Because atrial fibrillation is associated with advanced age and obesity, its prevalence is increasing worldwide. New treatments such as ablation and left atrial occlusion may reduce the need for anticoagulants in highly selected patients with atrial fibrillation, but overall the use of anticoagulants will increase in the foreseeable future. In the linked study (doi:10.1136/bmj.d6333), Pink and colleagues assess the incremental costs and benefits of dabigatran etexilate versus warfarin in patients with non-valvular atrial fibrillation.

Until recently, warfarin and related vitamin K inhibitors have been the only oral anticoagulants available. Warfarin is cheap and effective, but it doubles the risk of haemorrhage, requires careful monitoring, and has many drug interactions. Compared with warfarin, dabigatran has a wide therapeutic index, so no monitoring or dose adjustment is needed (except in patients with renal disease). Dabigatran works by inhibiting thrombin directly, so its onset of action is rapid, unlike warfarin. To date, dabigatran is the only new oral anticoagulant approved for atrial fibrillation in several countries, including the United States. Thus, dabigatran has the potential to be widely prescribed.

The potential economic consequences of widespread use of dabigatran rather than warfarin are profound. For example, on the basis of Pink and colleagues’ data, if all of the approximately 760 000 British patients with atrial fibrillation took dabigatran (at £919.80 (€1051; $1471)/year), the drug cost would be £700m directly, so its onset of action is rapid, unlike warfarin. To date, dabigatran is the only new oral anticoagulant approved for atrial fibrillation in several countries, including the United States. Thus, dabigatran has the potential to be widely prescribed.

The potential economic consequences of widespread use of dabigatran rather than warfarin are profound. For example, on the basis of Pink and colleagues’ data, if all of the approximately 760 000 British patients with atrial fibrillation took dabigatran (at £919.80 (€1051; $1471)/year), the drug cost would be £700m.

The authors use a Markov decision analytical model to discount future events, to extrapolate from the two year RE-LY (Randomized Evaluation of Long-Term Anticoagulation Therapy) trial, and they compare various health states using a well accepted metric, quality adjusted life year (QALY). In the base case, they calculate an incremental cost effectiveness of £23 082 per QALY. The advantage of QALYs is that this metric provides a common currency to account for complications of atrial fibrillation and its prophylaxis. Clinicians may feel uncomfortable extrapolating from a two year trial to a lifetime horizon, but no long term data are available for dabigatran. This extrapolation is therefore needed for Pink and colleagues to calculate the downstream consequences of stroke and stroke prophylaxis.

Although stroke is the most feared consequence of atrial fibrillation, prevention of stroke also has serious risks. The most important risk of prophylaxis is haemorrhage, especially intracranial haemorrhage, which is lower for treatment with dabigatran than with warfarin. In RE-LY, rates of intracerebral haemorrhage (per 100 patient years) were 0.30 with dabigatran 150 mg twice daily and 0.74 with warfarin. By explicitly incorporating intracranial haemorrhage into their model, Pink and colleagues captured the treatment specific rates of intracranial haemorrhage and the clinical consequences.

Although intracranial haemorrhage is the most important risk of any anticoagulant, other risks need to be considered. Dabigatran can also cause bleeding at other sites and dyspepsia. Pink and colleagues accounted for the cost and utility decrements of bleeds by modelling them explicitly: they estimate the cost of a major bleed as £1685 and the disutility as 0.1385—not enough to alter cost effectiveness significantly. Besides dyspepsia, RE-LY initially reported an increased risk of myocardial infarction with dabigatran, but a reanalysis found that this trend was not statistically significant. Pink and colleagues chose to incorporate an increased risk of myocardial infarction into their model. Whether this inclusion improves accuracy depends on whether the lower rate of myocardial infarction with warfarin is a real effect, which seems likely. In summary, Pink and colleagues’ model incorporates the relevant health states needed to estimate cost effectiveness accurately.

To be valid, the decision model also needs to quantify risks, costs, and utilities accurately. When these parameters were compared with those from other studies (table), Pink and colleagues’ results were similar. Although the baseline stroke rate in Pink and colleagues’ study is slightly higher than in the comparator studies, all four studies examined a range of stroke rates and stratified their results appropriately.
These studies found that dabigatran was likely to be cost effective for patients at high risk of stroke (Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack (CHADS2) score of 3 or more), unless international normalised ratio (INR) control was excellent. For example, at a CHADS2 score of 3, Pink and colleagues calculated a cost of £15 895 per QALY for centres with average INR control. In contrast, all studies found that the cost per QALY gained was high in patients at low risk of stroke.

In practice, clinicians should consider additional factors when choosing treatment, such as patient preference and adherence. For patients with a strong aversion to INR monitoring, dabigatran will be more cost effective than in typical patients. In contrast, for patients with poor adherence to treatment, dabigatran will be less cost effective because it has a shorter half life than warfarin.

Competing interests: The author has completed the ICMJE uniform disclosure form at www.icmje.org/doi_disclosure.pdf (available on request from the corresponding author) and declares: the submitted work was supported by the NIH, grant R01 HL097036; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could have influenced the submitted work. Provenance and peer review: Commissioned; not externally peer reviewed.

1 Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV, et al. 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;285:2370-5.
2 Pink J, Lane S, Pirimohamed M, Hughes DA. Dabigatran etexilate versus warfarin in management of non-valvular atrial fibrillation in UK context: quantitative benefit-harm and economic analyses. BMJ 2011;343:d3033.
3 Gage BF, Fihn SD, White RH. Warfarin therapy for an octogenarian who has atrial fibrillation. Ann Intern Med 2001;134:465-74.
4 Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361:1139-51.
5 Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation 2011;123:2562-70.
6 Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? Am J Med 2010;123:785-9.
7 Freeman JN, 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. Ann Intern Med 2011;154:1-11.
8 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;105:908-19.

Cite this as: BMJ 2011;343:d6980

© BMJ Publishing Group Ltd 2011
# Table

| Key parameters                     | Pink et al<sup>3</sup> | Shah and Gage<sup>5</sup> | Freeman et al<sup>4</sup> | Sorensen et al<sup>6</sup> |
|------------------------------------|------------------------|---------------------------|---------------------------|---------------------------|
| Age at start (years)               | 67                     | 70                        | 65                        | 69                        |
| Stroke risk:                       |                        |                           |                           |                           |
| Warfarin*                          | 1.38                   | 1.19                      | 1.20                      | 0.88                      |
| Dabigatran (150 mg)*               | 0.84                   | 0.90                      | 0.92                      | 0.68                      |
| Haemorrhage risk:                  |                        |                           |                           |                           |
| Warfarin†                          | 3.31                   | 3.36                      | 4.10                      | 3.06                      |
| Dabigatran (150 mg)*†              | 3.04                   | 3.12                      | 3.41                      | 2.69                      |
| Utility:                           |                        |                           |                           |                           |
| Dabigatran                          | 0.998                  | 0.994                     | 0.994                     | 1.0                       |
| Warfarin                           | 0.987                  | 0.987                     | 0.987                     | 1.0                       |
| Cost of dabigatran (per year)‡     | £919.80                | $3284                     | $4745                     | $C1168                    |

*For CHADS<sub>2</sub> (Congestive heart failure, Hypertension, Age≥75 years, Diabetes mellitus, previous Stroke/transient ischaemic attack) score=2 or base-case (depending on study) with rates per 100 patient years.
†Haemorrhage rates are for major bleeds, including intracranial haemorrhages.
‡£1=$1.6=$C1.6.