

How can epidemiological studies help us to prevent stroke? The example of atrial fibrillation

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Introduction

Stroke disease is a major cause of morbidity and mortality in the UK, with approximately 100,000 first ever strokes in Britain each year [1]. Stroke patients may occupy up to 20% of beds on acute general medical and geriatric wards [2]. In many western industrialized countries the mortality from stroke is falling, although questions remain as to the explanations for this and whether incidence is similarly falling [3, 4]. Nonetheless, with an ageing population the overall impact of stroke may continue to rise [5] and stroke is an eminently preventable disease, as shown by population trends and intervention studies.

Epidemiology is an applied as well as an academic discipline. Epidemiology is also the primary discipline underlying the public health and population perspective on health improvement. This review describes the value of epidemiological study within a public health perspective as it relates to stroke prevention, using the specific example of atrial fibrillation.

In order to be able to prevent stroke, we need to:

- (i) Understand factors associated with the incidence of stroke (risk factors) and have a feel for their contribution as causal (aetiological) factors.
- (ii) Know the extent of the contribution of individual causal factors and any interactions that may exist.
- (iii) Understand these issues at both an individual and population level.

Thus we need to understand the relative and absolute contribution of different risk factors to the risk (incidence) of stroke, such that we can identify which might be the most important risk factor for an individual patient at risk of stroke and advise accordingly. In addition, we need an understanding of which risk factors contribute most to the population burden of stroke (population attributable risk) since this knowledge will

help us to plan health policy aimed at reducing the population burden of the disease.

Epidemiology is ‘the study of the distribution and determinants of health related states or events in specified populations, and the application of this study to the control of health problems’ [6]. Put more simply, epidemiology is the science that makes sense of the frequency and patterns of disease. Alongside this, public health practice is concerned with the measurement of the health status of populations, the promotion of health, the prevention of disease, and the analysis and evaluation of health services [7].

In the UK, with the recent emphasis on health needs assessment and commissioning of services to meet those needs, including a central role for public health, we have seen the development of different models of needs assessment. The most widely applied is the epidemiologically-based health needs assessment model proposed by Stevens and Raftery [8]. This brings together an understanding of the *epidemiology* of the problem (within the population of interest), an understanding of the *effectiveness* of interventions (which range from individual patient-based treatments to population-based interventions such as health promotion programmes), and the availability and delivery of *services* to meet identified needs.

Epidemiological study to support this approach requires an understanding of the incidence and prevalence of the disease in the community, as well as an understanding of the distribution of severity of disease and its impact on individuals, the natural history of disease, and remediable risk factors to help prevent the incidence and progression of the problem. An understanding of effectiveness of treatments or health services requires a critical and systematic appraisal of the evidence base for interventions. A review of services is undertaken to determine the level of availability of facilities to deliver health care and health promotion, as well as the degree of implementation of effective interventions.

Atrial fibrillation as a risk factor for stroke

We have long known that atrial fibrillation is associated with an increased risk of stroke. One of the most comprehensive and detailed cohort studies exploring risk factors for cardiovascular and cerebrovascular disease has been the Framingham study [9–12]. This study has demonstrated that atrial fibrillation increases the risk of stroke approximately five fold, with an average individual risk of stroke of 5% per year. [10, 11] One of the primary aims of this study was to develop predictive equations, which would help calculate and communicate an individual's risk of developing cardiovascular disease, and hence contribute to effective prevention at both population and individual levels. The influence of this study has been immense.

Whilst atrial fibrillation associated with rheumatic valvular heart disease or valve replacement has an even higher risk of stroke [13], at a population level the most important contribution remains that of non-valvular atrial fibrillation, at least in westernised developed countries, where rheumatic valvular heart disease has become increasingly rare.

It is thought that the aetiology of stroke associated with atrial fibrillation is related to disturbed blood flow and stasis leading to the development of clots within the atria, which may then break off and pass into the cerebral circulation, causing thrombo-embolic stroke. Evidence for this has recently been strengthened by Doppler studies demonstrating small clots arising from patients in atrial fibrillation and detectable within the carotid circulation [14].

Subsequent to the initial demonstration of increased risk of stroke in non-valvular atrial fibrillation, we have gradually developed a more detailed understanding of how the risk of stroke in an individual depends upon the presence or absence of other clinical variables. Much of this understanding has come from the control arms of large randomized controlled trials of interventions to prevent stroke in atrial fibrillation [15, 16], but is very much consistent with the early data from Framingham and the Framingham equation for stroke [12, 17] and with a recent analysis of US peer review organization data sets [18]. The key features which increase the risk of stroke in patients with atrial fibrillation include increasing age, hypertension, diabetes, sex (higher in women), left ventricular dysfunction, a past history of stroke or TIA, and associated ischaemic heart disease. Some studies have demonstrated specific echocardiographic features associated with atrial fibrillation, but other than left-ventricular dysfunction their independent role is still open to debate.

Hence, there is strong epidemiological evidence from high quality prospective cohort studies, subsequently enhanced by further observational data associated with trials, that demonstrates the increased risk of stroke in patients with non-valvular atrial fibrillation. Variation in the base line risk associated with other clinical features is demonstrated in Figures 1 and 2 drawn from the

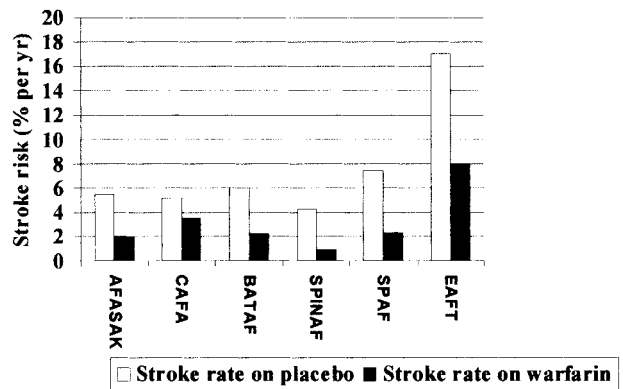


Figure 1. Stroke risk from results of trials of warfarin showing the absolute risk in the treatment and control arms. AFASAK=Copenhagen atrial fibrillation, aspirin and anticoagulation study. CAFA=Canadian atrial fibrillation and anticoagulation study. BAATAF=Boston area anticoagulation trial for atrial fibrillation. SPINAF=Stroke prevention in Non-rheumatic atrial fibrillation. SPAF=Stroke prevention in atrial fibrillation study. EAFT=European atrial fibrillation trial (a trial of secondary prevention including patients with TIA and minor stroke).

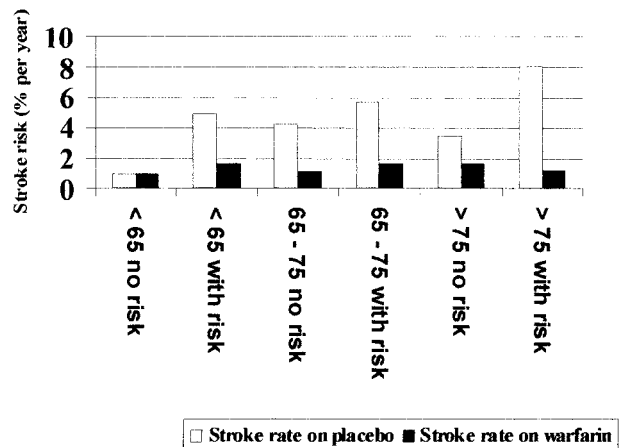


Figure 2. Age and sex stratified risk of stroke in SPAF trial for treatment and control arms.

initial trials of anticoagulation and aspirin in patients with atrial fibrillation.

Contribution of atrial fibrillation to stroke incidence

Not only does atrial fibrillation increase the risk of stroke, it is also apparent that strokes in patients with atrial fibrillation are more severe than those in patients in sinus rhythm. They are more likely to be severe or fatal (39% vs 28%), have higher 30 day and one year mortality (25% vs 14%, 63% vs 34%), and have higher stroke recurrence rates at one year (23% vs 8%). Survivors are also more likely to be disabled as a result

of their stroke [19]. Given the prevalence of atrial fibrillation in the US, the attributable risk of stroke was calculated as 1.5% for those in the 50–59 age group, rising to 23.5% for those aged 80–89, i.e. in the older age group up to a quarter of strokes might be associated with atrial fibrillation [11].

Interventions to prevent atrial fibrillation-associated stroke

Whilst it has long been known that patients with atrial fibrillation associated with valvular heart disease or valve replacements could have their risk of stroke considerably reduced by warfarin anticoagulation, it is only in the last ten years that the effectiveness of warfarin and aspirin in preventing stroke in patients with non-valvular atrial fibrillation has been thoroughly investigated. By 1994, several large randomized controlled trials had been undertaken exploring the effectiveness of warfarin and aspirin in preventing stroke [20]. As well as demonstrating a consistent reduction in stroke risk across these studies, these studies also contributed to our understanding of the effect of other clinical risk factors on stroke risk in patients with atrial fibrillation [16]. Equally important, these studies demonstrated that whilst the relative reduction is fairly consistent across all risk groups, the absolute risk reduction is dependent upon the baseline risk in the control group in the various trials or within sub-groups within the trials (Figures 1 and 2).

A recent excellent meta-analysis has summarized our knowledge base on warfarin and anti-platelet agents in this field [21]. Warfarin leads to a 62% (95% confidence interval, 48–72%) relative risk reduction in stroke in those with non-valvular atrial fibrillation, whilst aspirin leads to a 22% (2–38%) relative risk reduction. Furthermore, comparison of warfarin with aspirin demonstrated that warfarin produces a 36% (14–52%) relative risk reduction compared to aspirin, thus emphasising the greater absolute effectiveness of warfarin.

The absolute risk reduction depends on the baseline risk of stroke in an individual or population. This is reflected in calculations of numbers needed to treat. Thus, we would need to treat 37 ‘average’ patients with atrial fibrillation for one year to prevent one stroke, but if we consider patients over 75 with additional risk factors the number needed to treat falls to approximately 14. It is perhaps worth putting this in the context of other interventions associated with stroke prevention. Thus, results from the European Working Party on High Blood Pressure in the Elderly trial would require 142 patients to be treated for one year to prevent one stroke [22], whilst the MRC mild hypertension study, which incorporated patients with a diastolic blood pressure of over 100, gives a number to treat of 833 [23]. For patients with previous stroke and TIA, aspirin therapy prevents non-fatal stroke recurrence with a number needed to treat of 40 [24].

Thus, warfarin effectiveness in stroke prevention compares very favourably with other interventions that are widely implemented and promoted. Furthermore, Hart’s meta-analysis suggests that warfarin may be more effective in preventing disabling stroke, further underlining its clinical potential [21].

What is the prevalence and treatment of atrial fibrillation in the United Kingdom?

In order to understand the health needs within a population we need to have locally relevant epidemiological data. In this example the most important is the prevalence and current treatment levels of patients with atrial fibrillation within the UK. Data on atrial fibrillation prevalence and incidence are available from American and Australasian studies, but a large community-based prevalence study had not been undertaken in the UK until our study was completed in 1996 [25]. This showed that atrial fibrillation is indeed common in the population over 65, with an overall prevalence of 4.7%, rising to 10% in men 75 and over (Table 1). Furthermore, only 23% of patients identified in this prevalence study were currently taking warfarin. At the time of the study there were several sources of guidance for patient selection for warfarin anti-coagulation. Table 2 shows the proportion of patients in our prevalent population that would have been treated with warfarin given three different risk stratification schemes available at the time. Regardless of the validity of these schemes, it is clearly apparent that at that time the level of treatment within the population was considerably lower than might be expected; patients who might benefit from therapy were not being treated. This in itself is a measure of service delivery suggesting under-utilization of an evidence-based treatment. Furthermore, recent studies suggest that under-utilization remains a problem, despite the growing evidence base and emphasis on implementation [26].

Why is warfarin under-used?

There have been a number of reviews and studies that have explored reasons for under-utilization of warfarin in patients with atrial fibrillation [27]. Potential reasons

Table 1. Age and sex stratified prevalence of atrial fibrillation in a representative UK population

	Number of subjects seen	Prevalence (95% confidence intervals)
Females		
65–74 years	749	2.4% (± 1.0%)
75+ years	1157	5.6% (± 1.4%)
Males		
65–74 years	826	3.5% (± 1.2%)
75+ years	946	10.0% (± 1.8%)
Total	3678	4.7% (± 0.6%)

Table 2. Proportion of prevalent community cases of patients with atrial fibrillation (and 95% confidence intervals) with no irreversible contraindication to anti-coagulants and with risk factors for stroke, using accepted risk stratification schemes, compared to the proportion of those with atrial fibrillation currently anticoagulated

	All subjects
Pooled analysis	49%
(% with one or more risk factors)	41–57%
SPAF analysis	61%
(% with one or more risk factors)	53–69%
SPAF 3 analysis	41%
(% meeting trial inclusion criteria)	33–49%
Proportion currently taking warfarin	23%
	17–29%

The pooled analysis risk factors identified patients with a risk in excess of approximately 5% per annum and included a history of hypertension, cardiac failure, stroke or TIA, or diabetes. The SPAF study placebo arm identified patients with a risk in excess of 1% per annum with a history of stroke or thromboembolism, cardiac failure, hypertension; Left atrial enlargement beyond 2.5 cm/m² or left ventricular dysfunction on echocardiogram. The inclusion criteria for the SPAF 3 trial (high risk patients) were females aged 75 or greater, current systolic hypertension, recent heart failure or fractional shortening of 25% or less on M-mode echocardiography, history of stroke or thromboembolism.

range from lack of access of clinicians to the evidence base to enable appropriate advice to patients, through to concerns about the serious potential adverse effects of warfarin in older people. One example of a recognized service deficit lies in the use and availability of guidelines to support clinical practice. A survey in the Northern Region showed that only 6% of GPs had access to guidelines on anticoagulation, whilst 85% would have welcomed such guidelines [28]. However, a comprehensive national survey of available guidelines in 1996 not only demonstrated the scarcity of such guidelines, but also that the quality and range of guidelines available was hugely variable, with significant implications for patient therapy (Figure 3) [29]. Of particular concern

was the finding that the great majority of guidelines were not developed by any form of group process and did not incorporate systematic literature search or appraisal. Only one of the available guidelines could be classified as ‘evidence-based’ in that it incorporated an assessment of the strength of the evidence and graded its recommendations. Nonetheless, when we applied the 20 available guidelines to the first 100 community-based cases from our Northumberland prevalence study, anywhere between 13% and 100% of patients would have been recommended for treatment with warfarin. This variation was predominately due to variations in the recommendations and content of the guidelines, and not their clarity or ambiguity.

Can we produce better guidelines?

Given the dearth of available guidelines and the demand for them, we set out to develop guidelines using a systematic review of the evidence base. We decided to develop ‘evaluative’ guidelines, which not only take account of the evidence of effectiveness of the interventions, but also combine evidence of effectiveness, risk and harm with patient values and costs, thus developing, in effect, a ‘balance sheet’ to facilitate optimal decisions where there are alternative treatment choices. Whilst this approach to guidelines development has been suggested as appropriate by Woolf and Eddy, there had been little actual progress made in this field [30, 31]. The situation with warfarin anticoagulation appeared ideally suited to developing this guidelines technology further, given the wealth of epidemiological and effectiveness data available.

We decided to use a decision analytical approach to the development of guidelines, which involves incorporating probabilistic data (both risk and effectiveness), alongside health state values derived from appropriate patients [32]. A full description of the guidelines and their development is available in the original report of the study, but it was feasible to develop evaluative guidelines in this clinical setting [33]. However, this was not without its challenges, and it is likely that developing such guidelines in other clinical settings will be less easy, not least because of the absence of good cohort-based epidemiological data [34].

The data used in the decision-analytical model is shown schematically in Figure 4. Briefly, we used a Markov decision analysis to model the decision on warfarin treatment of patients in atrial fibrillation, using systematic literature review and appraisal, supplemented by additional research. The ‘optimal’ strategy for any particular patient is the decision – treat or do not treat – that yields the highest expected utility over his/her remaining life expectancy. For each component we sought to derive the most reliable and valid data from the highest quality epidemiological and intervention study sources. For example, the baseline risk of stroke in atrial fibrillation was derived from the Framingham study [12],

Figure 3. Number of patients (n = 100) with atrial fibrillation for whom anticoagulant treatment would have been recommended according to each guideline evaluated.

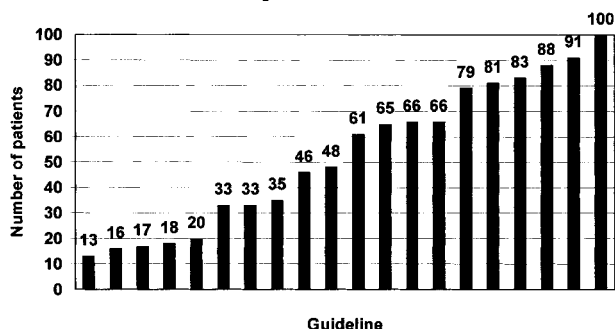


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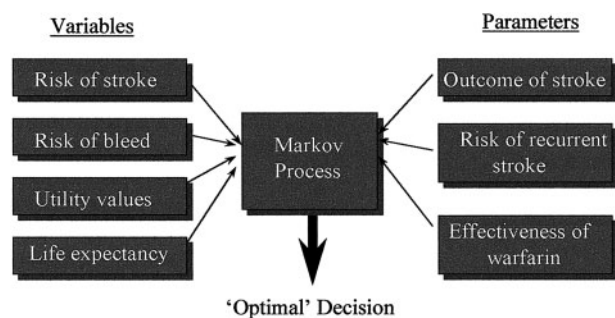


Figure 4. Components of the Markov decision analysis model.

in preference to data available from the pooled analysis of the control groups of randomized trials or the SPAF risk factor stratification schemes, both of which are derived from highly selected populations. To determine the risk of harm from warfarin (predominantly the risk of bleeding), we sought to identify a prospective inception cohort study of patients starting warfarin who were representative of the group of patients likely to be treated with non-valvular atrial fibrillation and monitored using an internationally accepted measure of anticoagulation control (the INR). Only one study met these stringent inclusion criteria, but this Italian study included 2,745 patients, with a mean follow-up of 267 days, monitored across multiple sites in routine clinical care [35]. This showed that the risk of major bleed was 1.1 per 100 patient years and the risk of minor bleed 6.2 per 100 patient years. This is valuable information, not least in the fact that it demonstrates that in routine clinical settings the risk of bleeding is comparable to that of the randomized controlled trials of warfarin. This is a particularly important observation since many of the expressed concerns about the risk-benefit ratio for warfarin anti-coagulation are based upon a view that the level of monitoring and degree of control provided in randomized controlled trials cannot be replicated in routine practice. Indeed, if this were the case, the risk-benefit ratio would change, but the results from the Paloretti study suggest otherwise. A recent further study has confirmed the trial efficacy and anticoagulation control with warfarin in routine practice in the UK [36].

The product of this evaluative guidelines project development was a flowchart and look-up tables to support clinical decisions on advising patients on warfarin anti-coagulation based upon average (median) health state values derived from a population study [32]. However, it was apparent, and incorporated into the guidance on use of the guidelines, that there was considerable inter-individual variation in the values that patients assign to relevant health states [37]. Furthermore, the optimal decision derived for any one patient from the decision-analytical model was highly sensitive to the patients' values and preferences. In particular, the disutility of warfarin therapy had a marked impact on the optimal decision.

For this reason, we recognized that recommendations based on median values might not appropriately reflect the individual views of each patient. We therefore set out to develop a means of applying the evidence-base to individual patients within the clinical consultation.

Applying evidence to individual patients

There has been a major shift in thinking about the delivery of health services, with a move away from paternalistic models of decision-making and health service delivery towards greater public and patient involvement [38, 39]. In both shared and informed decision making, there is a need to communicate the risks and benefits of treatments effectively to patients and to engage them in the decision-making process [40].

In view of this paradigm shift in the clinical consultation, we sought to develop a computerized decision support tool derived from the decision analytical model which could be used in the clinical consultation between patient and clinician as part of a process of shared decision making. Full details are available elsewhere [41], but we can illustrate the potential value of epidemiological data in the setting of clinical interventions through one component of the tool which seeks to communicate individual risk. This was developed through extensive consultation with patients and clinicians using structured qualitative methods of semi-structured interviews and focus groups. This component of the tool incorporates data from the Framingham equation to allow the individual risk of stroke to be displayed after entry of individual clinical details (see Figure 5). As a result of consultation process, the risk is shown figuratively (using the smiley faces) and the nature of the risk is further demonstrated through the random allocation of the stroke events through the sea of faces. The base line risk is also shown numerically as a percentage, as it was clear that patient preferences for figurative or numerical presentation of data varied. It is also possible to show the risk broken down into fatal, severe and mild stroke.

The Framingham equation incorporates remediable risk factors other than atrial fibrillation, in particular hypertension and smoking. For that reason, stroke risk reduction following blood pressure control and/or smoking cessation can also be depicted alongside the effect of warfarin. This not only allows the clinician to discuss the impact of warfarin treatment on risk of stroke, but also the potential impact of smoking reduction and blood pressure treatment and control on this risk. This recognizes the multifactorial nature of stroke risk and helps initiate wider health promotion discussion i.e. the consultation is not simply restricted to discussion of warfarin treatment. The risk factor screen not only shows the reduction in stroke risk after warfarin treatment, but also depicts the risk of major bleed, again both figuratively and as a percentage (Figure 6). This is just one example of the use of high quality epidemiological and

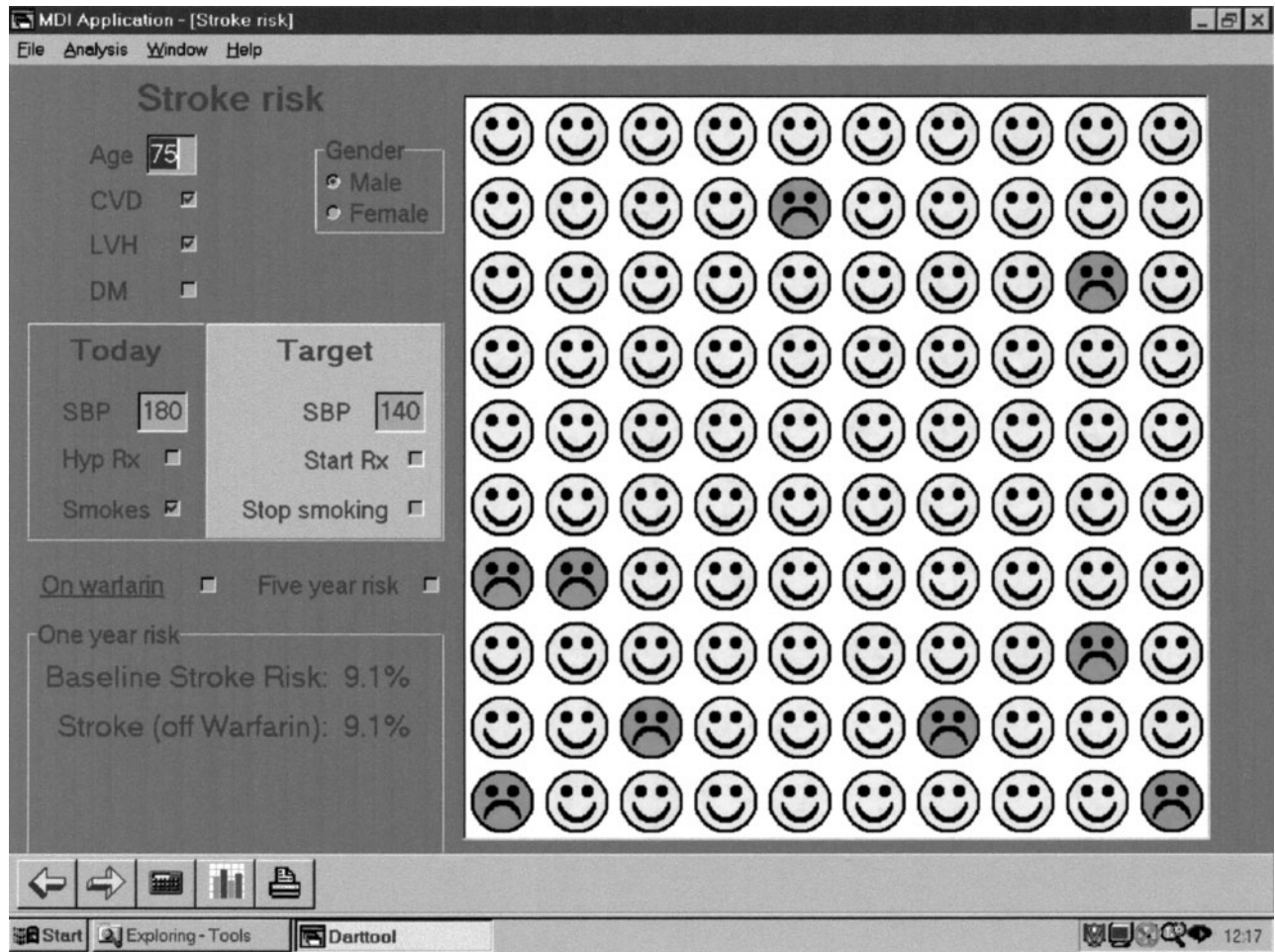


Figure 5. Data entry screen for discussing the individual risk of stroke with a patient.

clinical effectiveness data to communicate risks and benefits with patients in a clinical consultation.

Conclusions

This paper has discussed the potential value of epidemiological data for the prevention of stroke from a public health perspective, using the basic template of an epidemiologically based health needs assessment, and drawing upon a body of work on stroke prevention and atrial fibrillation, much of it undertaken in the north east of England. The value of epidemiological data has been demonstrated in a number of ways, from prevalence studies to determine the burden of disease in the population through to prospective cohort studies which allow predictive epidemiological data to be applied at a population or individual level to assess and communicate risk and benefit. Much of this discussion has centred on clinical interventions. This largely reflects the use of atrial fibrillation as the exemplar. A similar paper addressing smoking as a risk factor would also have necessarily incorporated other population-based interventions informed by epidemiological and effectiveness

data. Thus, for example, stroke prevention through smoking reduction would also need to take account of the effectiveness of fiscal policy on smoking cessation, issues of health promotion to support individual behaviour change, and the effectiveness of no-smoking policies in public places and the work place.

Ultimately, effective prevention of stroke is fundamentally dependent upon high quality data from epidemiological and intervention studies, thus informing the development of health policy as well as informing better individual clinical decisions. With the shift towards a culture of shared and informed decision-making, methods of incorporating this data in a way that is accessible and meaningful to both clinicians and patients is becoming increasingly important. Undoubtedly, one of the major challenges over forthcoming years will be further development of mechanisms for better informed decision-making, but this is likely to identify significant deficits in epidemiological data upon which such decisions can be supported [34]. The field of cardiovascular disease is relatively well served by high quality epidemiological studies, albeit some of these are becoming dated. In other settings, prospective natural history

Figure 6. Data entry screen for discussing with a patient the effect of warfarin anticoagulation on their individual risk of stroke and bleeding.

cohort studies are much less readily available and the dearth of such data may limit the capacity to support individual and population based decision-making.

Key points

- Epidemiological and public health perspectives are critical to disease prevention both for individual patients and at a population level.
- Prevention of stroke in atrial fibrillation illustrates the value of high quality epidemiological data.
- There are challenges to the appreciation, and communication, of risks and benefits of interventions for both clinicians and patients.
- Decision analysis and computer aided risk communication can support better access to epidemiological and effectiveness data, and better communication of clinical decisions.

References

1. Bamford J, Sandercock P, Dennis M, Burn J, Warlow C. A prospective study of acute cerebrovascular disease in the community: the Oxfordshire Community Stroke Project – 1981–1986. Incidence, case fatality rates and overall outcome at one year of cerebral infarction, primary intracerebral haemorrhage and subarachnoid haemorrhage. *J Neurol, Neurosurg Psychiatry* 1990; 53: 16–22.
2. Wade D, Wood V, Langton Hewer R. Use of hospital resources by acute stroke patients. *J R Coll Physicians Lond* 1985; 19: 48–52.
3. Bonita R, Stewart A, Beaglehole R. International trends in stroke mortality: 1970–1985. *Stroke* 1990; 21: 989–92.
4. Bonita R, Beaglehole R. The enigma of the decline in stroke deaths in the US. The search for an explanation. *Stroke* 1996; 27: 370–2.
5. Khaw KT. How many, how old, how soon? *Br Med J* 1999; 319: 1350–2.
6. Last JM. *A Dictionary of Epidemiology*. New York: Oxford University Press, 1995.
7. Department of Health. *Public Health in England*. London: HMSO, 1988.
8. Stevens A, Raftery J eds. *Health Care Needs Assessment: The Epidemiologically Based Needs Assessment Reviews*. Oxford: Radcliffe Medical Press Ltd., 1994.

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9. Wolf PA, Dawber TR, Thomas H Jr., Kannel WB. Epidemiologic assessment of chronic atrial fibrillation and risk of stroke: the Framingham study. *Neurology* 1978; 28: 973–7.
10. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation: a major contributor to stroke in the elderly. The Framingham Study. *Arch Intern Med* 1987; 147: 1561–4.
11. Wolf PA, Abbott RD, Kannel WB. Atrial fibrillation as an independent risk factor for stroke: the Framingham Study. *Stroke* 1991; 22: 983–8.
12. Wolf PA, D'Agostino RB, Belanger AJ, Kannel WB. Probability of stroke: a risk profile from the Framingham Study. *Stroke* 1991; 22: 312–8.
13. Askey JM, Bernstein S. The management of rheumatic heart disease in relation to systemic arterial embolism. *Prog Cardiovasc Dis* 1960; 3: 220–32.
14. Cullinane M, Wainwright R, Brown A, Monaghan M, Markus HS. Asymptomatic embolization in subjects with atrial fibrillation not taking anticoagulants: a prospective study. *Stroke* 1998; 29: 1810–5.
15. Hart RG, Pearce LA, McBride R, Rothbart RM, Asinger RW. Factors associated with ischemic stroke during aspirin therapy in atrial fibrillation: analysis of 2012 participants in the SPAF I-III clinical trials. The Stroke Prevention in Atrial Fibrillation (SPAF) Investigators. *Stroke* 1999; 30: 1223–9.
16. Hart RG, Halperin JL. Atrial fibrillation and stroke: concepts and controversies. *Stroke* 2001; 32: 803–8.
17. D'Agostino R, Wolf P, Belanger A, Kannel W. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. *Stroke* 1994; 25: 40–3.
18. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke – results from the National Registry of Atrial Fibrillation. *JAMA* 2001; 285: 2864–70.
19. Lin HJ, Wolf PA, Kelly-Hayes M *et al.* Stroke severity in atrial fibrillation. The Framingham Study. *Stroke* 1996; 27: 1760–4.
20. Anonymous. Risk factors for stroke and efficacy of antithrombotic therapy in atrial fibrillation. Analysis of pooled data from five randomized controlled trials. *Arch Intern Med* 1994; 154: 1449–57.
21. Hart RG, Benavente O, McBride R, Pearce LA. Antithrombotic Therapy To Prevent Stroke in Patients with Atrial Fibrillation: A Meta-Analysis. *Ann Intern Med* 1999; 131: 492–501.
22. Amery A, Birkenhäger W, Brixko P *et al.* Mortality and morbidity results from the European Working Party on High Blood Pressure in the Elderly Trial. *Lancet* 1985; 1: 1349–54.
23. Medical Research Council Working Party. MRC trial of treatment of mild hypertension: principal results. *Br Med J* 1985; 291: 97–104.
24. Antithrombotic Trialists' Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for the prevention of death, myocardial infarction and stroke in high risk patients. *Br Med J* 2002; 324: 71–86.
25. Sudlow M, Thomson RG, Thwaites B, Rodgers H, Kenny RA. Prevalence of atrial fibrillation and eligibility for anticoagulants in the community. *Lancet* 1998; 352: 1167–71.
26. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales, 1994–1998: analysis of data from the general practice research database. *Heart* 2001; 86: 284–8.
27. Bungard TJ, Ghali WA, Teo KK, McAlister FA, Tsuyuki RT. Why do patients with atrial fibrillation not receive warfarin? *Arch Intern Med* 2000; 160: 41–6.
28. Rodgers H, Sudlow M, Dobson R, Kenny RA, Thomson RG. Warfarin anticoagulation in primary care: a regional survey of present practice and clinicians' views. *Br J Gen Pract* 1997; 47: 309–10.
29. Thomson RG, McElroy H, Sudlow M. Guidelines on anticoagulant treatment in atrial fibrillation in Great Britain: variation in content and implications for treatment. *Br Med J* 1998; 316: 509–13.
30. Eddy DM. Assessing Health Practices and Designing Practice Policies: The Explicit Approach. Philadelphia: American College of Physicians, 1992.
31. Woolf S. Practice guidelines: a new reality in medicine 2: methods of developing guidelines. *Arch Intern Med* 1992; 152: 946–52.
32. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Decision analysis and guidelines for anticoagulant therapy to prevent stroke in patients with atrial fibrillation. *Lancet* 2000; 355: 956–62.
33. Thomson R, Parkin D, Eccles M, Sudlow M, Robinson A. Evaluative Development of Clinical Guidelines on the use of Treatments to Prevent Stroke Amongst Patients with Atrial Fibrillation for use in the Northern and Yorkshire Region. Newcastle: Department of Epidemiology and Public Health, Newcastle Medical School, 1997.
34. Hannaford PC, Owen-Smith V. Using epidemiological data to guide clinical practice: review of studies on cardiovascular disease and use of combined oral contraceptives. *Br Med J* 1998; 316: 984–7.
35. Palareti G, Leali N, Coccheri S *et al.* Bleeding complications of oral anticoagulant treatment: an inception-cohort, prospective collaborative study (ISCOAT). *Lancet* 1996; 348: 423–8.
36. Kalra L, Yu G, Perez I, Lakhani A, Donaldson N. Prospective cohort study to determine if trial efficacy of anticoagulation for stroke prevention in atrial fibrillation translates into clinical effectiveness. *Br Med J* 2000; 320: 1236–9.
37. Robinson A, Thomson R, Parkin D, Eccles M, Sudlow M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. *J Health Ser Res Pol* 2001; 6: 92–8.
38. Charles C, Whelan T, Gafni A. What do we mean by partnership in making decisions about treatment? *Br Med J* 1999; 319: 780–2.
39. Thomson R, Bowling A, Moss F. Engaging patients in decisions: a challenge to health care delivery and public health. *Qual Health Care* 2001; 10 (Suppl 1): i1.
40. Edwards A, Elwyn G. Understanding risk and lessons for clinical risk communication about treatment preferences. *Qual Health Care* 2001; 10 (Suppl 1): i9–i13.
41. Thomson RG, Robinson A, Greenaway J, Lowe P. Development and description of a decision analysis based decision support tool for stroke prevention in atrial fibrillation. *Qual Safety Health Care* 2002; 11: 25–31.