE trial (€3.49 after inflation and conversion to 2014 Irish Euro).

The GMS capitation agreement provides a set fee in respect of a number of special items of service, including the performance and interpretation of ECGs. As of 2013 the fee paid to GPs for this procedure is €24.80.[94] This is also lower than that reported in the UK trial, which was based on staff time and the cost of ECG consumables (€30.67 after inflation and conversion to Euro). However, it should be noted that GMS capitation fees have been reduced a number of times since 2008 due to budget cuts as a result of the economic recession, which accounts for some of the differences between current Irish costs and those reported in the UK study. The number of patients that will require ECG was estimated using data from the SAFE trial.[19]

7.2 Cost of AF treatment

The average cost per patient for treatment was calculated as a weighted average based on the current standard of care for patients with a diagnosis of AF, estimated using TILDA data.

7.2.1 Antithrombotic medication

The percentage of AF patients receiving warfarin, DOACs and antiplatelet therapy was reported in section 5.4.1. For warfarin it is assumed that the average dose for long term maintenance of INR levels is 5mg per day. The cost of INR testing is estimated from a micro-costing study using Irish GP practice and Irish hospital data (€26 per GP INR and €56 per hospital INR), assuming a split of 50:50 for patients attending the hospital/GP setting every six weeks for well controlled INR levels.[95;96] TILDA data showed that the majority (88%) of those reporting using DOACs were prescribed dabigatran (Pradaxa®) and a 2013 review by the HSE National Medicines Management Programme found that two thirds of patients prescribed dabigatran were prescribed the lower dose of 110mg/day.[43] This does not affect the cost calculation as both dosages cost the same. The cost of dabigatran is comparable to that of rivaroxaban (Xarelto®) and apixaban (Eliquis®). Of those on antiplatelet treatment, the majority (74%) were receiving aspirin monotherapy. Aspirin dosages in atrial fibrillation range from 75mg/day to 325/mg day. In this cost calculation an average daily dose of 75mg of nu-seals aspirin was assumed. Drug costs were obtained from the PCRS database.[97] Annual medication costs for each type of treatment based on these figures are shown in Table 7.1. Drug costs to the HSE were calculated per guidance provided by the National Centre for Pharmacoeconomics. A prescription fee of €2.50 per item, is only included in the analysis from the societal perspective.[98] It was assumed that all GMS prescriptions are dispensed once a month.

Table 7.1 Antithrombotic medication costs (€)

	Warfarin	DOACs	Aspirin
Wholesale Price	24.26	856.29	45.38
Pharmacy Price	26.20	924.79	49.01
Dispensing fee	60.00	60.00	60.00
Wholesaler rebate	-0.97	-34.25	-1.82
Total price	85.23	950.54	107.19
INR Testing	355.33	0	0
Total annual cost	440.56	951.54	107.19

7.2.2 Rhythm and rate control medication

TILDA data on medications being taken by those who reported that they had a diagnosis of AF revealed that approximately 79% were receiving rate control treatment and 12% were receiving rhythm control treatment, with 9% reporting that

they were receiving neither. That a higher proportion of patients are receiving rate control is consistent with published literature, but the degree of imbalance was greater than that reported elsewhere.[99] The drug most commonly prescribed for rate control was bisoprolol, and the most commonly prescribed rhythm control drug was amiodarone. It is assumed that the maintenance dose of amiodarone in AF is 200mg daily and of bisoprolol is 5mg daily. The total annual cost for rhythm and rate control drugs is shown in Table 7.2.

Table 7.2 Rhythm and rate control drug costs (€)

	Rate control	Rhythm control
Wholesale Price	23.66	99.82
Pharmacy Price	25.55	107.81
Dispensing fee	60.00	60.00
Wholesaler rebate	-0.95	-3.99
Total annual cost	84.60	163.82

Drug costs were obtained from the PCRS database, using prices for the most commonly reported brand prescribed for rate and rhythm control (Cardicor® and Cordarone X®, respectively). The average cost per patient was calculated as a weighted sum based on the proportion receiving each type of treatment. The cost of on-going blood and ECG testing associated with rhythm control is not included in the primary analysis. Sensitivity analysis was used to examine the potential effect of increasing the annual cost of rhythm control therapy to take account of testing.

7.3 Cost of stroke and adverse events

The major direct costs associated with stroke include acute hospital care, rehabilitation and long term care. Indirect costs include informal care-giving and productivity losses due to mortality and morbidity. It was also necessary to estimate the cost associated with systemic embolism and adverse events, specifically major bleeding events.

7.3.1 Cost of in-patient treatment for stroke

The latest available data on inpatient costs for stroke in acute hospital in Ireland comes from the 2013 Casemix Ready Reckoner, which is based on HIPE data from 2011. This provides estimates of the cost of treatment for four different categories of stroke, based on the clinical complexity of the treatment received and the number of patients in each category (see Table 7.3). The weighted mean estimate of the cost of inpatient hospital care per patient treated based on this data is €8,939. This is consistent with the results of the Cost of Stroke in Ireland study, which estimated the cost of acute hospital care for stroke as €9,153 per patient, based on Casemix data from 2007.[9]

Table 7.3 Casemix costs for stroke in Ireland in 2011

ADRG code	Description	Number of patients	Cost per patient
B70A	Stroke and other cerebrovascular disorders with catastrophic complication or comorbidity	949	€2,3643
B70B	Stroke and other cerebrovascular disorders with severe complication or comorbidity	1513	€9,973
B70C	Stroke and other cerebrovascular disorders without either catastrophic or severe complication or comorbidity	2644	€4,883
B70D	Stroke and other cerebrovascular disorders with either death of transfer within 5 days	630	€1,325

This analysis requires estimates of the cost of acute hospital care by severity of stroke. Two Asian studies examined the impact of acute stroke severity (NIHSS) on inpatient hospital costs, comparing costs for those with mild, moderate and severe stokes to the overall average cost.[100;101] While differences in the structure of health systems limit the transferability of cost data between countries, it was assumed that the relative impact of stroke severity on inpatient stroke costs should be consistent across different settings. Table 7.4 shows the results of combining data from these two studies on relative costs for mild, moderate and severe strokes compared with the overall average cost and applying it to inpatient stroke costs in Ireland. The average cost is applied to all fatal ischaemic stroke and all fatal and non-fatal haemorrhagic strokes. Based on the Cost of Stroke in Ireland study, it was assumed that 87% of acute hospital costs for stroke are borne by the public health system, 12% by private health insurers and 1% by out of pocket payments by patients.

Table 7.4 Inpatient treatment costs by severity of stroke

Severity	Ratio	Irish costs
All	1	€8,939
Mild	0.80	€7,164
Moderate	1.09	€9,736
Severe	1.67	€14,894

7.3.2 Cost of in-patient and community rehabilitation care

The Cost of Stroke in Ireland study examined annual costs of inpatient rehabilitation for incident strokes in 2007, reporting an average cost per individual patient of €2,090 (range €1,407 to €3,056).[9] When this is inflated to the present day using the latest available data from the consumer price index (CPI) for health commodities (2014), the current value is €2,412 (range €1,623 to €4,244).[102] It was assumed that the current standard of care for stroke rehabilitation is comparable to that in place in 2007. There is a lack of information on the cost of hospital rehabilitation by severity of stroke. However, there is data to suggest that in-hospital rehabilitation costs are directly correlated with stroke severity.[103] Therefore the analysis assumes

that the average is a weighted mean of the costs associated with mild, moderate and severe strokes, where there is a direct, linear correlation between costs and the severity of functional deficits on the Barthel scale. Using Irish National Audit of Stroke Care estimates on the percentage of mild, moderate and severe strokes included in the average figure, the cost of inpatient rehabilitation by stroke severity was estimated (Table 7.5).[41] Per the Cost of Stroke in Ireland study, it was assumed that 95% of acute hospital rehabilitation costs are borne by the public health system, 4% by private health insurers and 1% by out of pocket payments by patients.

The cost of community rehabilitation includes those associated with public health nursing, speech and language therapy, dietetics, physiotherapy and occupational therapy. The average cost per patient in the Cost of Stroke in Ireland study, inflated to 2014, is estimated at €904 (range €889 to €920). Using the same assumption as before (rehabilitation costs are directly correlated with severity of stroke), the cost of mild, moderate and severe stroke was estimated separately (Table 7.5). It is assumed that all costs associated with community rehabilitation apply in the first year only and are covered by public funding.

Table 7.5 Inpatient and community rehabilitation costs by stroke severity

Stroke severity	Cost of inpatient rehabilitation (range)	Cost of community rehabilitation (range)
Mild	€1,117 (751 to 1,965)	€419 (411 to 426)
Moderate	€2,233 (1,503 to 3,929)	€837 (823 to 852)
Severe	€3,350 (2,254 to 5,894)	€1,256 (1,235 to 1,278)

7.3.3 Cost of in-patient treatment for systemic embolism and GI bleeds

There is a lack of data on the cost of acute hospital treatment for systemic embolism and gastrointestinal bleeding in AF patients in Ireland. The best available estimates come from a technology appraisal carried out by the National Institute for Clinical Excellence in 2012 examining the use of DOACs in a UK setting.[104;105] This estimated a cost of £2,603 (range £2,082 to £3,124) for non-fatal systemic embolism and £1,749 (range £1,399 to £2,099) for non-fatal GI bleeding. When these are converted to 2014 Irish Euro the equivalent costs are €3,698 (€2,956 to €4,436) and €2,483 (€1,988 to €2,982), respectively. It was assumed that the breakdown of costs between the public health system, private health insurers and out of pocket payments is the same as that for acute stroke care (87%, 12% and 1%, respectively).

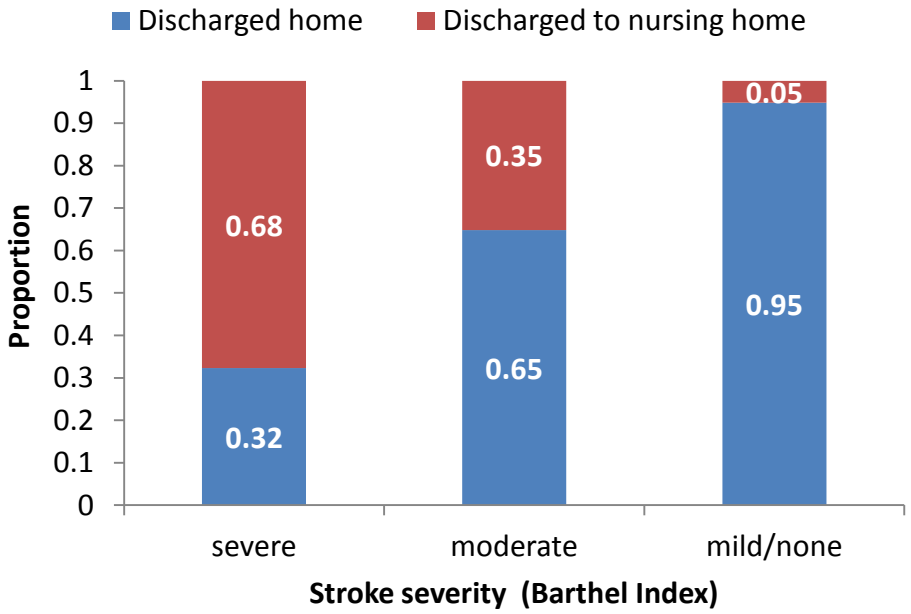
7.3.4 Annual cost of care by severity of stroke

Direct long term care costs associated with stroke include nursing home care, ambulatory care, community rehabilitation, assistive technology and medications.

Indirect costs include productivity losses as a result of morbidity and mortality, as well as the opportunity cost of informal care.[9]

Data on the proportion of stroke survivors with mild, moderate and severe functional deficits who are discharged home or to residential care were obtained from the INASC study (Figure 7.2).[41] These estimates were calculated based on the total number of patients discharged to either of these destinations, excluding discharges coded as 'unknown' or 'other'. Costs associated with discharges to another hospital for inpatient rehabilitation are included separately.

Figure 7.2 Discharge destination by stroke severity



The average cost per week for public and private institutions was calculated based on 2015 data from the HSE, which show that the average cost of care in public nursing homes is higher due to the increased proportion of patients with severe dependency in these (60%) compared with private institutions (35%).[106] The annual cost of nursing home care by stroke severity is calculated as a weighted sum reflecting the fact that there are approximately twice as many patients with severe stroke included in the calculation of the average cost of public nursing homes, compared with private nursing homes. The cost of care for patients with moderate and mild stroke is assumed to be the same (Table 7.6).

Table 7.6 Nursing home costs by severity of stroke

Nursing home	Weekly cost (95% CI)	Annual cost (95% CI) €
Private	€899 (614 to 1,185)	€46,760 (31,928 to 61,620)
Public	€1,245 (623 to 1,863)	€64,759 (32,396 to 96,876)

Weighted cost of severe stoke	€58,623 (32,237 to 84,889)
Weighted cost of moderate and mild stroke	€52,865 (32,087 to 73,607)

Previously published Irish data estimated that 73% of stroke-related nursing home costs in 2007 were funded from public resources.[9] However this was before the introduction of the Fair Deal Scheme in 2009, which changed the funding model to one where patients contribute 80% of their assessable income and 7.5% of the value of any assets per annum, with the state paying the remainder. A person's principal residence is only included in the financial assessment for the first three years of care, and this payment can be deferred and collected from the person's estate if they wish. The latest available data from the HSE reported that in 2013 the level of patient contribution to nursing home care amounted to 6.4% of the total cost, with a marked difference in the percentage of costs paid for by the state between private (99%) and public nursing homes (84%).[107] However, these figures do not include deferred payments so they are likely to be an underestimate of the true proportion of costs borne by patients. Uncertainty surrounding this estimate does not affect the economic analysis conducted using a societal perspective. For the analysis from the payer perspective, it was assumed that the HSE pays approximately 84% of the cost of nursing home care, based on 2013 data from public nursing homes only. This was varied in a sensitivity analysis.

Ambulatory care costs associated with outpatient visits and GP care were estimated from the Cost of Stroke in Ireland study (inflated to 2014) and applied to all stroke survivors (€726, range €637 to €815). GP care is a major component of this cost and the reported breakdown of public and out of pockets costs are 73% and 27%, respectively, for the overall stroke population. However, since the analysis models an older cohort, the proportion of people with a medical or GP card is likely to be higher. It was previously estimated that 81% of those over 65 years had a medical or GP card, so in the primary analysis of screening for over 65s it was assumed that 81% of the cost of ambulatory care is borne by the public health system. Total medication costs (including dispensing fees and rebates, but not prescription fees) associated with acute treatment are also taken from the Cost of Stroke in Ireland study, inflated to 2014 and applied to all stroke survivors (€1,849, range €1,649 to €2,049). As with ambulatory care, it was assumed that the 81% of these costs will be paid for by the health service through the GMS for medical card holders.

For stroke patients who are discharged home there may be costs associated with the provision of assistive technology and home modifications to allow them to live as independently as possible. The estimated total costs for aids, appliances and home modifications in 2007 was between €8 and €10 million.[9] National stroke audit data from that year estimated that 56% of all patients were discharged home after a stroke.[41] Combining the available data on stroke incidence, discharge destination

and costs (inflated to 2014) the average cost for assistive technology and home modification for patients discharged home was estimated to be €2,113 (range €1,761 to €2,642). Assuming that costs for those discharged home are directly correlated with stroke severity (per the Barthel scale) allowed estimation of the average cost per patient discharged home with mild, moderate and severe functional deficits, as well as the total average costs by stroke severity (Table 7.7).

Table 7.7 Assistive technology and home modification costs, by stroke severity

Stroke severity	Average cost for patient discharged home	Overall average cost per patient
Mild	€1,504 (1,254 - 1,881)	€1,429 (1,191 - 1,787)
Moderate	€3,610 (3,009 - 4,514)	€2,346 (1,956 - 2,934)
Severe	€5,114 (4,262 - 6,394)	€1,636 (1,364 - 2,046)

The Cost of Stroke in Ireland study concluded that there was insufficient data available to estimate the proportion of these costs that were funded through the public health service. For the purposes of this analysis, it was assumed that 37% of costs are paid for by the HSE on the basis that items that are provided through the HSE aids and appliances funding account for 46% of the total cost and approximately 81% of patients have a medical card, which allows the holder to receive a prescribed aids and appliances free of charge.[108] The cost of aids and appliances were applied as a once-off charge in year one.

As well as direct costs for treatment, stroke is also associated with indirect productivity losses for those voluntarily providing informal care to stroke patients. The cost of informal care was previously estimated in Ireland using the human capital approach, which calculated the economic value of the time spent by caregivers using 2007 data on labour costs for those in employment and the value of leisure time (taken as one third the median hourly wage) for the unemployed.[9] Using international estimates of between nine and 20 hours of care being provided per week by informal caregivers, along with Irish data on average employment rates in under 65s and labour costs (€21.76 per hour), the average annual cost of informal care per stroke patient is estimated to be €10,938 (range €6,789 to €15,087).[9;109-114] In the analysis it was assumed that informal care is provided to all patients who are discharged home with moderate or severe dependency. The cost of informal care is only included in the analysis undertaken using a societal perspective.

The parameter estimates described above are used to estimate the total annual costs associated with haemorrhagic stroke and mild, moderate and severe ischaemic stroke from both a payer and societal perspective (Tables 7.8 to 7.11).

Table 7.8 Long term average annual cost of care after mild stroke

Description	Payer perspective	Societal perspective
Nursing home	€2220 (1348, 3092)	€2643 (1604, 3680)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€529 (441, 661)	€1429 (1191, 1787)
Informal care	€0	€0
Total recurring annual cost	€4306 (3200, 5412)	€5216 (4090, 6544)

* cost applied as a once-off payment in year 1

Table 7.9 Long term average annual cost of care after moderate stroke

Description	Payer perspective	Societal perspective
Nursing home	€15542 (9434, 21641)	€18503 (11230, 25762)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€868 (724, 1086)	€2346 (1956, 2934)
Informal care	€0	€7394 (4590, 10199)
Total recurring annual cost	€17628 (11286, 23961)	€28472 (18106, 38825)

* cost applied as a once-off payment in year 1

Table 7.10 Long term average annual cost of care after severe stroke

Description	Payer perspective	Societal perspective
Nursing home	€33485 (18414, 48489)	€39864 (21921, 57725)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€605 (505, 757)	€1636 (1364, 2046)
Informal care	€0	€3640 (2250, 5021)
Total recurring annual cost	€35571 (20266, 50809)	€46079 (26457, 65610)

* cost applied as a once-off payment in year 1

Table 7.11 Long term average annual cost of care after haemorrhagic stroke

Description	Payer perspective	Societal perspective
Nursing home	€11005 (5633, 16376)	€13101 (6706, 19495)
Ambulatory care	€588 (516, 660)	€726 (637, 815)
Medication	€1498 (1336, 1660)	€1849 (1649, 2049)
Aids and appliances*	€580 (483, 725)	€1567 (1306, 1960)
Informal care	€0	€5063 (3143, 6984)
Total recurring annual cost	€13091 (7485, 18696)	€20739 (12135, 29343)

* cost applied as a once-off payment in year one

7.3.5 Productivity costs

Productivity losses associated with stroke morbidity and mortality represent an important cost from a societal perspective. Both national and international studies have produced consistent estimates of the proportion of employed people who have to give up working as a result of stroke (45% to 65%).[9;41;115-118] However, while there is evidence to show that functional ability is one of the main predictors of whether or not someone will return to work, there are conflicting estimates on the precise proportion of patients who will return to work after mild, moderate or severe stroke.[119-121] In this analysis the simplifying assumption was made that no patients left with severe functional deficits or discharged to a nursing home return to work. For those with mild or moderate deficits the results of a previously published study, which found that 37% of patients with mild or moderate deficits who were employed prior to first-ever stroke fail to return to employment afterwards, were applied.[115] Lost productivity was calculated using the human capital approach using Irish data from 2010 to 2014 on employment rates and average earnings by year of age within the modelled cohort (inflated to 2014, see Figures 7.3 and 7.4).[122;123] Total productivity loss by age at death to 85 years is calculated using discounting to incorporate the time value of future earnings into the overall sum, which is itself discounted to reflect the year in which the productivity loss is incurred. Cumulative productivity losses by age at death or disability are shown in Figure 7.5.

Figure 7.3 Employment rate by age

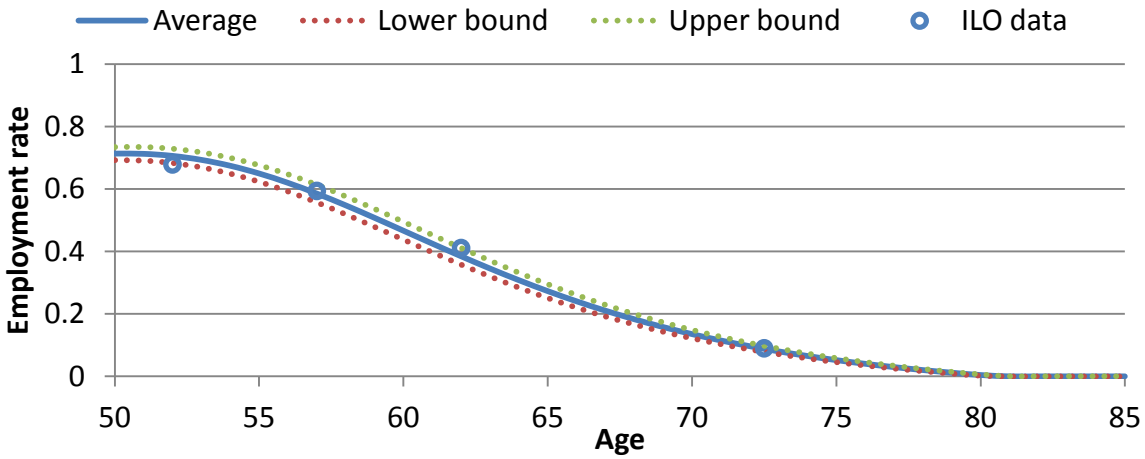


Figure 7.4 Average annual earnings by age

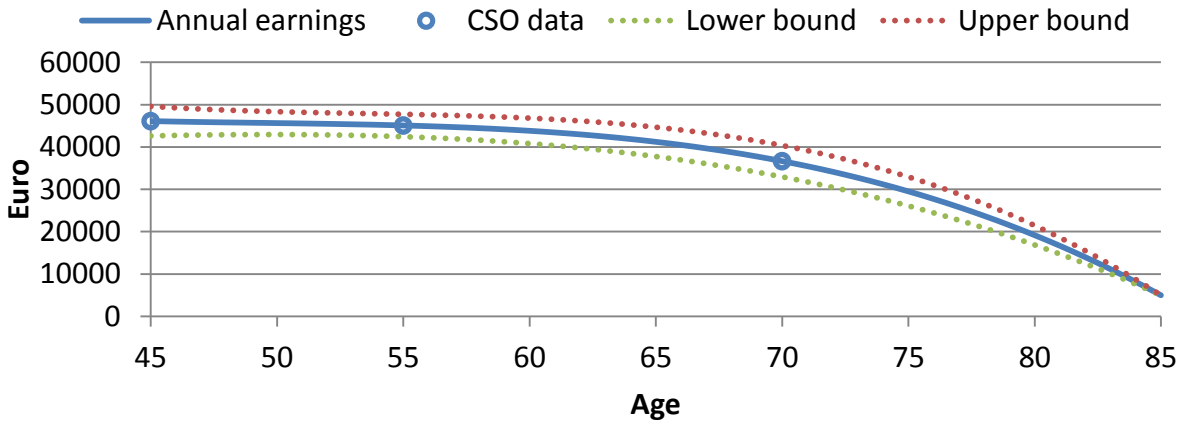
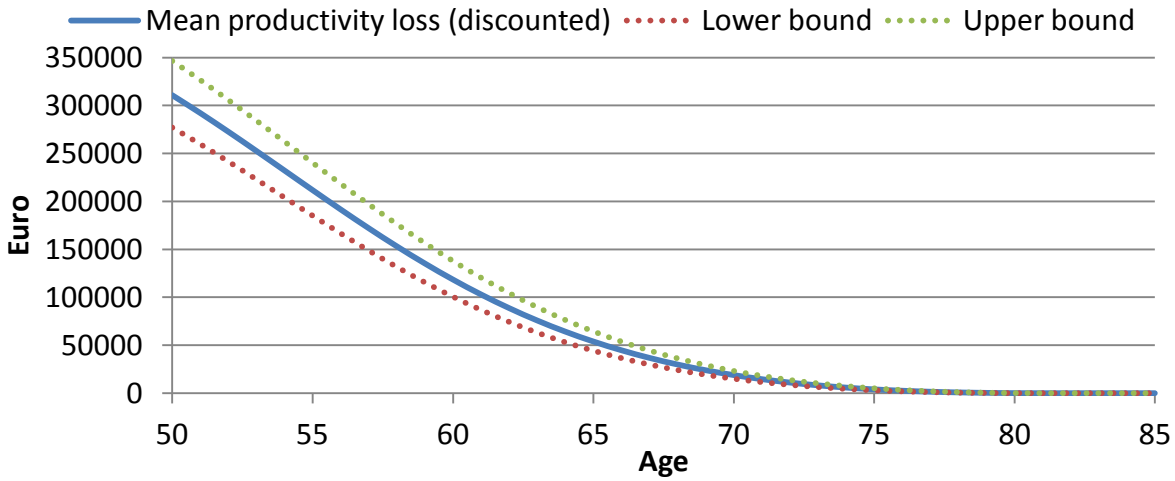


Figure 7.5 Total discounted productivity loss by age



7.4 Limitations of the cost data

There are a number of limitations associated with the estimation of the costs of screening for AF and treating stroke. Opportunistic screening, where a two stage test is designed to be carried out as part of a GP consultation when the patient is attending for some other issue, is more challenging to cost compared with traditional invitational programmes that offer screening at a dedicated centre. It was decided to cost the time needed to perform pulse palpation and to use a set fee for an ECG performed in primary care. It is possible that any future GP contract might regard screening as part of routine care that does not attract a fee. However, even if this were the case there would still be an opportunity cost associated with screening, which would be the value of the alternative use of that time during a consultation. Therefore the estimates outlined above are appropriate for the evaluation of the AF screening programme currently being considered.

Potential limitations in regard to the cost of stroke treatment include the fact that the most recent Casemix data on inpatient treatment costs is derived from 2011. However CSO data on inflation within the health sector between 2011 and 2014 was low (2.8%), so the impact of this should be minimal. Casemix provides the overall average costs for patients treated (weighted by the presence or absence of complications) rather than by severity of stroke. To estimate individual costs for those with mild, moderate or severe stroke it was assumed that treatment costs are directly correlated with acute severity. While the limited available evidence on this issue supports this assumption, there is uncertainty about the relative cost differences.

There was a lack of Irish data on the hospital costs for systemic embolism and GI bleeds, so these costs were estimated using UK data (converted to 2014 Irish Euro). While there are caveats associated with using international data, given the similarities between Ireland and the UK in how hospitals are funded and access to treatment, this was considered to be the best available option for capturing these costs.

The analysis uses average costs for long term care for mild, moderate and severe stroke, which combines data on those for whom AF was or was not a contributing factor. This captures the cost implications of screening if the higher cost associated with AF stroke are assumed to be as a result of increased AF stroke severity, which increases the likelihood of death and significant long term functional impairment. While it is generally accepted that the reason AF strokes cost more to treat is because they are more severe, a recent Irish study found that AF was associated with substantially greater two-year costs in those with mild-moderate stroke (no difference was observed in severe stroke).[124;125] The authors' did not discuss the reasons for this cost difference within the mild/moderate severity category, and

acknowledge that confounding and lack of power may partially explain some of the findings. The analysis models mild and moderate stroke costs separately. The work carried out as part of the Irish National Audit of Stroke Care and the Cost of Stroke in Ireland study, both of which were based on data from 2007, are used to inform this analysis. All costs reported in these studies were inflated to 2014 and it was assumed that the overall findings in relation to stroke care are applicable to present day.

Estimates of the cost of informal care are associated with a high degree of uncertainty and are based on evidence showing an average of between nine and 20 caregiver hours being provided per week. In the absence of data on the difference in the mean number of hours provided for those with moderate and severe disability, the overall average was applied to both, rather than assuming that the level of informal care provided is directly correlated with the degree of dependency. Given the number of hours per week involved, it is likely that informal care compliments, rather than replaces, other support services. Uncertainty about the relationship between the mix of formal and informal care prevented any assumptions about relative costs of informal care in moderate and severe stroke.

8 Economic analysis

An economic evaluation was conducted using a decision analysis model to compare the costs and benefits of a prospective national AF screening programme in Ireland with the current standard of care, in order to inform decision making regarding the introduction of AF screening in Ireland.

8.1 Methods

8.1.1 Type of economic evaluation

A cost-utility analysis was carried out where costs are measured in Euro and utility is measured in quality-adjusted life years (QALYs).

8.1.2 Target population and setting

The target population in the primary analysis was men and women aged 65 or over in Ireland. The setting was the Irish health system, where screening was carried out within GP-led primary care services. Stroke treatment was set in the acute public hospital sector and long term care was set in both public and private residential nursing homes and in the community, depending on where patients are discharged following a stroke.

8.1.3 Technology and comparators

The technology being assessed was annual opportunistic AF screening of all men and women aged 65 or over by pulse palpation followed by ECG if an irregular pulse is detected. ECGs were performed in primary care and read by a GP with the aid of computerised interpretation algorithms. Screening takes place in GP practices when a patient attends for an appointment for any reason. The primary comparator is routine care, where testing for AF is generally only done when patients present with signs or symptoms indicative of the arrhythmia. The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and was consistent with the best available evidence on the effectiveness of screening.

8.1.4 Perspective, time horizon and discounting

The primary analysis was carried out from the perspective of the publicly funded health and social care system in Ireland. A secondary analysis was conducted using a societal perspective that included costs that fall on patients and private health insurers, as well as indirect costs associated with informal care and lost productivity. The time horizon over which the costs and benefits of screening was calculated was 25 years and both costs and benefits were discounted at 5%.

8.1.5 Model structure

A Markov model was used to simulate costs and clinical outcomes in a hypothetical cohort of men and women with and without screening over the course of 25 years, using a cycle length of one year. The model estimated the number of people with diagnosed and undiagnosed AF in each group, as well as the incidence and severity of AF-related stroke in treated and untreated individuals. The first year of survival post-stroke was included as a separate state due to the significantly higher mortality rate in that compared with subsequent years. A diagram of the structure of the model is shown in Figure 8.1

8.1.6 Sensitivity and scenario analysis

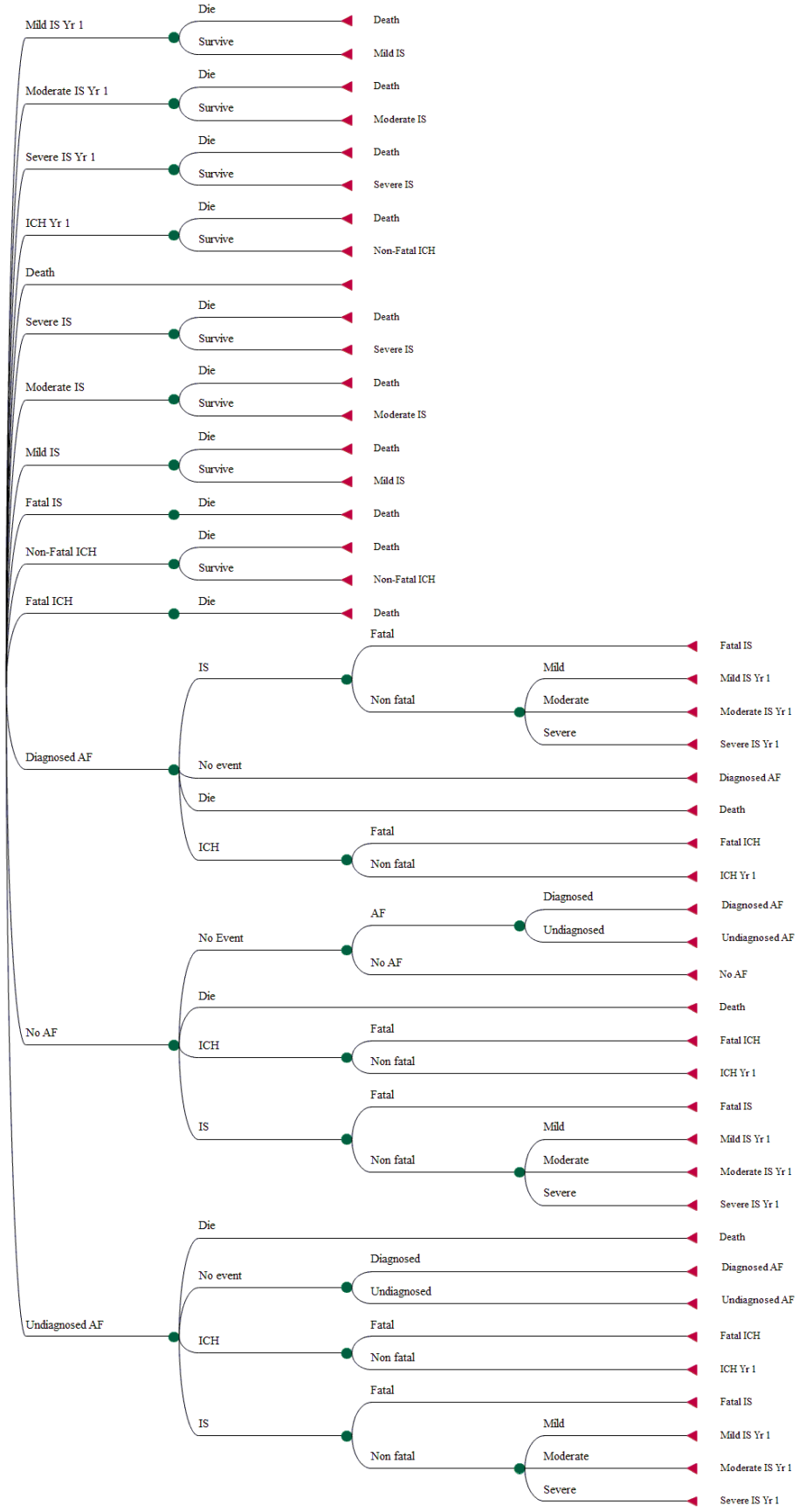
Stochastic analysis methods were used to capture the uncertainty and variability associated with the input parameters, which were varied within plausible ranges derived from published evidence and expert opinion. All estimates of the incremental costs and benefits of screening were calculated using Monte Carlo simulation, using 10,000 iterations. Each iteration sampled parameter values from their defined distribution, providing the mean estimate of the incremental costs and benefits, along with the level of uncertainty associated with this estimate.

Deterministic univariate sensitivity analysis was performed to estimate the effect of uncertainty regarding individual parameter estimates. In this analysis, the model is run with each parameter in turn fixed at its upper and lower bounds while all other parameters are held at their average value. Scenario analysis was carried out to examine the potential impact of changes to some of the key parameters associated with screening. These are described in the section outlining how each parameter was estimated.

8.1.7 Budget impact analysis

A budget impact analysis was performed from the perspective of the public health system only, which reports the incremental costs associated with screening over a five-year time horizon. Given the level of uncertainty surrounding estimates of future healthcare costs and budget allocations, the applicability of any analysis beyond this time period is limited. Indirect costs are excluded from this analysis and VAT (value added tax) is applied where relevant. No discounting is applied. The results of the BIA show the total incremental cost associated with the intervention, including treatment costs for stroke. It does not take into consideration any additional clinical benefit produced as a result of screening.

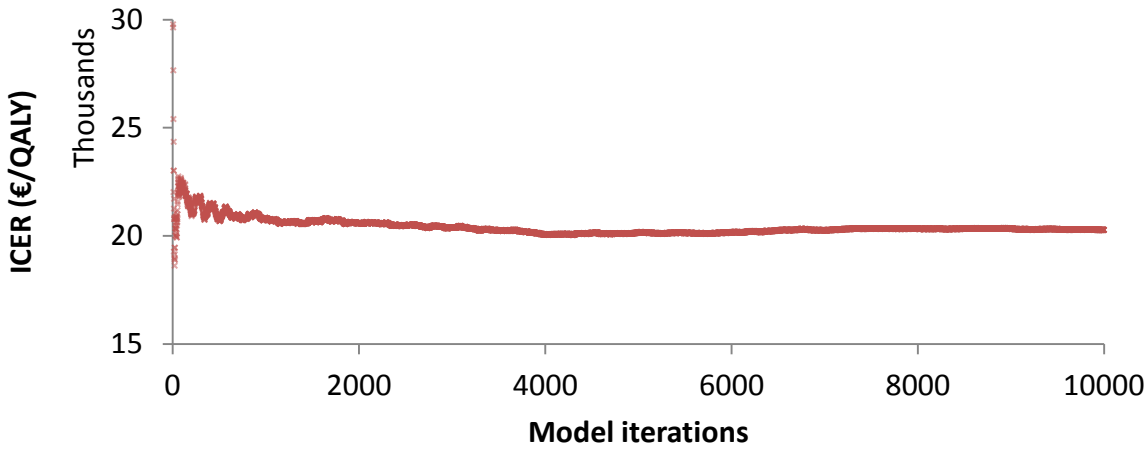
Figure 8.1 Model structure



8.2 Cost-effectiveness results

Convergence in the estimated cost-effectiveness of screening in the probabilistic model was achieved after approximately 4,000 iterations (Figure 8.2). All results presented here are based on the full 10,000 simulations comparing a strategy of opportunistic screening in primary care with no screening (routine practice).

Figure 8.2 Convergence of ICER estimates in model



8.2.1 Payer perspective results

Table 8.1 provides a summary of the absolute effects of screening and routine care, including the average undiscounted number of AF cases diagnosed, strokes avoided and life years gained if screening was implemented within the current cohort of 65 year olds in Ireland (n=42,330). The model outputs indicate that one additional case of AF is diagnosed for every 22 people opportunistically screened for 25 years from the age of 65, and one stroke is avoided for every 270 people screened over the same period.

Table 8.1 Absolute outcomes for screening and routine care based on the current Irish population of men and women aged 65 years (N=42,330)

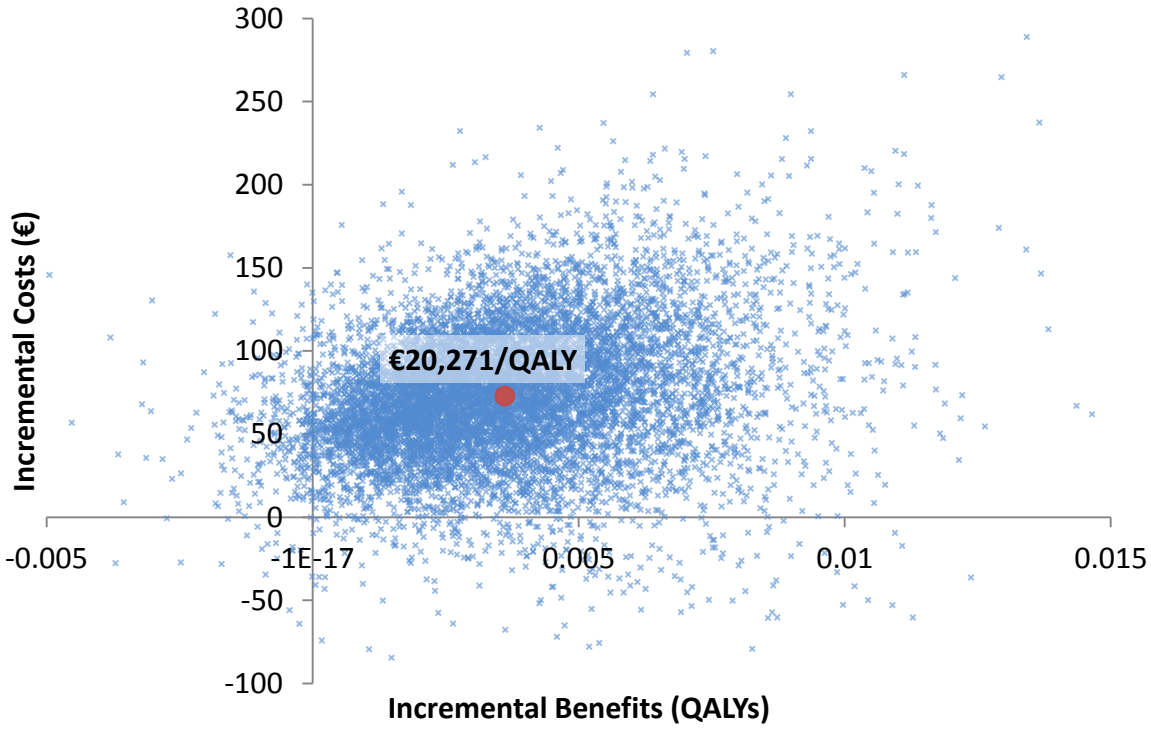
Outcome	Cases	Routine care	Screening	ICER (undiscounted)
AF cases detected	Total	5756	7700	€1,697 per additional AF case detected
	Incremental		1944	
Ischaemic strokes	Total	4293	4108	€54,203 per stroke avoided
	Incremental		-185	
Haemorrhagic strokes	Total	1285	1313	
	Incremental		28	

The incremental cost-effectiveness ratio (ICER) for AF screening in over 65s compared with routine care from the perspective of the HSE is €20,271/QALY (Table 8.2). The cost-effectiveness plane is shown in Figure 8.2.

Table 8.2 ICER calculation (payer perspective)

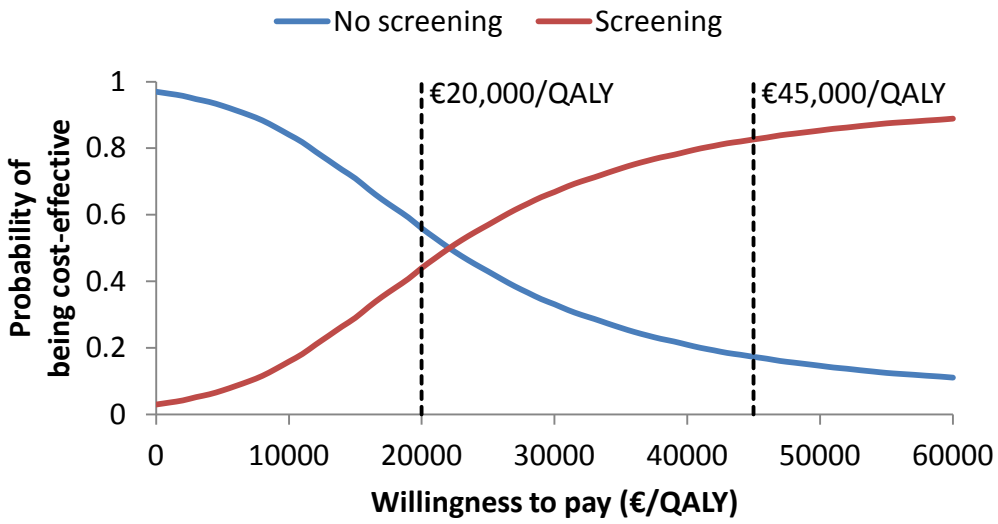
Strategy	Cost (€)	Incremental Cost (€)	Effect (QALYs)	Incremental Effect (QALYs)	ICER
No screening	3,854	-	7.8127	-	€20,271/QALY
Screening	3,927	73	7.8164	0.0036	

Figure 8.2 Cost-effectiveness plane (payer perspective)



The cost-effectiveness acceptability curve (CEAC) showing the probability of screening being the optimal strategy for a range of willingness-to-pay (WTP) thresholds is shown in Figure 8.3. Screening has a 44% probability of being cost-effective at a WTP threshold of €20,000/QALY and an 83% probability of being cost-effective at a WTP threshold of €45,000/QALY.

Figure 8.3 Cost-effectiveness acceptability curve (CEAC, payer perspective)



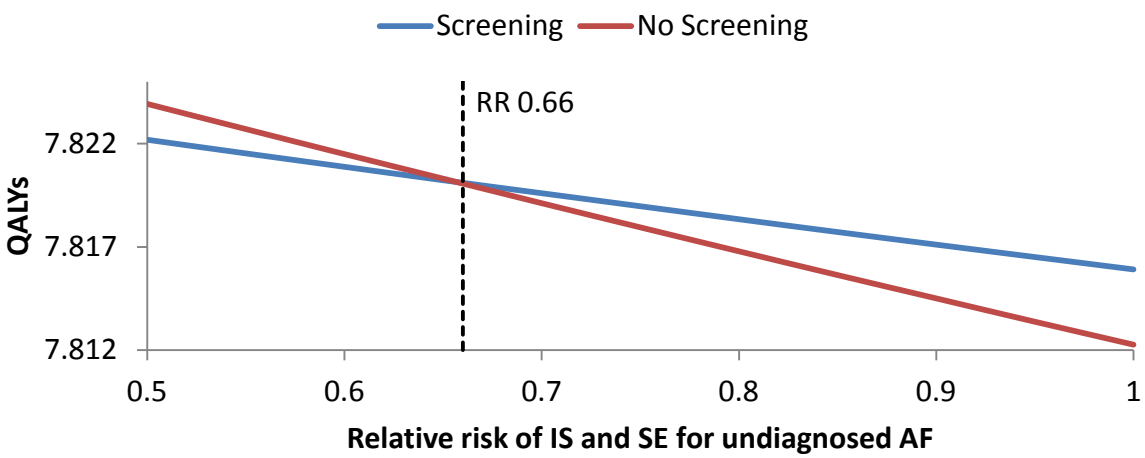
8.2.2 Sensitivity and scenario analysis

Given the uncertainty surrounding some of the key parameters in the model, extensive sensitivity and scenario analysis was carried out to examine what the impact of changes to these parameters would be on the overall cost-effectiveness results.

8.2.2.1 Stroke risk profile of asymptomatic AF patients

Uncertainty surrounding the benefits of early detection in asymptomatic AF patients was one of the main reasons why the UK National Screening Committee recommended that AF screening should not be offered by the NHS. While the $CHA_2DS_2VAS_c$ tool for calculating the risk of stroke in atrial fibrillation does not distinguish between asymptomatic and symptomatic individuals, some studies in asymptomatic device-detected AF have suggested that the risk of stroke in asymptomatic AF may be 33% to 50% less than in symptomatic individuals (see Section 3.2). A sensitivity analysis was conducted to examine the effect of screening if the risk of stroke and systemic embolism in the additional people that would be detected by screening was less than in those detected through routine care (Figure 8.4).

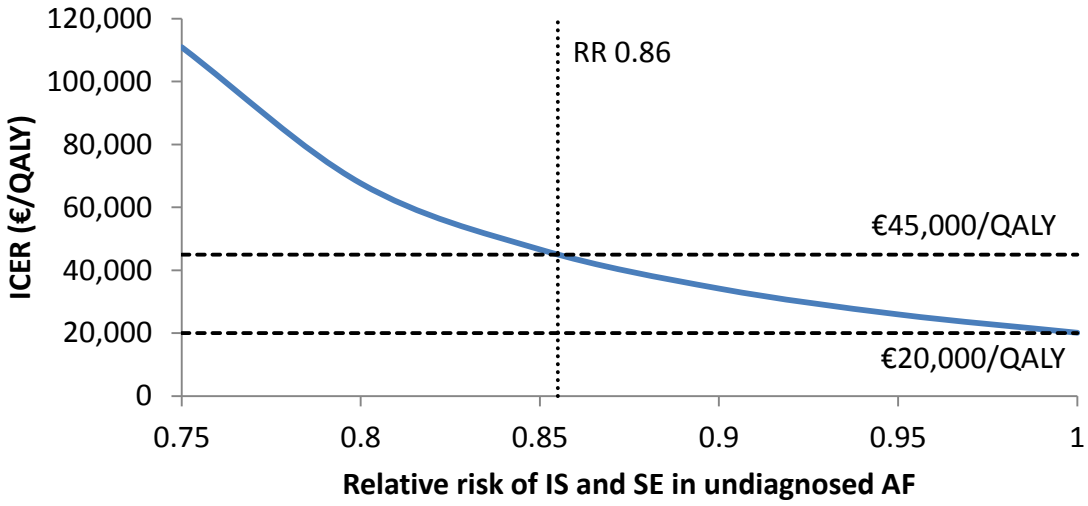
Figure 8.4 Impact of reduced risk of stroke in asymptomatic AF on effectiveness of screening and routine care



IS – Ischaemic Stroke, SE – Systemic Embolism, AF – Atrial Fibrillation, RR – Relative Risk, QALY – Quality Adjusted Life Year

This suggests that if the relative risk of stroke and systematic embolism in screen-detected patients is more than a third lower (RR<0.66) than that of AF patients identified through routine practice then the harms of screening outweigh the benefits. The impact on cost-effectiveness is shown in Figure 8.5, which shows that if the relative risk of stroke and systemic embolism is more than 14% lower in screen-detected patients compared with symptomatic patients, then screening would be considered not cost-effective using a willingness-to-pay threshold of €45,000/QALY.

Figure 8.5 Impact of reduced risk of stroke in asymptomatic AF on cost-effectiveness of screening



IS – Ischaemic Stroke, SE – Systemic Embolism, AF – Atrial Fibrillation, RR – Relative Risk, QALY – Quality Adjusted Life Year, ICER – Incremental Cost Effectiveness Ratio

8.2.2.2 Start ages for screening

The screening cohort in the primary analysis was men and women over 65 years. Table 8.3 shows the expected impact of varying the start age of screening between 50 and 70 years. The time horizon over which all programmes were evaluated was from the start of screening to age 90 years.

Table 8.3 ICERs for screening versus routine care at start ages between 50 and 70 years

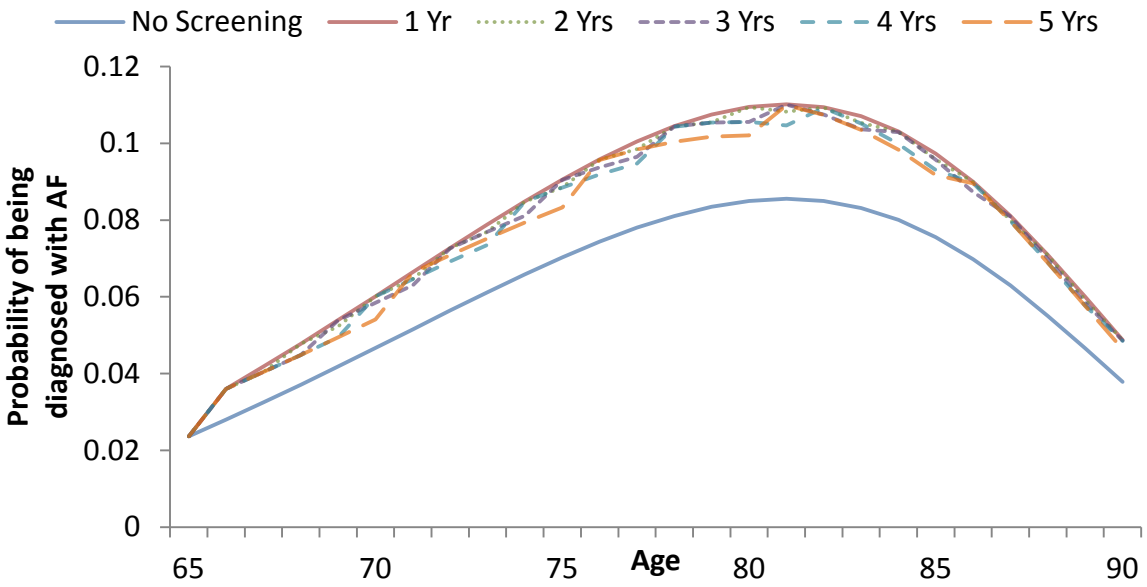
Start Age	ICER compared to routine care
50 Years	€50,578/QALY
55 Years	€38,004/QALY
60 Years	€28,134/QALY
65 Years	€20,271/QALY
70 Years	€14,594/QALY

Sensitivity analysis comparing each start age to a comparator of routine care (as opposed to each other) found that reducing the start age of screening would tend to decrease the cost effectiveness of a prospective screening programme. This was expected given the sharp increase in the incidence of AF with advancing age. Increasing the start age is likely to improve the cost-effectiveness of the programme further. However, caution needs to be exercised when interpreting these results, as the impact of opportunistic screening on AF detection has only been studied in a population of aged 65 years and over. Therefore any extension of the age range of screening requires an assumption that the clinical effectiveness estimates apply equally across all ages, which may not be the case. In addition, the ICER compared to routine care at different starting ages does not provide information on the relative cost-effectiveness of one screening strategy compared to the next best alternative.

8.2.2.3 Screening intervals

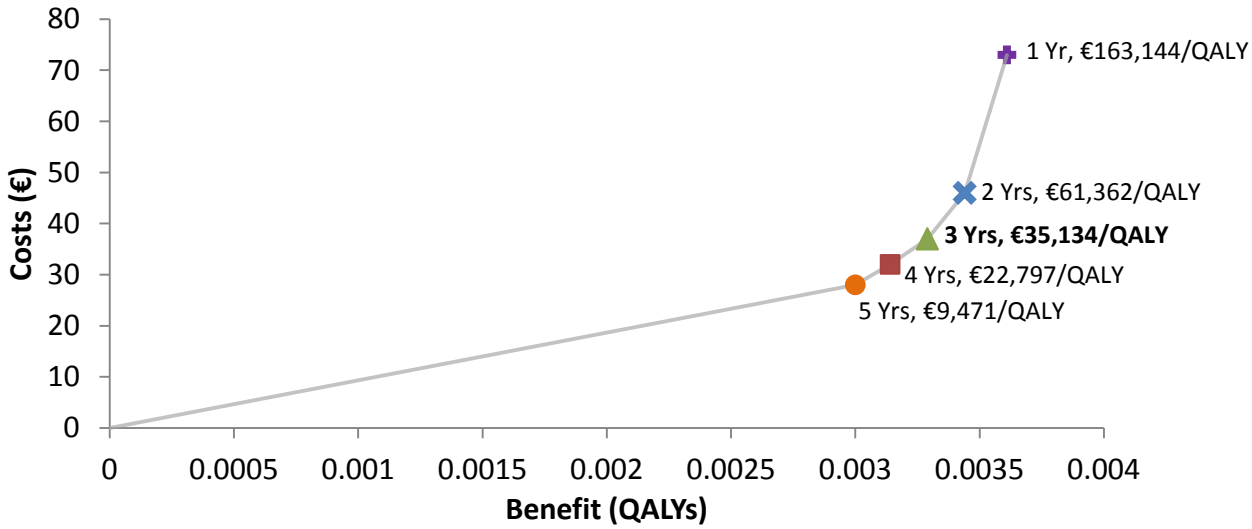
A scenario analysis was carried out to compare the annual screening programme evaluated in the primary analysis to programmes with an extended screening interval of between two and five years. In this scenario, incident AF cases in interval years have the same probability of being diagnosed as they do under routine care, whereas in screening years there is an increase in the detection of both incident cases and undetected prevalent cases from the interval period (Figure 8.6).

Figure 8.6 Modelled probability of AF diagnosis by age for different screening intervals



The cost-effectiveness plane comparing different screening intervals for a start age of 65 years is shown in Figure 8.7. This reveals that when the screening interval is lengthened, the rate of decrease in costs is greater than the rate of decrease in benefits, resulting in a lower ICER compared with no screening. It also shows that the ICER for annual screening compared with the next best option in the scenario analysis (screening every second year) far exceeds conventional willingness to pay thresholds used in Ireland. If extending the screening interval beyond one year is considered a realistic option, then at a willingness-to-pay threshold of €45,000/QALY the optimal screening strategy would be opportunistic screening every three years.

Figure 8.7 Scenario analysis comparing different screening intervals with a start age of 65 years

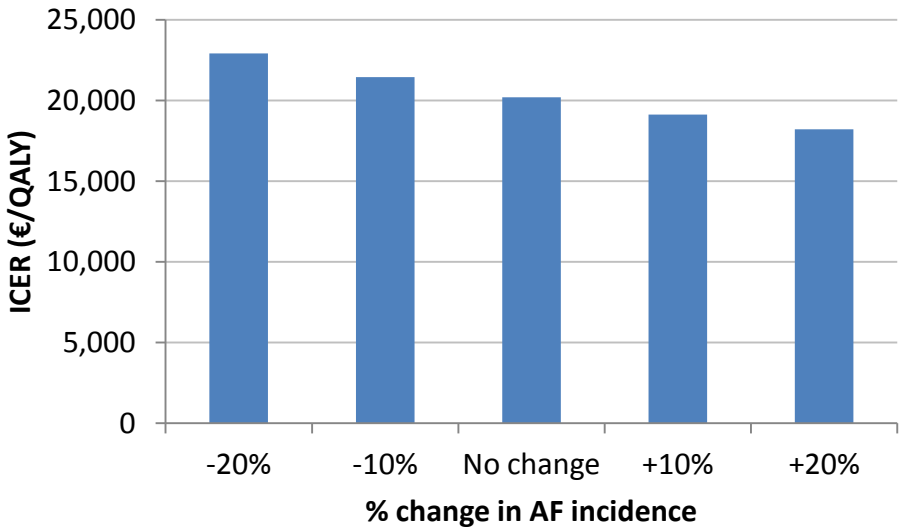


Caution needs to be applied when interpreting these results as the data on clinical effectiveness results were obtained from a once-off annual screen, raising questions as to whether or not they can be directly applied to longer screening intervals. Another important consideration is the feasibility of implementing extended screening intervals beyond one year in the context of an opportunistic programme requiring a one minute pulse palpation in patients who attend a GP consultation for a different reason.

8.2.2.4 AF incidence

Accurate estimation of the total incidence of AF is difficult, as the arrhythmia may be intermittent or associated with nonspecific symptoms such as fatigue and dyspnoea. The impact of uncertainty regarding AF incidence on the cost-effectiveness of screening was examined by varying incidence rates by ±20% (Figure 8.8).

Figure 8.8 ICER estimates with changing AF incidence rates



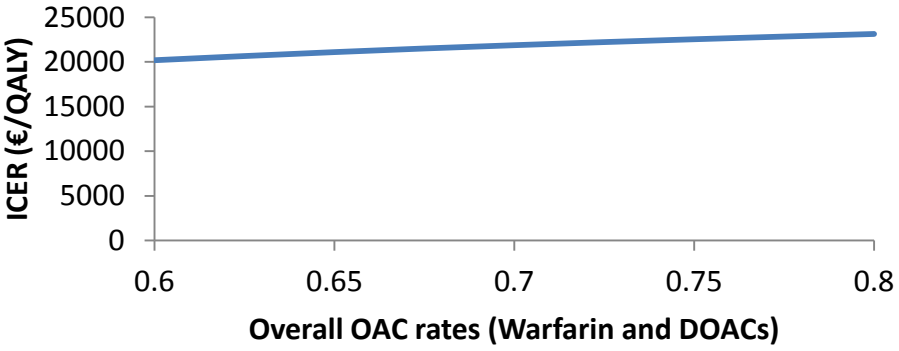
As expected, screening becomes more cost-effective as the estimated incidence of AF in the screening population increases, although the change is modest. The sensitivity analysis indicates the risk that the cost-effectiveness of screening is overestimated due to uncertainty about AF incidence is low, since the data used is more likely an underestimate rather than an overestimate of true AF incidence, and even a 20% overestimation would result in an ICER of less than €25,000/QALY.

8.2.2.5 Changes to OAC rates as a result of screening

In the primary analysis the conservative approach of assuming that the standard of care for AF will remain the same if a screening programme is introduced was adopted. However, as demonstrated in the STROKESTOP study, screening has the potential to increase treatment rates of AF both by identifying previously undiagnosed cases and by improving oral anticoagulation (OAC) rates among those with a prior diagnosis. Although definitive data on current OAC rates and direct oral

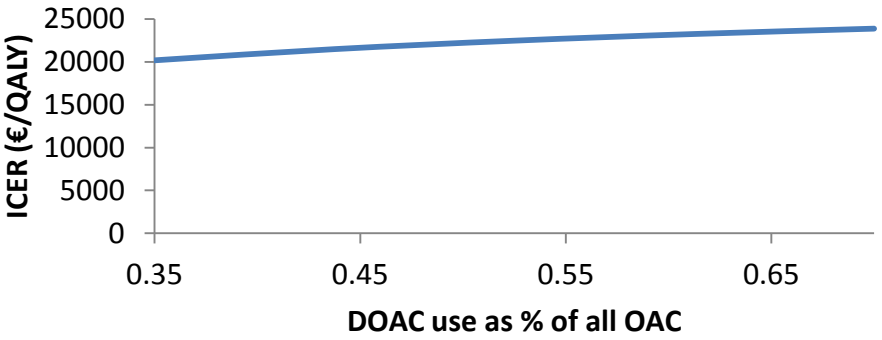
anticoagulant (DOAC) use in AF patients is lacking, it was estimated that approximately 60% are anticoagulated and 35% of these are taking DOACs (see section 5.4.1). Figure 8.9 and 8.10 show the impact of increasing OAC rates and DOAC use as a result of screening on cost-effectiveness.

Figure 8.9 Impact of increasing OAC rates as a result of screening on cost-effectiveness



OAC – Oral Anticoagulant, DOAC – Direct Oral Anticoagulant, ICER – Incremental Cost Effectiveness Ratio

Figure 8.10 Impact of increasing DOAC use as a result of screening on cost-effectiveness



OAC – Oral Anticoagulant, DOAC – Direct Oral Anticoagulant, ICER – Incremental Cost Effectiveness Ratio

Results show that the marginal increase in benefits from greater OAC and DOAC use is matched by the marginal increase in costs, so there is no major change in the incremental cost effectiveness ratio (ICER) estimate even with large increases in DOAC use.

Recent analysis of DOAC use in Ireland suggests that a significant proportion of patients are prescribed doses that are non-inferior to warfarin. To examine the impact of suboptimal DOAC prescription a worst-case scenario was examined where all those on DOACs had the same reduction in risk of ischaemic stroke and systemic embolism as those on warfarin, while retaining the same risk of bleeding (and costs). Results are shown in Table 8.4, which indicates that the impact on the overall cost-

effectiveness of screening versus routine care is minimal (approximately 3% increase in ICER).

Table 8.4 Effect of suboptimal DOAC dosing on ICER for screening

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	3,855	-	7.80914	-	€20,789/QALY
Screening	3,930	74	7.81272	0.00358	

Recent UK guidelines for the management of AF recommend against offering aspirin monotherapy solely for stroke prevention for people with atrial fibrillation.[126] The most recent Irish and UK data suggests that aspirin is currently being used for this purpose in up to a third of patients (section 5.4.1). As this is likely to reduce over time in light of the UK guidelines, a sensitivity analysis was carried out to estimate the cost-effectiveness of screening being introduced into an environment with very high OAC rates, using the extreme case of 100% DOAC use. The results of this scenario analysis (Table 8.5) show that this would not significantly affect the cost-effectiveness results.

Table 8.5 Effect of introducing screening in the context of very high rates of DOAC use

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	4,091	-	7.81706	-	€21,795/QALY
Screening	4,234	143	7.82363	0.00657	

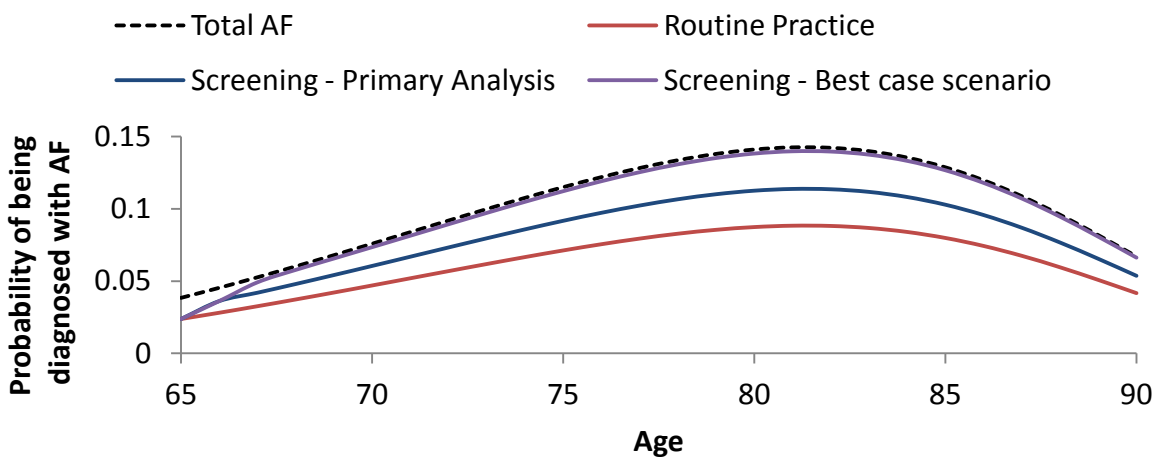
8.2.2.6 Screening sensitivity and the effectiveness of routine practice

In the primary analysis it was conservatively assumed that incident cases that are not detected the first time the person with AF is screened will remain undetected in subsequent years. Results of a sensitivity analysis of the effect of a screening programme where latent cases have the same probability of being detected each year are shown in Table 8.6. Figure 8.11 shows the difference in the proportion of AF cases diagnosed over time in this scenario compared with the primary analysis. As anticipated it results in a higher rate of case-detection and an increase in the cost-effectiveness of screening (lower ICER).

Table 8.6 ICER calculation for best case scenario for effectiveness of opportunistic screening

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	3,846	-	7.80987	-	€12,809/QALY
Screening	3,940	94	7.81718	0.00731	

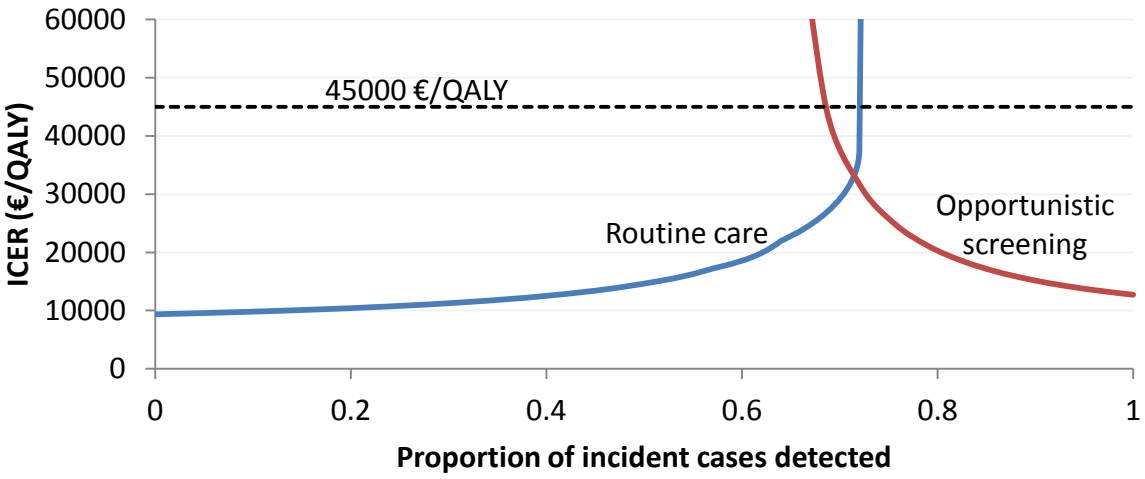
Figure 8.11 Probability of being diagnosed with AF in primary analysis and best case scenario for effectiveness of opportunistic screening



In the absence of data on the effect of disease progression on detection rates of latent AF this was not modelled separately. Rather, it was assumed that disease progression is similar across comparators and does not contribute to significant differences between groups.

Figure 8.12 shows the impact of varying the effectiveness of routine care and opportunistic screening on the overall cost-effectiveness estimate. This shows that given current estimates of the proportion of cases identified by routine care (62%), opportunistic screening would be cost-effective at a willingness-to-pay of €45,000/QALY as long as it increased the rate of AF detection to at least 70%. Conversely, if the sensitivity of pulse palpation and ECG at detecting incident cases is 80%, then screening would be cost-effective as long as the rate of AF detection in routine practice was less than 72%.

Figure 8.12 Univariate sensitivity analysis of the impact of the effectiveness of routine practice and opportunistic screening on cost-effectiveness



8.2.2.7 Uptake of screening and the cost of pulse palpation

Uncertainty relating to the uptake of screening has implications for both the clinical effectiveness and costs associated with screening. In the SAFE trial 69% of patients had their pulse taken, and 81% of those without a previous diagnosis of AF who were found to have an irregular pulse consented to having an ECG.[19] In this analysis it was assumed that the overall uptake of opportunistic screening is likely to be higher than that observed in a trial setting due to the absence of the requirement for formal consent and the fact that pulse palpation is a well known and accepted part of routine GP care. However, a worst case scenario could see significantly decreased AF detection in opportunistic screening due to a low acceptance rate of screening among patients. Costs of pulse palpation may also be higher than that included in the primary analysis, due to a higher proportion of tests being carried out by GPs rather than practice nurses, or due to underestimation of practice nurse costs from failing to include GP contributions to nurse salaries in the calculation of the cost of staff time. An Irish study of GP attendance rates reported that estimates derived from practice data are likely to be higher than self reported estimates, the kind collected by TILDA.[65;127] If the TILDA data is an underestimate then as well as lending further support to the assumption that all those in the screening cohort attend a GP consultation at least once a year, it may reduce the estimated opportunity cost of pulse palpation, which is based on the GMS capitation fee.

To examine the impact of this uncertainty, a sensitivity analysis was conducted that varied uptake between 50% and 100%, and varied the cost of pulse palpation between €2.88 and €14.40 (Figures 8.13 and 8.14).

Figure 8.13 Impact of decreasing uptake of screening on cost-effectiveness

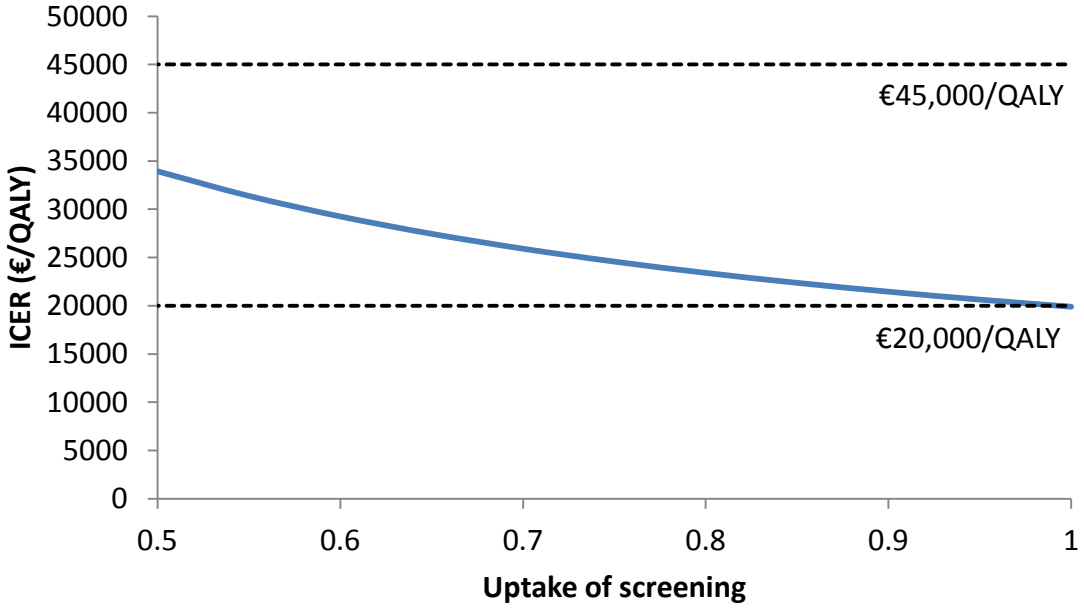
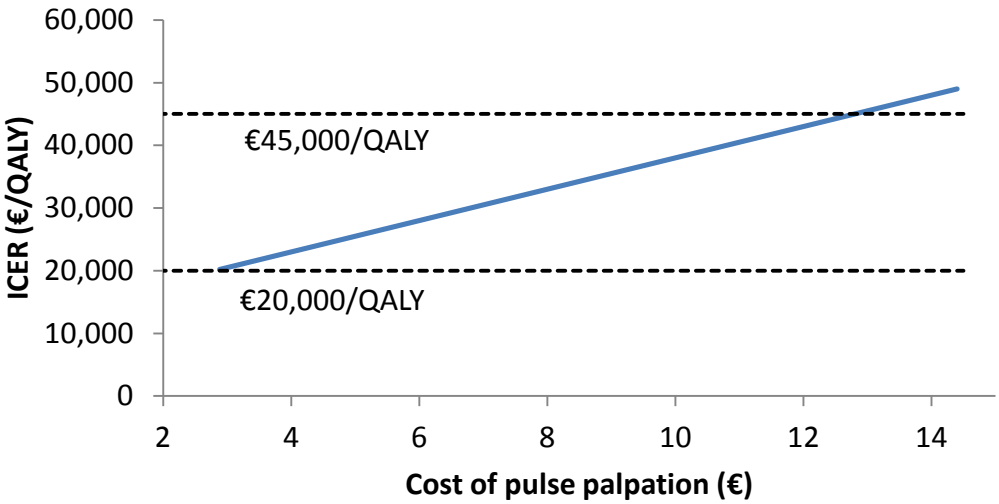
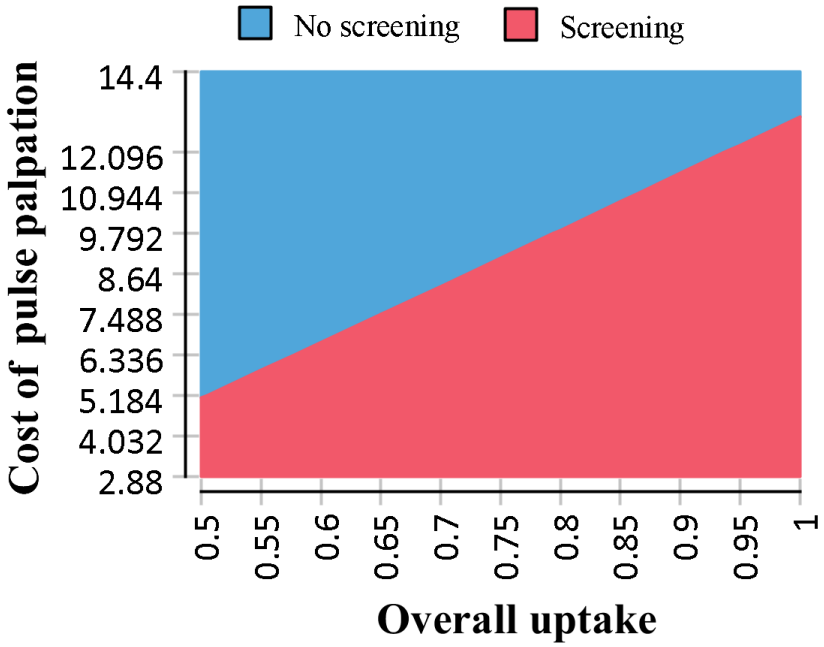


Figure 8.14 Impact of increasing cost of pulse palpation on cost-effectiveness



Results of univariate sensitivity analysis showed that the overall results were relatively insensitive to changes in the uptake of screening or the opportunity cost of pulse palpation, with the ICER for screening remaining cost-effective at a willingness-to-pay threshold of €45,000/QALY. A two-way sensitivity analysis examining the impact of simultaneous changes in both these parameters is shown in Figure 8.15. This shows that the intervention is likely to be cost-effective at a willingness-to-pay threshold of €45,000/QALY unless the opportunity cost of pulse palpation during a routine GP visit is greatly underestimated and uptake rates are significantly overestimated.

Figure 8.15 Two-way sensitivity analysis of screening uptake and cost of pulse palpation (WTP = €45,000/QALY)



8.2.2.8 Inclusion of costs of additional testing as part of an AF diagnosis

The draft AF care pathway developed by the HSE specifies that blood tests and an echocardiogram should be carried out in patients diagnosed with AF.[11] The costs of additional tests for structural heart disease were not included in the primary analysis because the benefits associated with diagnosing and treating these concomitant conditions were not included. Including the incremental costs, but not the incremental utility associated with these tests would bias the analysis in favour of routine care. However, the potential impact of these additional costs was examined in a sensitivity analysis. In the absence of HSE cost data for echocardiography and blood testing prices were obtained from private health clinics. Prices for echocardiography ranged from €81 to €250, and prices for blood testing ranged from €20 to €30.[128-130] For the purposes of the sensitivity analysis a conservative (high) estimate of a combined cost of €250 for additional testing for each new diagnosis of AF was used. The results of the cost-effectiveness analysis that includes these costs are presented in Table 8.7, which show that their inclusion increases the ICER by approximately 16%.

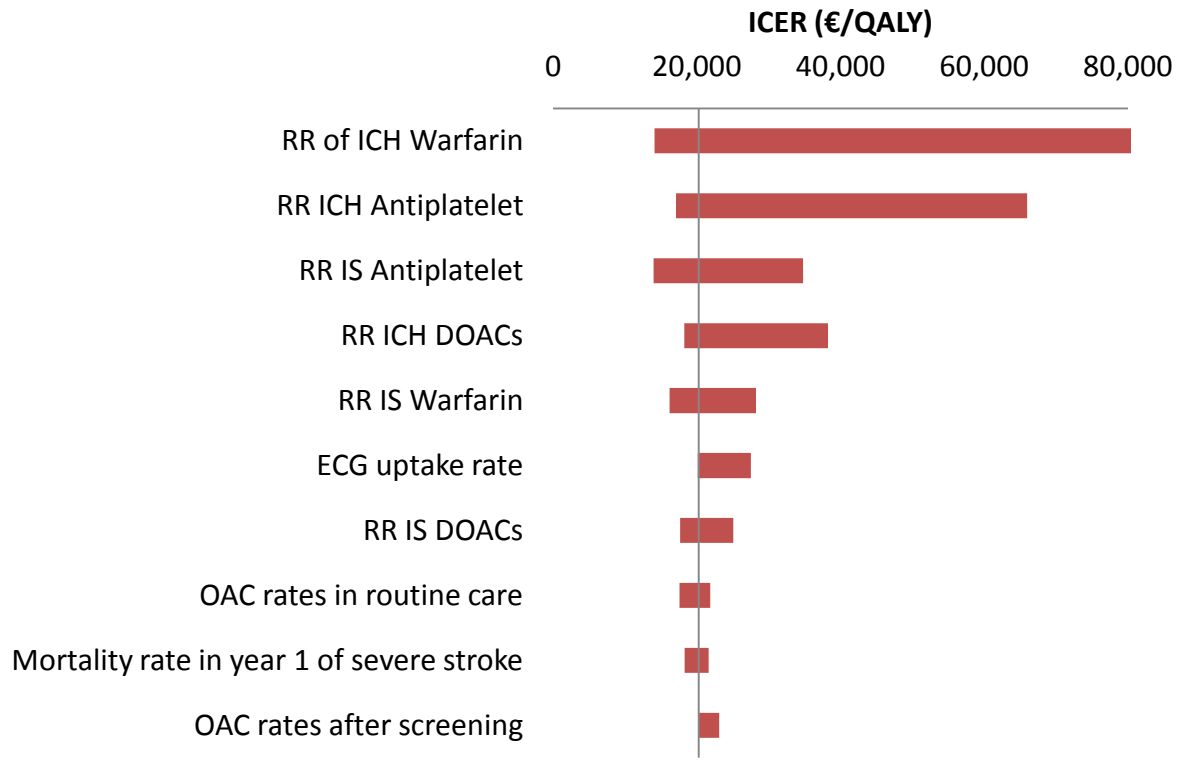
Table 8.7 Inclusion of costs of blood testing and echocardiography for each diagnosed AF case

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	3,886	-	7.81185	-	€23,423/QALY
Screening	3,971	85	7.81548	0.00363	

8.2.2.9 Deterministic sensitivity analysis

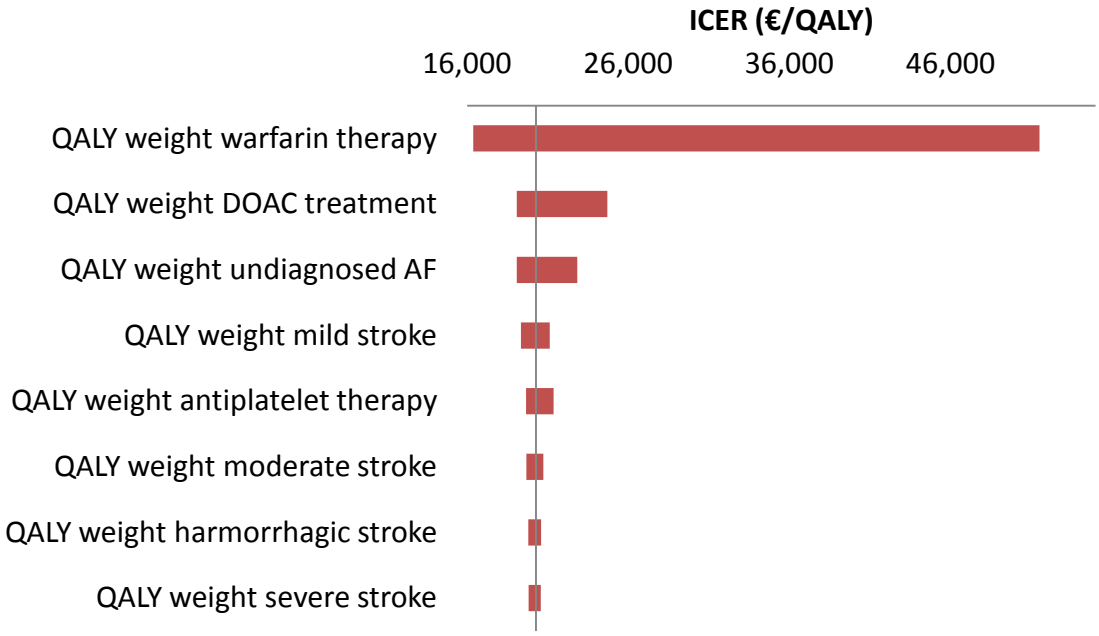
In addition to the scenarios examined in detail above, deterministic univariate sensitivity analysis was carried out for all the parameters in the model by varying them within their 95% confidence bounds or by ±20%, to assess the sensitivity of the overall results to individual parameter uncertainty. Separate tornado plots showing the potential impact of uncertainty regarding transition probabilities, utilities and costs on the overall ICER for screening are shown in Figures 8.16, 8.17 and 8.18.

Figure 8.16 Tornado plot – Transition probabilities



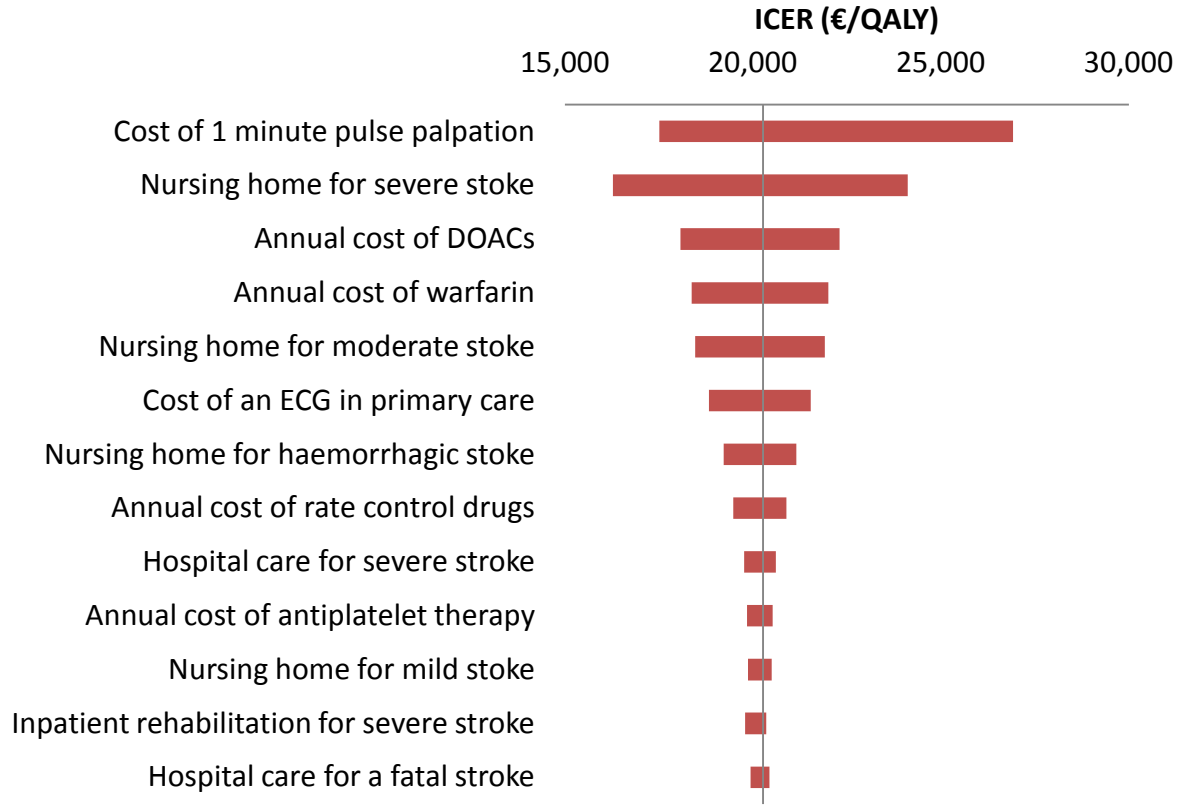
RR – Relative Risk; ICH – Intracranial Haemorrhage; IS – Ischaemic Stroke; DOAC – Direct Oral Anticoagulant; AF – Atrial Fibrillation; ECG – Electrocardiogram; OAC – Oral Anticoagulant

Figure 8.17 Tornado plot – Utilities



QALY – Quality Adjusted Life Year; DOAC – Direct Oral Anticoagulant; AF – Atrial Fibrillation; ICH – Intracranial Haemorrhage; GI – Gastrointestinal

Figure 8.18 Tornado plot - Costs



DOAC – Direct Oral Anticoagulant; ECG – Electrocardiogram; ICH – Intracranial Haemorrhage;

The high degree of uncertainty regarding the impact of antithrombotic therapy on haemorrhagic stroke risk is evident from the tornado plots for transition probabilities. Due to the relative rarity of this outcome, the bounds around the pooled estimate in the Cochrane review of the effectiveness of warfarin and aspirin were extremely wide ([0.54 to 10.50] and [0.22, 7.80], respectively). Uncertainty in relation to the impact of being prescribed warfarin on quality of life also has the potential to significantly affect the overall ICER - the lower bound for warfarin anticoagulation was 0.953, which when combined with the high usage rates represents a potentially significant utility loss. The results also show that any potential reversal of reductions in the GMS fee for ECGs that were introduced in the last number of years due to the economic recession are unlikely to significantly alter the results of the analysis. Sensitivity analysis of the impact of increasing the cost of rhythm control treatment to take into account the cost of blood and ECG testing every three months, and increasing the cost of DOACs by adding the cost of renal function tests every three months does not significantly impact the overall cost-effectiveness results for the comparison of AF screening to routine practice. Similarly, any decreases in the annual cost of warfarin through the use of near patient testing in primary care, or increases in warfarin effectiveness by achieving higher TTR rates is unlikely to significantly affect the overall results.

8.2.3 Societal perspective results

The analysis from the societal perspective includes the same benefits as the payer perspective along with the total cost of treatment whether it falls on the public health service, patients or private health insurers. It also includes costs associated with informal care and lost productivity due to stroke morbidity and mortality. The ICER from the societal perspective for screening versus routine care is €23,004/QALY (Table 8.8). The cost-effectiveness plane and cost-effectiveness acceptability curve (CEAC) are shown in Figures 8.19 and 8.20. The average cost per patient for both comparators is increased, but the ICER is comparable to that of the payer perspective. From the perspective of society, screening has a 79% chance of being cost-effective at a willingness-to-pay threshold of €45,000/QALY.

Table 8.8 ICER calculation (societal perspective)

Strategy	Cost (€)	Incremental Cost (€)	Effect (QALY)	Incremental Effect (QALY)	ICER
No screening	14,529	-	7.81643	-	€23,004/QALY
Screening	14,613	84	7.82007	0.00364	

Figure 8.19 Cost-effectiveness plane (societal perspective)

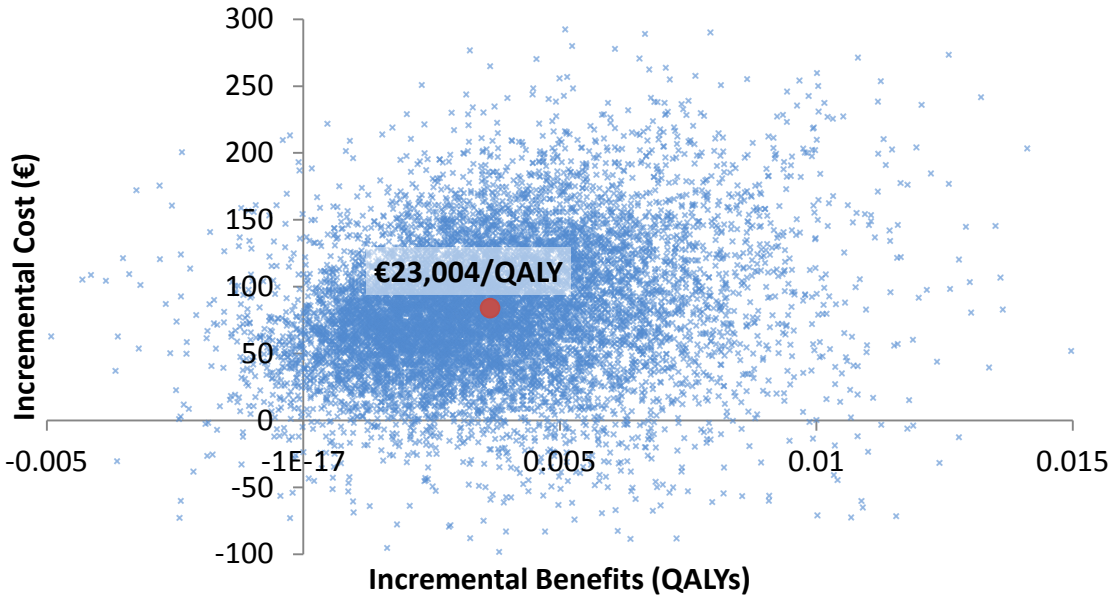
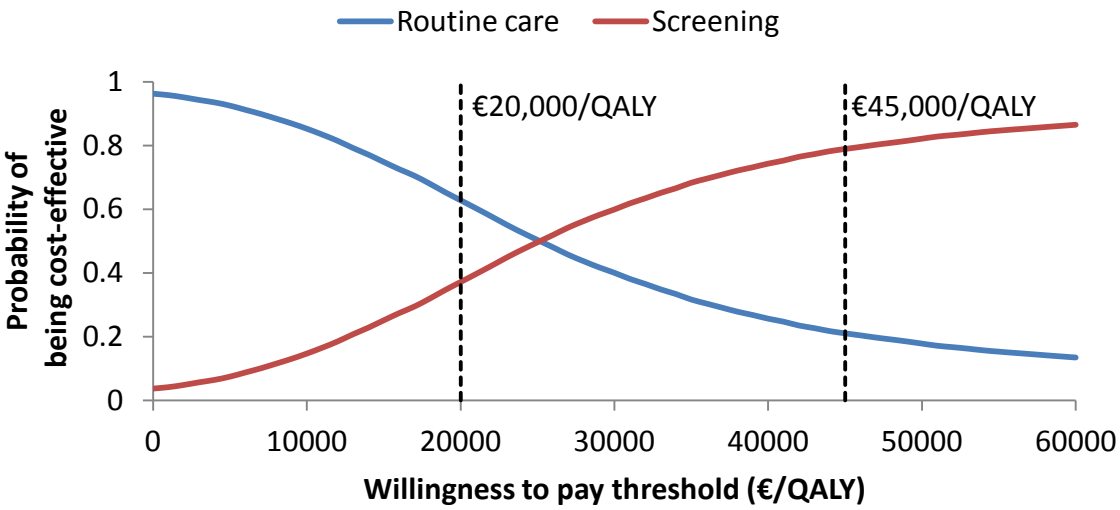


Figure 8.20 Cost effectiveness acceptability curve (CEAC, societal perspective)



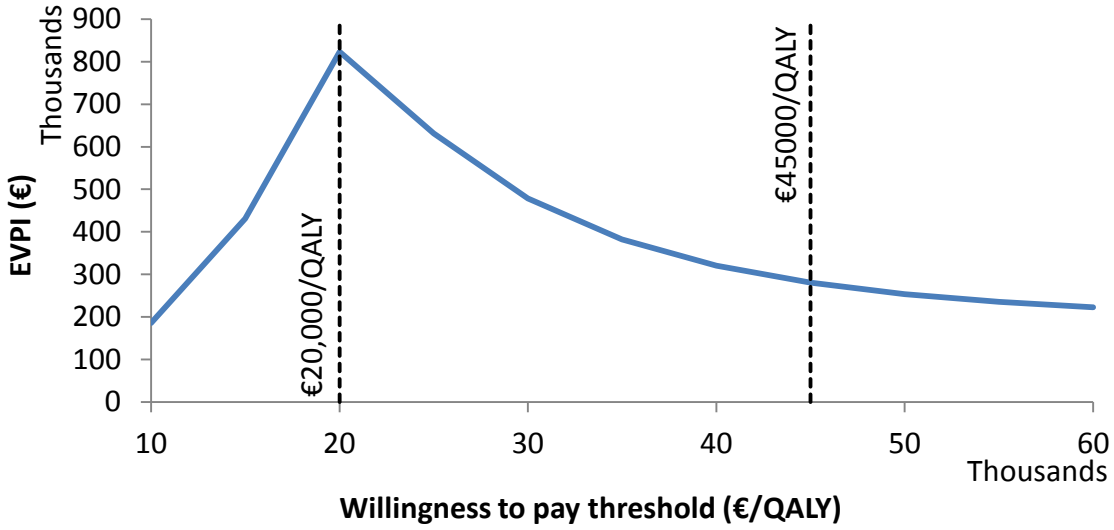
8.4 Value of information analysis

Expected value of perfect information (EVPI) analysis provides a way to investigate the value of acquiring more evidence before deciding whether or not to introduce opportunistic screening for AF. It examines both the probability that a decision based on existing evidence will be wrong and the consequences of a wrong decision, and uses this to calculate the monetary value of acquiring perfect information, thus eliminating the possibility of taking the wrong option. The results of this analysis provide an upper bound on the value of acquiring more information, since additional

research would generally only inform a small subset of parameters and is unlikely to ever generate perfect information, so some level of uncertainty will remain.

EVPI analysis uses the data from the cost-effectiveness analysis to calculate the expected value of perfect information each time the decision is made for a patient. Therefore the overall EVPI is the combined EVPI for all patients who stand to benefit from the additional information. The value of additional information is low when there is little uncertainty about which option is the most cost-effective at a given willingness-to-pay threshold, since more information is unlikely to change the result. However, where there is a lot of uncertainty as to which comparator is the most cost-effective, the value of additional information increases. The EVPI calculation for opportunistic AF screening versus routine practice is shown in Figure 8.21. This shows that the value of perfect information to inform decision making at a WTP threshold of €45,000/QALY is approximately €280,000. This relatively low EVPI estimate reflects the low level of uncertainty about the cost-effectiveness of screening, which has an 83% chance of being cost-effective at this WTP threshold (see Section 8.2.1).

Figure 8.21 Expected value of perfect information (EVPI) from the perspective of the HSE



8.5 Budget impact results

A budget impact analysis (BIA) was conducted to calculate the total incremental costs of screening from the perspective of the HSE over a five year time horizon. No discounting was applied. VAT is applied where applicable in a BIA, however given the fact that oral medications, nursing home care and medical aids and appliances attract a VAT rate of zero, no additional tax costs were incurred. In this economic analysis the opportunity cost of pulse palpation was calculated based on the cost of staff time. As such it does not represent an additional direct cost to the HSE and is not included in the BIA, so the cost of screening includes the direct cost of ECGs

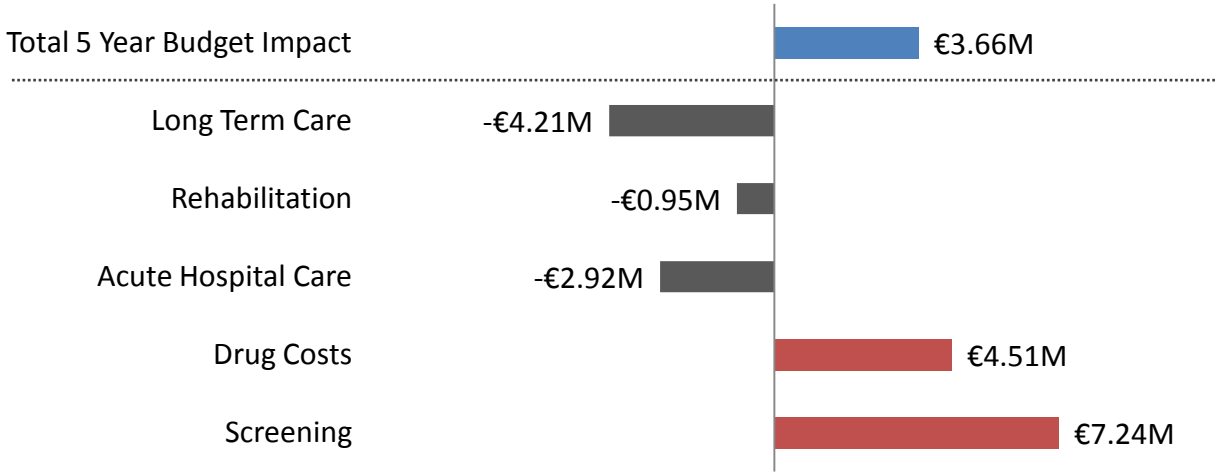
only. The five-year BIA was calculated for the same screening cohort as used in the cost-effectiveness analysis, with the difference being that the cost-effectiveness analysis was a longitudinal analysis of a cohort of 65 years olds over the course of 25 years whereas the BIA is a cross-sectional analysis of the total annual screening cohort of 65 to 90 year olds. Costs included in the BIA are shown in Table 8.9.

Direct costs to the HSE were combined with 2014 CSO data on the total screening population by single year of age and results of the economic model showing the proportion of patients in each health state by year of age up to the end of the fifth year of screening. For the calculation of the savings in nursing home costs it was assumed that all strokes avoided through screening would have survived to the end of the five year time horizon in the absence of screening. Figure 8.22 shows the total five year budget impact along with a breakdown of cost components, showing that the additional screening and drugs costs associated with the intervention outweigh the cost savings associated with the decrease in stroke incidence and severity.

Table 8.9 Costs included in the budget impact analysis

Screening (ECG only)	Post-stroke aids and appliances
Rhythm or rate control medication	Post-stroke ambulatory care
Antithrombotic medication	Post-stroke community rehabilitation
Acute hospital treatment for stroke	Post-stroke medication
Inpatient rehabilitation for stroke	Post-stroke nursing home care

Figure 8.22 Breakdown of total five year budget impact of AF screening by cost component



Results of the BIA show that the anticipated total incremental cost of opportunistic AF screening to the HSE over five years is approximately €3.66 million. The majority of the cost is made up of the cost of screening ECGs in primary care, which are expected to cost over €1.45 million annually in the context of a national programme where all screening ECGs are funded by the health service. The other major cost driver is expenditure on medications for rhythm or rate control and antithrombotic therapy for those diagnosed with AF. Incremental AF drug costs peak at approximately €1.48M in the first year of screening, since more new cases are picked up in the prevalent screen, before dropping to approximately €0.28M in incident screening rounds, with the cumulative incremental cost over five years being approximately €4.96M. The increased expenditure on AF screening and treatment is mitigated by anticipated savings in the costs associated with stroke care. This analysis assumes that no strokes are avoided in the first year of screening, but from year two onwards the risk of stroke in those diagnosed with AF is reduced as a result of antithrombotic therapy in AF patients identified through screening in previous years. By the end of the fifth year of screening it is estimated that the intervention will have been associated with an overall decrease of approximately 1.9% in the incidence of first ever stroke in the screened cohort. When the five-year saving in post-stroke medication costs are taken into account the total incremental cost of drugs is €4.51M. Cumulative savings in the costs of acute care, medication, rehabilitation and long-term care associated with this reduction in stroke over the five year time horizon is estimated to be approximately €8.53M.

8.6 Impact of screening on specialist referrals

Opportunistic screening for AF in primary care is unlikely to require major reorganisation of existing services or significantly impact existing patient care pathways, since AF is already routinely detected and treated in primary care. Increased diagnosis of AF is, however, likely to result in an increase in the number of specialist referrals and further clinical investigations carried out.

The HSE National Clinical Programme for Stroke conducted a multi-site prospective observational study on the feasibility of opportunistic AF screening of over 65's in general practice in Ireland, which included a total of 37 GP practices covering an estimated population of approximately 25,000 people aged 65 years or over.[44] Over the course of the six month study period, the pilot study screened 7,262 patients and detected 55 new AF cases. The (6 month) rate of detection of new cases of AF out of the entire screened population (omitting those with a prior diagnosis of AF) was 0.008. The observed AF rate in the pilot study prior to screening was 10.1%. This is almost twice the AF prevalence rate in over 65's reported internationally.[131-133] In this analysis using a nationally representative population of over 65's with an observed AF prevalence of 5.25%, where opportunistic screening detects approximately 80% of AF cases, compared with the 62% of cases detected with

routine practice, the estimated (1 year) rate of detection in the first year is 0.016. More new cases are detected in the first year (prevalent screen) because there are more undiagnosed cases in the group at the start of screening than when the group has been screened annually for a number of years. Based on this analysis, the estimated annual AF detection rate of detection after year one (incidence screens) is 0.003. There are no estimates available in the literature with which this can be compared, as no published studies were identified that examined the impact of annual AF screening over successive screening rounds.

The Irish AF screening pilot study reported health service utilisation for those diagnosed with AF. Using this the increase in the number of specialist referrals associated with the introduction of screening for the total Irish population aged 65 years or over was estimated (Table 8.10). The expected increase in cardiology referrals in the first year is equivalent to 20% of the total number of people currently on the waiting list for a public outpatient cardiology appointment (14,425 as of May 2015).[134]

Table 8.10 Estimated annual increase in specialist referrals after the introduction of a national AF screening programme

Referral	Prevalent screen: Year 1 (range)	Incident screens : Year 2 onwards (range)
Cardiology	2,864 (2,183 to 3,820)	550 (419 to 734)
Medical	174 (132 to 231)	33 (25 to 44)
Geriatric	347 (265 to 463)	67 (51 to 89)
Emergency Department	1,736 (1,323 to 2,315)	333 (254 to 445)
Medical Assessment Unit	1,302 (992 to 1,736)	250 (191 to 333)

8.7 Discussion

The results indicate that opportunistic screening for AF in over 65s in primary care is likely to be cost-effective using conventional willingness-to-pay thresholds in Ireland, with an incremental cost-effectiveness ratio (ICER) of approximately €20,271/QALY compared with routine care. The total five year budget impact associated with screening to the HSE, which includes reductions in stroke treatment costs, is estimated to be approximately €3.7 million.

The results of the economic analysis are sensitive to potential changes in a number of parameters used in the analysis. Among the most important of these is the risk profile of screen-detected patients. The undiagnosed cohort includes those that are completely asymptomatic as well as those in whom AF symptoms are unexplained or misattributed. This analysis found that if the relative risk of ischaemic stroke and

systemic embolism in screen-detected patients is more than 14% lower than that of cases detected in routine care, then screening would not be considered cost-effective using conventional willingness-to-pay thresholds. No differentiation is made between these groups for the purposes of calculating AF stroke risk per the CHA_2DS_2-VASc score, but there are some studies in asymptomatic device-detected AF that have suggested that the risk of ischaemic stroke could be up to 50% lower in asymptomatic AF.[23] However, recent analysis of data from nine European countries in the EORP-AF Pilot General Registry found that asymptomatic AF had a higher one-year mortality than symptomatic AF.[68] Two studies are currently underway to examine the balance of benefits and harms of OAC treatment in asymptomatic AF.[135] The STROKESTOP study, which has already posted interim results for AF detection (see section 3.1.2), will follow screen-detected AF patients in whom OAC was used, to measure the impact of treatment on stroke rates.[20] The study is expected to be completed in 2019. The ARTESiA trial is examining the benefits of DOAC treatment for people with implantable device detected atrial high rate episodes (AHREs).[136] The primary outcomes are stroke and major bleeding events and results are also expected to be available in 2019. Of these two studies the STROKESTOP trial is more suited to answering the question of interest in this analysis, as it includes those who may have been experiencing mild, unrecognised symptoms, rather than being limited to those who have completely asymptomatic AF.

Decreasing the age at which screening starts reduces the cost-effectiveness of any prospective programme. Starting screening at age 50 is unlikely to be cost-effective at a willingness to pay threshold of €45,000/QALY, and ICERs for start ages between 55 to 70 years range from €38,000/QALY to €15,000/QALY compared to no screening. The length of the screening interval also has a significant impact on cost-effectiveness results. In a scenario analysis that varied the frequency of opportunistic pulse palpation between once every year to once every five years for all over 65s, screening once every three years was identified as the optimal strategy at a willingness to pay threshold of €45,000/QALY. However, these results need to be interpreted with caution, as all the available evidence on the effectiveness of screening comes from studies carried out in people aged 65 years and over, and no studies have as yet compared the results of using different screening intervals. Other influential parameters include the rate of AF detection in routine care and the sensitivity of the two stage screening test. The analysis found that screening is likely to be cost-effective if it increases the rate of AF detection by at least 8%.

The cost-effectiveness estimates were not greatly altered by plausible changes in the baseline incidence of AF or changes to the proportion of people who are prescribed DOACs, warfarin or antiplatelet therapy. The results were also relatively insensitive to changes in the opportunity cost of pulse palpation and the intervention remained

cost-effective when uptake rates were lowered to represent a worst case scenario for opportunistic screening.

Among the limitations of this analysis is that while both Irish and UK data sources indicate that the proportion of AF cases detected by routine care is approximately 60%, there is a lack of data on the effect of age on AF detection. In this analysis it was assumed that the rate of undiagnosed AF was consistent across all ages. If it were the case that incident AF had a higher probability of remaining undiagnosed in younger or older age groups this may have implications for the optimal start age of screening. Another limitation is the lack of studies involving multiple AF screening rounds over a period of years, as all studies to date have evaluated once off screening in a particular age group. A conservative approach was adopted in the primary analysis, by assuming that prevalent cases that are undetected in the initial screening round remain undetected in subsequent screening rounds. This is likely to underestimate the clinical effectiveness of multiple rounds of screening. The opposite approach of assuming that undiagnosed AF has an equal chance of being detected in each round risks overestimating the impact of screening, since it is likely that factors such as whether asymptomatic AF is paroxysmal or persistent, or has atypical electrocardiographic presentation, make undetected cases more likely to remain undetected. However as the results show, AF screening is likely to be cost effective even using a conservative approach to estimating the impact of multiple screening rounds.

8.8 Key points

- A Markov model was developed to compare the costs and benefits of annual opportunistic AF screening in primary care for a cohort of men and women aged 65 years and older over a 25 year time horizon. The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and is consistent with the best evidence on the effectiveness of screening.
- There is a high level of uncertainty regarding a number of key parameters needed to estimate the cost-effectiveness of AF screening in Ireland. In this analysis conservative estimates of the effectiveness of screening on AF detection were used and a sensitivity analysis was conducted to estimate the impact of uncertainty in this and other parameters.
- Based on the results of the primary analysis, a strategy of annual opportunistic screening would result in 1,944 additional AF cases being detected in the screened cohort compared with current practice.
- Based on the estimated current standard of care for antithrombotic therapy in patients with AF, this will result in approximately 157 fewer strokes.

- Screening is associated with an incremental cost-effectiveness ratio of €20,271/QALY, giving it an 83% probability of being cost-effective at a willingness-to-pay threshold of €45,000/QALY.
- The cost-effectiveness results are sensitive to changes in the start age of screening, the frequency of screening and the baseline risk of ischaemic stroke and systemic embolism in those who would not have been diagnosed with AF through routine practice in the absence of screening.
- Changes in the proportion of AF patients who are prescribed warfarin, direct oral anticoagulants and antiplatelet therapy are unlikely to have a major impact on the cost-effectiveness of screening.
- Budget impact analysis, which did not include a set fee for pulse palpation, showed that the total incremental cost of opportunistic AF screening to the HSE over five years is approximately €3.7 million. This includes the additional costs associated with screening and pharmacological treatment of AF patients, as well as reductions in the cost of stroke care over the five year time horizon.
- It is estimated that screening could result in approximately 2,864 additional referrals for an outpatient cardiology appointment in the first year after implementation, and approximately 550 additional referrals every year thereafter.

9 Discussion and conclusion

This analysis combined the best available data on the effect of antithrombotic treatment on stroke outcomes with a conservative estimate of the increase in AF detection associated with repeated annual pulse palpation, which assumed that incident cases that are not detected by screening remain undetected in subsequent screening rounds. Results of the economic analysis found that a national annual opportunistic AF screening programme for adults aged 65 years and older in primary care is likely to be cost-effective using a willingness-to-pay threshold of €45,000/QALY. The total five year budget impact of screening for the HSE, which includes saving as a result strokes avoided over the five year time horizon, is estimated to be approximately €3.66M.

The results are sensitive to changes in the stroke risk profile of the additional AF cases identified by screening. If the relative risk of ischaemic stroke and systemic embolism in screen-detected AF patients was more than 14% lower than those detected in routine practice, then screening would no longer be cost-effective at a willingness-to-pay threshold of €45,000/QALY. In the absence of definitive evidence of any difference in the risk profile of undiagnosed versus diagnosed AF, it is generally assumed that the risk of stroke is similar for both.[68;137] Two studies are currently in progress that will examine the benefits of oral anticoagulation in asymptomatic or screen-detected AF patients.[136;138] However both of these are not due to be completed until 2019.

The primary analysis compared the cost-effectiveness of a national AF screening programme involving annual opportunistic pulse palpation for men and women aged 65 years and over in primary care with routine practice (no screening). The choice of comparator was informed by the recommendations contained in the National Cardiovascular Policy 2010-2019 and the pilot AF screening project conducted by the HSE National Clinical Programme for Stroke and is consistent with the best available evidence on the effectiveness of screening. A sensitivity analysis indicated that lowering the start age decreases the cost-effectiveness of screening. Conversely, increasing the start age to 70 years would have an ICER of approximately €15,000/QALY compared with routine care. If it is assumed that increasing the screening interval beyond once per year does not affect the performance of the screening programme, then this would increase the cost-effectiveness of a prospective programme with a three year screening interval being the optimal strategy at a willingness to pay threshold of €45,000/QALY. However, these results need to be interpreted with caution, as all the available evidence on the effectiveness of screening comes from studies carried out in people aged 65 years and over, and no studies have as yet compared the results of using different screening intervals. Based on the available data screening is estimated to result in an absolute increase of 18% in the rate of AF diagnosis in the screened cohort. A

sensitivity analysis that varied the estimates of the proportion of AF cases detected by routine practice and screening found that the intervention is likely to remain cost-effective as long as it increases the detection rates of AF by at least 8%. A budget impact analysis from the perspective of the HSE estimated a total incremental cost of screening over five years of approximately €3.7 million. The annual incremental cost of AF drug therapy is higher in the first year of screening as a greater number of people are detected in the first (prevalent) screen compared to subsequent (incident) screens. Screening is expected to decrease spending on acute hospital stroke care and long-term residential care for stroke survivors.

A review of previously published economic analyses identified two studies that examined the cost-effectiveness of AF screening using pulse palpation in primary care, both of which concluded that it was likely to be cost-effective compared with routine practice. However, no country was identified as having a national AF screening programme currently in place. In July 2014, the UK National Screening Committee recommended against offering screening for all those aged 65 years and over, due to a lack of evidence demonstrating that those identified as at risk of stroke through screening would benefit from early diagnosis.[23] This decision is due to be reviewed in 2017, by which time an NIHR funded HTA that is currently in progress to examine the cost-effectiveness of screening in the UK is expected to have been published.[139] More recently, the Swedish Dental and Pharmaceutical Benefits Agency, whose remit is to determine which pharmaceutical and medical devices shall be subsidised by the state, has concluded that the benefits of primary preventive screening with thumb ECG (per the STROKESTOP trial) justifies the costs of screening. They do, however, point out that there is currently no information regarding when to initiate a national screening programme (i.e. at which cut-off age the method becomes cost-effective) and that they intend to evaluate this in a separate report in the future.

There are a number of issues with regard to the implementation of a screening programme that fall outside the scope of this report, which could potentially affect decision making. These include identification of appropriate methods for flagging patient's notes in GP practices to ensure that screening is offered to everyone in the target population. The SAFE trial in the UK restricted participation to GP practices that had computerised record keeping systems specifically for this purpose. This analysis also assumes that all GP practices have access to ECG equipment with interpretative software, which may not be the case for a minority of practices in Ireland. Given the potential implications that a national screening programme has for the number of specialist referrals and requests for additional investigations, consideration may need to be given to the development of referral guidelines for GPs in advance of its introduction.

In conclusion, although previous cost-effectiveness analyses have concluded that screening would likely be cost-effective, there is considerable uncertainty associated with key parameters that could have a significant impact on the findings. No other country has as yet implemented a national AF screening programme. An economic analysis comparing the costs and benefits of annual opportunistic screening of men and women aged 65 years and older in primary care in Ireland found that the intervention is likely to be cost-effective using conventional willingness-to-pay thresholds, assuming that those detected through screening have a comparable stroke risk profile as those detected through routine practice. Screening is also associated with significant incremental costs of approximately €3.7 million over the first five years.

10 References

(1) Levy S, Camm AJ, Saksena S, Aliot E, Breithardt G, Crijns H, et al. International consensus on nomenclature and classification of atrial fibrillation. *Europace.* 2003; 5(2) pp.119-22.

(2) Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke.* 1991; 22(8) pp.983-8.

(3) Feinberg WM, Blackshear JL, Laupacis A, Kronmal R, Hart RG. Prevalence, age distribution, and gender of patients with atrial fibrillation: Analysis and implications. *Archives of Internal Medicine.* 1995; 155(5) pp.469-73.

(4) Go AS, Hylek EM, Phillips KA. Prevalence of diagnosed atrial fibrillation in adults: National implications for rhythm management and stroke prevention: the anticoagulation and risk factors in atrial fibrillation (atria) study. *JAMA.* 2001; 285(18) pp.2370-5.

(5) Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. *Europace.* 2013; 15(4) pp.486-93.

(6) Benjamin EJ, Levy D, Vaziri SM, D'Agostino RB, Belanger AJ, Wolf PA. Independent risk factors for atrial fibrillation in a population-based cohort: The framingham heart study. *JAMA.* 1994; 271(11) pp.840-4.

(7) Kerr CR, Humphries K. Gender-Related Differences in Atrial Fibrillation*. *Journal of the American College of Cardiology.* 2005; 46(7) pp.1307-8.

(8) Lip GYH. Stroke and bleeding risk assessment in atrial fibrillation: when, how, and why? *European Heart Journal.* 2013; 34(14) pp.1041-9.

(9) Economic and Social Research Institute (ESRI), Royal College of Surgeons in Ireland (RCSI). *Cost of Stroke in Ireland*. Dublin, Ireland: Irish Heart Foundation; 2010.

(10) Kelly PJ, Crispino G, Sheehan O, Kelly L, Marnane M, Merwick A, et al. Incidence, Event Rates, and Early Outcome of Stroke in Dublin, Ireland: The North Dublin Population Stroke Study. *Stroke.* 2012; 43(8) pp.2042-7.

(11) HSE National Clinical Programme for Stroke. *Appendix 19: Atrial Fibrillation Care Pathway (June 2012 Draft).* 2012, [Online]. Available from: http://hse.ie/eng/about/Who/clinical/natclinprog/strokeprogramme/Policy_Documents/moc.pdf. Accessed on: 22 June 2015.

(12) Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace.* 2010; 12(10) pp.1360-420.

(13) Furberg CD, Psaty BM, Manolio TA, Gardin JM, Smith VE, Rautaharju PM. Prevalence of atrial fibrillation in elderly subjects (the Cardiovascular Health Study). *Am J Cardiol.* 1994; 74(3) pp.236-41.

(14) Savelieva I, Camm AJ. Clinical relevance of silent atrial fibrillation: Prevalence, prognosis, quality of life, and management. *J Intervent Card Electrophysiol.* 2000; 4(2) pp.369-82.

(15) Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, et al. Stroke associated with atrial fibrillation--incidence and early outcomes in the north Dublin population stroke study. *Cerebrovasc Dis.* 2010; 29(1) pp.43-9.

(16) Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Geneva: World Health Organization; 1968.

(17) Department of Health. *Changing Cardiovascular Health: National Cardiovascular Health Policy 2010 – 2019*. Dublin, Ireland: Department of Health (Ireland); 2010.

(18) Moran PS, Flattery MJ, Teljeur C, Ryan M, Smith SM. Effectiveness of systematic screening for the detection of atrial fibrillation. *Cochrane Database Syst Rev.* 2013; 4 p.CD009586.

(19) Hobbs FDR, Fitzmaurice DA, Mant J, Murray E, Jowett S, Bryan S, et al. A randomised controlled trial and cost-effectiveness study of systematic screening (targeted and total population screening) versus routine practice for the detection of atrial fibrillation in people aged 65 and over. The SAFE study. *Health Technol Assess.* 2005; 9(40) p.iii-71.

(20) Svennberg E, Engdahl J, Al-Khalili F, Friberg L, Frykman V, Rosenqvist M. Mass Screening for Untreated Atrial Fibrillation: The STROKESTOP Study. *Circulation.* 2015;

(21) Perula-de-Torres LA, Martinez-Adell MA, Gonzalez-Blanco V, Baena-Diez JM, Martin-Rioboo E, Parras-Rejano JM, et al. Opportunistic detection of atrial fibrillation in subjects aged 65 years or older in primare care: a randomised clinical trial of efficacy. DOFA-AP study protocol. *BMC family practice.* 2012;

(22) Personal communication. 9 June 2015.

(23) UK National Screening Committee. *The UK NSC recommendation on Atrial Fibrillation screening in adults.* 2014, [Online]. Available from: www.screening.nhs.uk/atrialfibrillation. Accessed on: 26 May 2015.

(24) Cowan C, Healicon R, Robson I, Long WR, Barrett J, Fay M, et al. The use of anticoagulants in the management of atrial fibrillation among general practices in England. *Heart.* 2013; 99(16) pp.1166-72.

(25) Holt TA, Hunter TD, Gunnarsson C, Khan N, Cload P, Lip GY. Risk of stroke and oral anticoagulant use in atrial fibrillation: a cross-sectional survey. *Br J Gen Pract.* 2012; 62(603) p.e710-e717.

(26) Maeda K, Shimbo T, Fukui T. Cost-effectiveness of a community-based screening programme for chronic atrial fibrillation in Japan. *Journal of Medical Screening.* 2004; 11(2) pp.97-102.

(27) Lowres N, Neubeck L, Salkeld G, Krass I, McLachlan AJ, Redfern J, et al. Feasibility and cost-effectiveness of stroke prevention through community screening for atrial fibrillation using iPhone ECG in pharmacies. The SEARCH-AF study. *Thromb Haemost.* 2014; 111(6) pp.1167-76.

(28) Rhys GC, Azhar MF, Foster A. Screening for atrial fibrillation in patients aged 65 years or over attending annual flu vaccination clinics at a single general practice. *Qual Prim Care.* 2013; 21(2) pp.131-40.

(29) Aronsson M, Svennberg E, Rosenqvist M+, Engdahl J, Al-Khalili F, Friberg L, et al. Cost-effectiveness of mass screening for untreated atrial fibrillation using intermittent ECG recording. *Europace.* 2015;

(30) Jaime CJ, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value Health.* 2014; 17(2) pp.174-82.

(31) Frewen J, Finucane C, Cronin H, Rice C, Kearney PM, Harbison J, et al. Factors that influence awareness and treatment of atrial fibrillation in older adults. *QJM.* 2013; 106(5) pp.415-24.

(32) Heeringa J. Atrial fibrillation: is the prevalence rising? *Europace.* 2010; 12(4) pp.451-2.

(33) Schnabel RB, Yin X, Gona P, Larson MG, Beiser AS, McManus DD, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *The Lancet.* 2015;(0)

(34) Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. *Journal of the American College of Cardiology.* 2001; 37(2) pp.371-8.

(35) Chen RL, Balami JS, Esiri MM, Chen LK, Buchan AM. Ischemic stroke in the elderly: an overview of evidence. *Nat Rev Neurol.* 2010; 6(5) pp.256-65.

(36) Wren M, Kelly P. *Deriving a Method to Estimate Incidence of Stroke in Ireland*. Dublin: ESRI; Working Paper No. 469. 2013.

(37) Wolf PA, Kannel WB, McGee DL. Duration of atrial fibrillation and imminence of stroke: The Framingham Study. *Stroke.* 1983; 14(5) pp.664-7.

(38) Lin HJ, Wolf PA, Kelly-Hayes M, Beiser AS, Kase CS, Benjamin EJ, et al. Stroke Severity in Atrial Fibrillation: The Framingham Study. *Stroke.* 1996; 27(10) pp.1760-4.

(39) Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ.* 2014; 348

(40) Granger CV, Dewis LS, Peters NC, Sherwood CC, Barrett JE. Stroke rehabilitation: analysis of repeated Barthel index measures. *Arch Phys Med Rehabil.* 1979; 60(1) pp.14-7.

(41) The National Audit of Stroke Care Research Team. *Irish National Audit of Stroke Care (INASC)*. Dublin, Ireland: Irish Heart Foundation; 2008.

(42) Hannon N, Sheehan O, Kelly L, Marnane M, Merwick A, Moore A, et al. Stroke Associated with Atrial Fibrillation - Incidence and Early Outcomes in the North Dublin Population Stroke Study. *Cerebrovasc Dis.* 2009; 29(1) pp.43-9.

(43) Barry M. *Re: Issues in relation to prescribing safety of New Oral AntiCoagulants (NOACs).* 2014, [Online]. Available from: www.hse.ie/eng/about/Who/clinical/natclinprog/medicinemanagementprogramme/NOACs.pdf. Accessed on: 12 May 2015.

(44) Smyth B, Marsden P, Corcoran R, Walsh R, Brennan C, McSharry K, Clarke J, Kelly PJ, and Harbison J. *Feasibility of opportunistic screening for atrial fibrillation in a rural area with low population density [Unpublished Draft]*. 2015.

(45) Robson J, Dostal I, Mathur R, Sohanpal R, Hull S, Antoniou S, et al. Improving anticoagulation in atrial fibrillation: observational study in three primary care trusts. *Br J Gen Pract.* 2014; 64(622) p.e275-e281.

(46) Chen HS, Wen JM, Wu SN, Liu JP. Catheter ablation for paroxysmal and persistent atrial fibrillation. *Cochrane Database of Systematic Reviews.* 2012;

(47) Aguilar M, I, Hart R. Antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews.* 2005;

(48) Aguilar M, I, Hart R. Oral anticoagulants for preventing stroke in patients with non-valvular atrial fibrillation and no previous history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews.* 2005;

(49) Aguilar M, I, Hart R, Pearce LA. Oral anticoagulants versus antiplatelet therapy for preventing stroke in patients with non-valvular atrial fibrillation and no history of stroke or transient ischemic attacks. *Cochrane Database of Systematic Reviews.* 2007;

(50) Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants

with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *The Lancet.* 2015; 383(9921) pp.955-62.

(51) Dogliotti A, Paolasso E, Giugliano RP. Current and new oral antithrombotics in non-valvular atrial fibrillation: a network meta-analysis of 79ΓÇà808 patients. *Heart.* 2014; 100(5) pp.396-405.

(52) Connolly SJ, Laupacis A, Gent M, Roberts RS, Cairns JA, Joyner C. Canadian Atrial Fibrillation Anticoagulation (CAFA) Study. *J Am Coll Cardiol.* 1991; 18(2) pp.349-55.

(53) Gullov AL, Koefoed BG, Petersen P, Pedersen TS, Andersen ED, Godtfredsen J, et al. Fixed minidose warfarin and aspirin alone and in combination vs adjusted-dose warfarin for stroke prevention in atrial fibrillation: Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study. *Arch Intern Med.* 1998; 158(14) pp.1513-21.

(54) Pengo V, Zasso A, Barbero F, Banzato A, Nante G, Parissenti L, et al. Effectiveness of fixed minidose warfarin in the prevention of thromboembolism and vascular death in nonrheumatic atrial fibrillation. *Am J Cardiol.* 1998; 82(4) pp.433-7.

(55) Reynolds MW, Fahrbach K, Hauch O, Wygant G, Estok R, Cella C, et al. Warfarin anticoagulation and outcomes in patients with atrial fibrillation: a systematic review and metaanalysis. *Chest.* 2004; 126(6) pp.1938-45.

(56) RYAN F, BYRNE S, O'Shea S. Randomized controlled trial of supervised patient self-testing of warfarin therapy using an internet-based expert system. *Journal of Thrombosis and Haemostasis.* 2009; 7(8) pp.1284-90.

(57) Molony S. *Warfarin treatment - Getting the balance right*. Forum . 2010. ICGP.

(58) Hylek EM, Go AS, Chang Y, Jensvold NG, Henault LE, Selby JV, et al. Effect of Intensity of Oral Anticoagulation on Stroke Severity and Mortality in Atrial Fibrillation. *New England Journal of Medicine.* 2003; 349(11) pp.1019-26.

(59) O'Donnell M, Oczkowski W, Fang J, Kearon C, Silva J, Bradley C, et al. Preadmission antithrombotic treatment and stroke severity in patients with atrial fibrillation and acute ischaemic stroke: an observational study. *Lancet Neurol.* 2006; 5(9) pp.749-54.

(60) Hannon N, Arsava EM, Audebert HJ, Ay H, Crowe M, N+i Chr+¦in+in D, et al. Antithrombotic treatment at onset of stroke with atrial fibrillation, functional outcome, and fatality: a systematic review and meta-analysis. *Int J Stroke.* 2015; p.n/a.

(61) Ottosen TP, Svendsen ML, Hansen ML, Brandes A, Andersen G, Husted SE, et al. Preadmission oral anticoagulant therapy and clinical outcome in patients

hospitalised with acute stroke and atrial fibrillation. *Dan Med J.* 2014; 61(9) p.A4904.

(62) Indredavik B, Rohweder G, Lydersen S. Frequency and effect of optimal anticoagulation before onset of ischaemic stroke in patients with known atrial fibrillation. *J Intern Med.* 2005; 258(2) pp.133-44.

(63) Schwammenthal Y, Bornstein N, Schwammenthal E, Schwartz R, Goldbourt U, Tsabari R, et al. Relation of Effective Anticoagulation in Patients With Atrial Fibrillation to Stroke Severity and Survival (from the National Acute Stroke Israeli Survey [NASIS]). *The American Journal of Cardiology.* 2010; 105(3) pp.411-6.

(64) Mant J, Fitzmaurice DA, Hobbs FD, Jowett S, Murray ET, Holder R. Accuracy of diagnosing atrial fibrillation on electrocardiogram by primary care practitioners and interpretative diagnostic software: analysis of data from screening for atrial fibrillation in the elderly (SAFE) trial. *BMJ (Clinical research ed).* 2007;

(65) Trinity College Dublin. *The Irish Longitudinal Study on Ageing (TILDA).* 2015, [Online]. Available from: http://tilda.tcd.ie/. Accessed on: 13 July 2015.

(66) ESRI. *Living in Ireland Survey.* 2015, [Online]. Available from: www.ucd.ie/issda/data/livinginirelandlii/. Accessed on: 13 July 2015.

(67) Evans T. *Atrial fibrillation prevalence estimates.* 2015, [Online]. Available from: http://www.yhpho.org.uk/default.aspx?RID=207429.

(68) Boriani G, Laroche C, Diemberger I, Fantecchi E, Popescu MI, Rasmussen LH, et al. Asymptomatic Atrial Fibrillation: Clinical Correlates, Management, and Outcomes in the EORP-AF Pilot General Registry. *The American Journal of Medicine.* 2015; 128(5) pp.509-18.

(69) Luengo-Fernandez R, Gray AM, Bull L, Welch S, Cuthbertson F, Rothwell PM. Quality of life after TIA and stroke: ten-year results of the Oxford Vascular Study. *Neurology.* 2013; 81(18) pp.1588-95.

(70) Singer RB. Pitfalls of inferring annual mortality from inspection of published survival curves. *J Insur Med.* 1994; 26(3) pp.333-8.

(71) Poon MT, Fonville AF, Al-Shahi SR. Long-term prognosis after intracerebral haemorrhage: systematic review and meta-analysis. *J Neurol Neurosurg Psychiatry.* 2014; 85(6) pp.660-7.

(72) Dennis MS, Burn JP, Sandercock PA, Bamford JM, Wade DT, Warlow CP. Long-term survival after first-ever stroke: the Oxfordshire Community Stroke Project. *Stroke.* 1993; 24(6) pp.796-800.

(73) Fogelholm R, Murros K, Rissanen A, Avikainen S. Long term survival after primary intracerebral haemorrhage: a retrospective population based study. *J Neurol Neurosurg Psychiatry.* 2005; 76(11) pp.1534-8.

(74) Hillen T, Coshall C, Tilling K, Rudd AG, McGovern R, Wolfe CDA. Cause of Stroke Recurrence Is Multifactorial: Patterns, Risk Factors, and Outcomes of Stroke Recurrence in the South London Stroke Register. *Stroke.* 2003; 34(6) pp.1457-63.

(75) Schlegel D, Kolb SJ, Luciano JM, Tovar JM, Cucchiara BL, Liebeskind DS, et al. Utility of the NIH Stroke Scale as a predictor of hospital disposition. *Stroke.* 2003; 34(1) pp.134-7.

(76) Ahmed R, Zuberi BF, Afsar S. Stroke scale score and early prediction of outcome after stroke. *J Coll Physicians Surg Pak.* 2004; 14(5) pp.267-9.

(77) Adams HP, Jr., Davis PH, Leira EC, Chang KC, Bendixen BH, Clarke WR, et al. Baseline NIH Stroke Scale score strongly predicts outcome after stroke: A report of the Trial of Org 10172 in Acute Stroke Treatment (TOAST). *Neurology.* 1999; 53(1) pp.126-31.

(78) Ara R, Brazier JE. Using Health State Utility Values from the General Population to Approximate Baselines in Decision Analytic Models when Condition-Specific Data are Not Available. *Value in Health.* 2011; 14(4) pp.539-45.

(79) Thrall G, Lane D, Carroll D, Lip GY. Quality of life in patients with atrial fibrillation: a systematic review. *Am J Med.* 2006; 119(5) pp.448-19.

(80) Chung EH, Pursell I, King DR, Mounsey JP, Schwartz JD, Kumar P, et al. Minimally symptomatic patients with atrial fibrillation are actually moderately symptomatic and have significant symptom reduction with rhythm control. *Heart Rhythm.* 2013; 10(5) p.S388.

(81) Sorensen SV, Kansal AR, Connolly S, Peng S, Linnehan J, Bradley-Kennedy C, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in atrial fibrillation: a Canadian payer perspective. *Thromb Haemost.* 2011; 105(5) pp.908-19.

(82) Sullivan PW, Arant TW, Ellis SL, Ulrich H. The cost effectiveness of anticoagulation management services for patients with atrial fibrillation and at high risk of stroke in the US. *Pharmacoeconomics.* 2006; 24(10) pp.1021-33.

(83) Savelieva I, PAQUETTE M, Dorian P, LUDERITZ B, CAMM A. Quality of life in patients with silent atrial fibrillation. *Heart.* 2001; 85(2) pp.216-7.

(84) Radholm K, +ûstgren CJ, Alehagen U, Falk M, Wressle E, Marcusson J, et al. Atrial fibrillation (AF) and co-morbidity in elderly. A population based survey of 85 years old subjects. *Archives of Gerontology and Geriatrics.* 2011; 52(3) p.e170-e175.

(85) Roalfe AK, Bryant TL, Davies MH, Hackett TG, Saba S, Fletcher K, et al. A cross-sectional study of quality of life in an elderly population (75 years and over) with atrial fibrillation: secondary analysis of data from the Birmingham Atrial Fibrillation Treatment of the Aged study. *Europace.* 2012; 14(10) pp.1420-7.

(86) Freeman JV, Zhu RP, Owens DK, Garber AM, Hutton DW, Go AS, et al. Cost-Effectiveness of Dabigatran Compared With Warfarin for Stroke Prevention in Atrial Fibrillation. *Annals of Internal Medicine.* 2011; 154(1) pp.1-11.

(87) Gage BF, Cardinalli AB, Owens DK. The effect of stroke and stroke prophylaxis with aspirin or warfarin on quality of life. *Archives of Internal Medicine.* 1996; 156(16) pp.1829-36.

(88) O'Brien CL, Gage BF. Costs and effectiveness of ximelagatran for stroke prophylaxis in chronic atrial fibrillation. *JAMA.* 2005; 293(6) pp.699-706.

(89) Tengs TO, Lin TH. A meta-analysis of quality-of-life estimates for stroke. *Pharmacoeconomics.* 2003; 21(3) pp.191-200.

(90) CADTH. *Antithrombotic Agents for the Prevention of Stroke and Systemic Embolism in Patients With Atrial Fibrillation.* Ottawa, Ontario: Canadian Agency for Drugs and Technologies in Health; 2013.

(91) HIQA. *Guidelines for the Economic Evaluation of Health Technologies in Ireland*. Dublin, Ireland: Health Information and Quality Authority; 2014.

(92) *Swiftbrook Medical Centre*. 2015, [Online]. Available from: www.swiftbrookmedical.ie/surgery_consultation_fees. Accessed on: 12 May 2015.

(93) *The Albany Clinic*. 2015, [Online]. Available from: www.albanyclinic.ie/prices.html. Accessed on: 12 May 2015.

(94) Primary Care and reimbursement Service (PCRS). *Circular no. 009/2013 - Reduction of payments to General Practitioners Regulations SI no 277 and 278.* 2013, [Online]. Available from: www.hse.ie/eng/staff/PCRS/circulars/FEMPI%202013.pdf. Accessed on: 12 May 2015.

(95) NCPE. Personal communication. 2015.

(96) HSE National Clinical Programme for Stroke. *Warfarin Clinic Survey*. Dublin, Ireland: Health Services Executive (HSE); 2012.

(97) PCRS. *PCRS Reimbursement Items.* 2015, [Online]. Available from: www.sspcrs.ie/druglist/pub. Accessed on: 12 May 2015.

(98) National Centre for Pharmacoeconomics (NCPE). *Guidelines for Inclusion of Drug Costs in Pharmacoeconomic Evaluations.* 2015, [Online]. Available from:

http://www.ncpe.ie/wp-content/uploads/2012/02/Final-Guidelines-for-Inclusion-of-Drug-Costs-in-Pharmacoeconomic-Evaluation-v1.13-180314.pdf. Accessed on: 22 May 2015.

(99) Lip GYH, Laroche C+, Dan GA, Santini M, Kalarus Z, Rasmussen LH, et al. Real-World Antithrombotic Treatment in Atrial Fibrillation: The EORP-AF Pilot Survey. *The American Journal of Medicine.* 2014; 127(6) pp.519-29.

(100) Yoon SS, Chang H, Kwon YD. Itemized Hospital Charges for Acute Cerebral Infarction Patients Influenced by Severity in an Academic Medical Center in Korea. *J Clin Neurol.* 2012; 8(1) pp.58-64.

(101) Chang KC, Tseng MC. Costs of Acute Care of First-Ever Ischemic Stroke in Taiwan. *Stroke.* 2003; 34(11) p.e219-e221.

(102) Central Statistics Office (CSO). *Consumer Price Index.* 2015, [Online]. Available from: www.cso.ie. Accessed on: 15 May 2015.

(103) Cotte FE, Chaize G, Kachaner I, Gaudin AF, Vainchtock A, Durand-Zaleski I. Incidence and Cost of Stroke and Hemorrhage in Patients Diagnosed with Atrial Fibrillation in France. *Journal of Stroke and Cerebrovascular Diseases.* 2014; 23(2) p.e73-e83.

(104) National Institute for Health and Clinical Excellence (NICE). *TA249: Dabigatran Etexilate for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation*. London, England: National Institute for Health and Care Excellence; 2012.

(105) Zheng Y, Sorensen SV, Gonschior AK, Noack H, Heinrich-Nols J, Sunderland T, et al. Comparison of the Cost-effectiveness of New Oral Anticoagulants for the Prevention of Stroke and Systemic Embolism in Atrial Fibrillation in a UK Setting. *Clinical Therapeutics.* 2014; 36(12) pp.2015-28.

(106) Health Services Executive (HSE). *Nursing Homes Support Scheme, a Fair Deal.* 2015, [Online]. Available from: www.hse.ie/nhss/. Accessed on: 18 May 2015.

(107) Health Services Executive (HSE). *Annual Report and Financial Statements 2013*. Dublin, Ireland: HSE; 2014.

(108) Citizens Information Board. *Community care services - Technical Aids.* 2015, [Online]. Available from: www.citizensinformation.ie/en/health/care_in_your_community/community_care_services.html. Accessed on: 18 May 2015.

(109) Dewey HM, Thrift AG, Mihalopoulos C, Carter R, Macdonell RA, McNeil JJ, et al. Informal care for stroke survivors: results from the North East Melbourne Stroke Incidence Study (NEMESIS). *Stroke.* 2002; 33(4) pp.1028-33.

(110) Hickenbottom SL, Fendrick AM, Kutcher JS, Kabeto MU, Katz SJ, Langa KM. A national study of the quantity and cost of informal caregiving for the elderly with stroke. *Neurology.* 2002; 58(12) pp.1754-9.

(111) Patel A, Knapp M, Evans A, Perez I, Kalra L. Training care givers of stroke patients: economic evaluation. *BMJ.* 2004; 328(7448) p.1102.

(112) van Exel NJ, Brouwer WB, van den BB, Koopmanschap MA, van den Bos GA. What really matters: an inquiry into the relative importance of dimensions of informal caregiver burden. *Clin Rehabil.* 2004; 18(6) pp.683-93.

(113) Tooth L, McKenna K, Barnett A, Prescott C, Murphy S. Caregiver burden, time spent caring and health status in the first 12 months following stroke. *Brain Inj.* 2005; 19(12) pp.963-74.

(114) Hervas A, Cabases J, Forcen T. [Cost of informal care for stroke victims in a non-institutionalized general population]. *Gac Sanit.* 2007; 21(6) pp.444-51.

(115) O'Brien AN, Wolf TJ. Determining work outcomes in mild to moderate stroke survivors. *Work.* 2010; 36(4) pp.441-7.

(116) Horgan F, Walsh M, Galvin R, Loughnane C. *Experiences and long-term needs reported by stroke survivors living in the community in Ireland*. Dublin, Ireland: National Disability Authority (NDA); 2014.

(117) Saeki S, Ogata H, Okubo T, Takahashi K, Hoshuyama T. Factors influencing return to work after stroke in Japan. *Stroke.* 1993; 24(8) pp.1182-5.

(118) Saeki S, Ogata H, Okubo T, Takahashi K, Hoshuyama T. Return to work after stroke. A follow-up study. *Stroke.* 1995; 26(3) pp.399-401.

(119) Saeki S, Toyonaga T. Determinants of early return to work after first stroke in Japan. *J Rehabil Med.* 2010; 42(3) pp.254-8.

(120) Tanaka H, Toyonaga T, Hashimoto H. Functional and occupational characteristics predictive of a return to work within 18 months after stroke in Japan: implications for rehabilitation. *Int Arch Occup Environ Health.* 2014; 87(4) pp.445-53.

(121) Wozniak MA, Kittner SJ. Return to work after ischemic stroke: a methodological review. *Neuroepidemiology.* 2002; 21(4) pp.159-66.

(122) ILO. *International Labour Organisation.* 2015, [Online]. Available from: www.ilo.org. Accessed on: 18 May 2015.

(123) CSO. *Central Statistics Office (Ireland).* 2015, [Online]. Available from: www.cso.ie. Accessed on: 18 May 2015.

(124) Jorgensen HS, Nakayama H, Reith J, Raaschou HO, Olsen TS. Acute stroke with atrial fibrillation. The Copenhagen Stroke Study. *Stroke.* 1996; 27(10) pp.1765-9.

(125) Hannon N, Daly L, Murphy S, Smith S, Hayden D, Ni Chroinin D, et al. Acute Hospital, Community, and Indirect Costs of Stroke Associated With Atrial Fibrillation: Population-Based Study. *Stroke.* 2014; 45(12) pp.3670-4.

(126) National Institute for Health and Clinical Excellence (NICE). *Atrial fibrillation: the management of atrial fibrillation*. London, England: NICE; CG180. 2014.

(127) Behan W, Molony D, Beamer C, Cullen W. Are Irish adult general practice consultation rates as low as official records suggest? A cross sectional study at six general practices. *Ir Med J.* 2013; 106(10) pp.297-9.

(128) *Blackrock Clinic*. 2015, [Online]. Available from: www.blackrock-clinic.ie/emergency-department/what-does-it-cost/. Accessed on: 24 June 2015.

(129) *Vista Primary Care*. 2015, [Online]. Available from: www.vistaprimarycare.ie/echocardiogram.html. Accessed on: 24 June 2015.

(130) *Clane General Hospital*. 2015, [Online]. Available from: www.clanehospital.ie/services/open-access-cardiology.303.html. Accessed on: 24 June 2015.

(131) Rietbrock S, Heeley E, Plumb J, van ST. Chronic atrial fibrillation: Incidence, prevalence, and prediction of stroke using the Congestive heart failure, Hypertension, Age >75, Diabetes mellitus, and prior Stroke or transient ischemic attack (CHADS2) risk stratification scheme. *Am Heart J.* 2008; 156(1) pp.57-64.

(132) Miyasaka Y, Barnes ME, Gersh BJ, Cha SS, Bailey KR, Abhayaratna WP, et al. Secular trends in incidence of atrial fibrillation in Olmsted County, Minnesota, 1980 to 2000, and implications on the projections for future prevalence. *Circulation.* 2006; 114(2) pp.119-25.

(133) Sudlow M, Thomson R, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet.* 1998; 352(9135) pp.1167-71.

(134) National Treatment Purchase Fund (NTPF). *National outpatient wait list numbers.* 2015, [Online]. Available from: www.ntpf.ie/home/outpatient.htm. Accessed on: 8 June 2015.

(135) Keach JW, Bradley SM, Turakhia MP, Maddox TM. Early detection of occult atrial fibrillation and stroke prevention. *Heart.* 2015;

(136) Healey J. *NCT01938248: Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation (ARTESiA).* 2015,

[Online]. Available from: https://clinicaltrials.gov/ct2/show/NCT01938248. Accessed on: 29 June 2015.

(137) Quinn FR, Gladstone D. Screening for undiagnosed atrial fibrillation in the community. *Curr Opin Cardiol.* 2014; 29(1) pp.28-35.

(138) Friberg L, Engdahl J, Frykman V, Svennberg E, Levin LA, Rosenqvist M. Population screening of 75- and 76-year-old men and women for silent atrial fibrillation (STROKESTOP). *Europace.* 2013;

(139) National Institute for Health Research (NIHR). *HTA - 14/141/01: Screening Strategies for Atrial Fibrillation: A Systematic Review and Cost-Effectiveness Analysis.* 2015, [Online]. Available from: http://www.nets.nihr.ac.uk/projects/hta/1414101. Accessed on: 8 June 2015.

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