MANAGING THROMBOEMBOLIC RISKS OF ATRIAL FIBRILLATION: CAN WE AFFORD INCREASED EFFICACY OF THE NOVEL ANTICOAGULANTS AND DEVICES?

Bela Merkely,[1] Eszter M. Vegh,[2] Attila Roka[2]

1. Director, Heart Center, Semmelweis University, Budapest, Hungary
2. Massachusetts General Hospital, Boston, MA, United States

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ABSTRACT

Ischaemic/embolic complications are the most common severe consequences of atrial fibrillation. Although chronic anticoagulation with warfarin has been available for decades, it was consistently shown to be underutilised; multiple drug interactions and dietary issues further complicate its use. Recently, several pharmacological and non-pharmacological alternatives have been shown to have an efficacy that is similar or slightly superior to warfarin. Novel anticoagulant agents (dabigatran, rivaroxaban, apixaban) have the advantage of a fixed dose, without the need of regular monitoring. Non-pharmacological options include left atrial appendage ligation or percutaneous closure. Although all these options are more expensive than warfarin, they have the potential of being more cost-effective – preventing very expensive complications or having less side-effects (such as haemorrhagic stroke), requiring less or no monitoring, and having fewer interactions with diet, thus, improving quality of life. Multiple studies of simulated cost-efficacy analyses have been published recently, addressing these questions, which will be reviewed in this paper. In the era of cost-conscious utilisation of healthcare resources, these new treatment options may increase the number of patients benefitting from effective therapies, reducing the number of ischaemic complications of atrial fibrillation.

Keywords: Atrial fibrillation, new oral anticoagulants, non-pharmacological treatment, cost efficiency.

THROMBOEMBOLIC RISK MANAGEMENT IN ATRIAL FIBRILLATION

Atrial fibrillation (AF) is the most common cardiac arrhythmia, affecting around 2.7 million people in the United States.[1] By 2050, this number will exceed 12 million in the United States alone. Despite advances in rhythm control strategies over the last decade, the majority of these patients today still live with either recurrent or chronic AF.

The main goal of therapy is to decrease the risk of complications arising from AF. On average, patients with AF have a mortality which is approximately double the age-appropriate population without AF. The risk for ischaemic stroke is increased 4 to 5-fold, however, the actual risk varies approximately 20-fold in the AF group. Various scoring methods have been developed for risk stratification, including $CHADS_2$ and CHA_2DS_2-VASc. For decades, the cornerstone of treatment was the vitamin K antagonist, warfarin (and a few of its derivatives in select countries). Primary prevention studies showed a consistent benefit trend of warfarin compared to placebo, revealing a relative risk reduction of 68%, a reduction in annual stroke rate from 4.5% to 1.4%, and 31 ischaemic strokes prevented each year for every 1,000 patients treated.[2] Warfarin was superior to antiplatelet agents in multiple controlled studies. However, warfarin is a difficult medication to take long-term, due to the need of regular monitoring (INR measurement), which adds to the cost of utilisation and impairs the patient's lifestyle. Less than 60% of patients have an INR that is consistently within the therapeutic

range – this was demonstrated in multiple clinical trials and did not change much overall, despite significant efforts to mitigate responsible factors (improving compliance, point-of-care INR checking and testing for genetic variability).[3]

NEW ORAL ANTICOAGULANT AGENTS

Dabigatran is a direct, competitive inhibitor of thrombin. It is administered in a prodrug form, which is promptly metabolised. It can be administered at a fixed dose and does not require coagulation monitoring. Pharmacokinetics are affected by renal function, as 80% is excreted renally. While it is not metabolised by the cytochrome P450 system, several drug interactions exist with p-glycoprotein inhibitors (dronedarone, amiodarone, verapamil, quinidine and ketoconazole increase dabigatran concentration). Dabigatran was evaluated in the Randomized Evaluation of Long-Term Anticoagulant Therapy (RE-LY) trial, which compared open-label warfarin with two fixed doses of dabigatran (110 or 150 mg twice daily, D110 and D150) in patients with AF and at least one additional stroke risk factor. For the primary outcome of stroke or systemic embolism, both D110 and D150 were non-inferior to warfarin (1.53%, 1.11% and 1.69% per year, respectively). The risk of haemorrhagic stroke was lower with both D110 and D150, compared to warfarin. A difference in overall survival did not attain statistical significance between the three groups; however, there was a trend towards the superiority of D150. The rate of gastrointestinal bleeding was higher with D150 (1.15%/year) than with D110 (1.12%) or warfarin (1.02%). Life-threatening bleeding was lower in the D150 (1.45%) and D110 groups (1.22%), compared to warfarin (1.80%) respectively. A similar trend was seen with intracranial bleeds. Rates of early drug discontinuation was higher with dabigatran (16% vs. 10% warfarin at 1 year), mostly due to dyspepsia.[4] The incidence of myocardial infarction was higher with D150 than with warfarin (relative risk increased by 33%) in a large meta-analysis of dabigatran trials.[5]

Rivaroxaban is a direct factor Xa inhibitor, which is metabolised by the CYP3A4 system. The ROCKET AF trial showed non-inferiority to warfarin in 14,264 patients with non-valvular AF who were at moderate to high risk of stroke (mean $CHADS_2$ score 3.5). 55% of patients had ischaemic events prior to enrolment. The primary endpoint was composite ischaemic/haemorrhagic stroke and systemic embolism (1.7%/year with rivaroxaban, 2.2%/year with warfarin, $p<0.001$ for non-inferiority). Lower rates of intracranial haemorrhage and fatal bleeding occurred in the rivaroxaban group than in the warfarin group, however, there was no difference in the composite major bleeding rate.[6]

Apixaban is also a direct and factor Xa inhibitor, which is metabolised by the CYP3A4 system. The half-life is shorter than rivaroxaban's (8-15 hours), requiring twice daily administration. The ARISTOTLE trial compared apixaban to warfarin for the prevention of stroke (ischaemic or haemorrhagic) or systemic embolisation among patients with AF and at least one additional risk factor for stroke. It achieved superiority regarding the primary endpoint (stroke or systemic embolisation, 1.27% for apixaban versus 1.6% for warfarin at 1.8 years). Main reduction ways observed in the rate of haemorrhagic strokes, while ischaemic or uncertain strokes were affected less. The study also showed a mortality benefit with apixaban (3.52% versus 3.94%).[7] So far there have been no large randomised, prospective studies completed comparing the new agents against each other.

COST-EFFECTIVENESS

The most common serious complications from AF itself or its management (ischaemic stroke, major bleeding) are expensive to treat, and even with optimal treatment may impair the quality of life. A new drug may be superior to an older one in several respects: it may be more effective in the treatment of the targeted condition, may have less side-effects or require less monitoring, etc. The new oral anticoagulant agents have at least the efficacy of warfarin in stroke prevention, with a simpler dose administration and no need for regular monitoring. Most of these factors can be accounted for and included in cost-efficacy analyses. For new treatments, a way to summarise these events is to calculate the incremental cost-effectiveness ratio (ICER) - the cost of an additional quality-adjusted life-year (QALY) over the old medication. This method integrates the cost of the treatment with the drug, differences in therapeutic efficacy (mortality and morbidy from the disease and its complications), side-effect profile (risk of bleeding issues), and other factors (such as cost of monitoring).

Most data regarding cost-efficiency of the new oral anticoagulant agents (NOACs) are from

models simulating drug use in patients with event rates and drug effects calculated from the large randomised studies. Several factors affect the results of such calculations: characteristics of the typicial patient profile (age, comorbidities), geographical setting (price of medications, costs regarding INR monitoring, travel), time horizon of simulated follow-up (may be required for up to 40 years after initiation of treatment), and the presumed event rates and their distribution. Most commonly, a Markov cohort model is generated to run the calculations on a large number of simulated patients.

Recently, several studies have been published regarding the NOACs. Most data are available for dabigatran and implies that it is a cost-effective alternative to warfarin.[8-19] Both rivaroxaban[18-20] and apixaban[19,21,22] have a smaller number of completed studies so far, however, the results are similarly encouraging. Comparison of the results from these simulated cost-effectiveness studies is often not straightforward due to the differences in models used, currencies used in the calculations, characteristics of simulated patients enrolled, and geographical settings (Figure 1). Overall, the cost for each QALY gained was less than $50,000 (USD) in the majority of these studies for the NOACs versus warfarin, which is the presumed threshold for willingness-to-pay in most simulation settings.

As this patient population is not homogenous, regarding the risk of thromboembolic complications, the cost-effectiveness should be stratified accordingly. Three studies reported models stratified by $CHADS_2$ score. In two simulations, higher $CHADS_2$ score resulted in more projected cost and those patients benefitted less from the NOAC therapy.[19,20] However Lee et al.[20] found rivaroxaban was cost-effective in the full range of patients. In a study of apixaban, two-way analysis for various baseline risks of stroke and ICH was performed. Apixaban was described as cost-effective in a wide range of those risk factors, and became more beneficial in higher $CHADS_2$ score values.[21] A Canadian comparative analysis with apixaban, rivaroxaban, warfarin, and two doses of dabigatran, showed that dabigatran 150 mg dominated (more QALYs, less cost) over

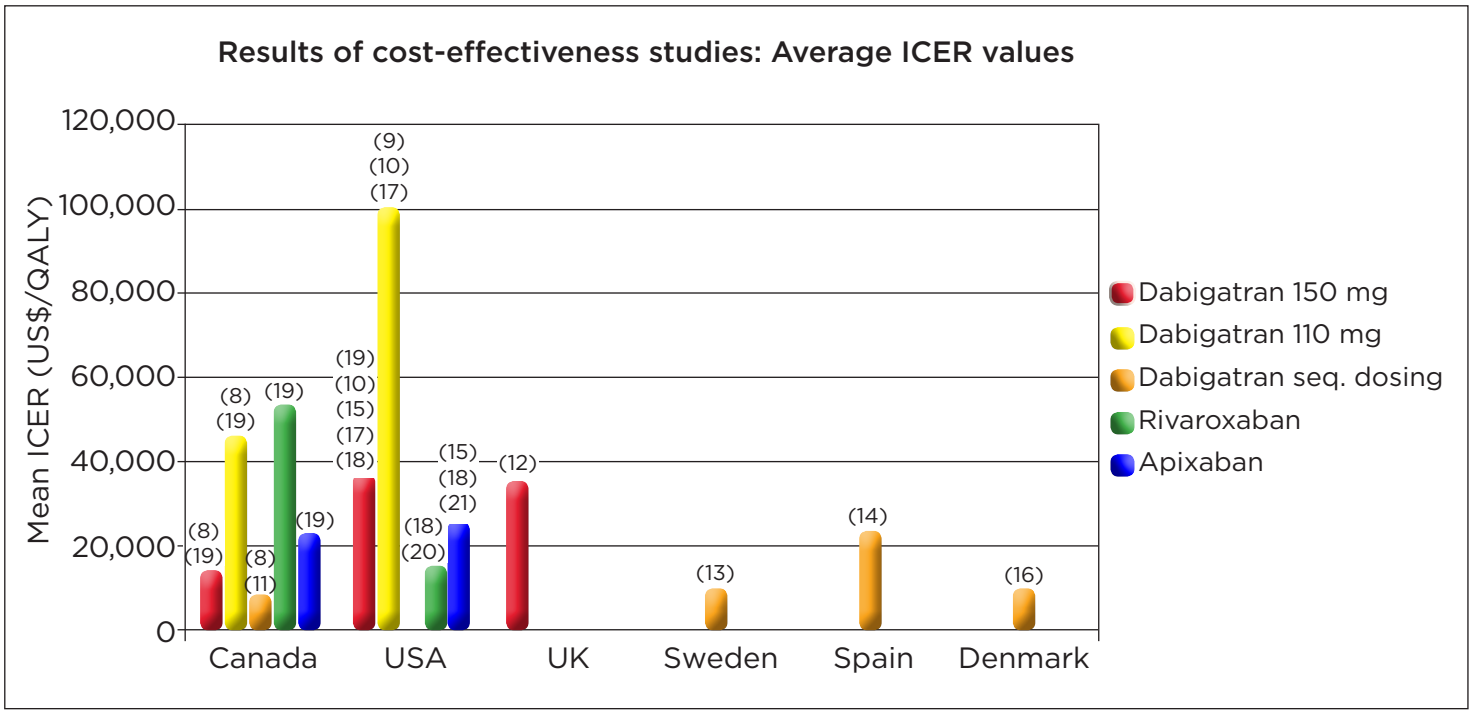

Figure 1. Cost-effectiveness of dabigatran, rivaroxaban and apixaban in studies simulated in various healthcare systems (versus warfarin).
The incremental cost-effectiveness ratio (ICER) is favourable; less than $50,000 (USD) for each quality-adjusted life year (QALY) increment for each medication in all healthcare systems. Dabigatran with sequential dosing (150 mg bid for patients <80 years, 110 mg bid for patients ≥80 years) was found to be highly cost efficient $25,000 (USD) or less per QALY increment).

most other agents, independent of the $CHADS_2$ score.[19]

Non-pharmacological prevention of stroke

Numerous novel devices and procedures are in various stages of clinical testing, aiming to prevent AF-related stroke on a non-pharmacological basis, by excluding the left atrial appendage from the circulation. Epicardial suture ligation (capturing the orifice with a snare and suturing it) does not leave any permanent endocardial implants.[23-25] Closing devices could be implanted with a catheter-based, transseptal approach under fluoroscopic and transoesophageal echocardiography (TOE) guidance, placing a self-expanding metal-frame covering the orifice of left atrial appendage.[26,27] The Watchman® Left Atrial Appendage (LAA) Closure Technology system (Atritech, Inc., Plymouth, MN) was compared to continuous oral anticoagulation with warfarin in the PROTECT AF prospective, unblinded, randomised trial: 707 patients with at least one risk factor (age >75 years, hypertension, heart failure, diabetes, or prior stroke/TIA) were enrolled and followed-up for a mean 2.3 years. The Watchman® device was non-inferior to warfarin (3.0% versus 4.3% per 100 patient-years for the primary endpoint: composite of stroke, systemic embolism and cardiovascular death). Safety events (pericardial tamponade, procedure-related stroke) were specific to the procedure itself, thus they were mostly observed in the device group;[28] however, the improvement of the quality of life was higher in this group at 12 months: the physical score improved in 34.9%, unchanged in 29.9% of the device treated patients, while 24.7% improved and 31.7% were unchanged in the warfarin group.[29] Single and multicentre studies confirmed the safety of the Amplatzer® Cardiac Plug (St. Jude Medical Inc, St. Paul, MN, USA).[27,30,31] In comparision to the Watchman device, implantation of the Amplatzer® device seems to have similar procedural time and complication rate.[32] The new Lifetech LAmbre™ Device was recently announced, that has a thinner sheath (8-10 French) for easier access and the ability to be recaptured and repositioned (Lifetech Scientific Corp., Shenzhen, China).[33]

Due to the relatively low number of overall procedures performed and a learning curve, which is steeper for devices than for new medications, cost-efficiency for non-pharmacological options may be significantly affected by these facts alone. Review of data will be required once more clinical experience is gained, allowing a more robust estimate of complications, which could be used to develop reliable models to estimate cost-efficacy (similarly to the NOACs).

CONCLUSION

The new oral anticoagulant agents have been shown to be cost-effective in a wide range of healthcare systems in simulated models. Given the significant expense of the management of atrial fibrillation and its complications, their use should be encouraged. The first feasibility and safety experiences with non-pharmacological treatments are promising, the Watchman® device was proven to be non-inferior to warfarin in the prevention of stroke. Further prospective studies, comparing the efficacy of the new agents against each other, may identify subsets of patients where one of the new agents or a non-pharmacological option may be more advantageous. Periodic review of registry data, may reveal specific issues or additional benefits that may affect the cost-effective utilisaton of these new treatment options.

Table 1. Treatment options for long-term prevention of stroke in non-valvular atrial fibrillation.

Pharmacological	Non-pharmacological
Warfarin	Epicardial suture ligation of atrial appendage
Dabigatran	Watchman® system
Rivaroxaban	Amplatzer® Cardiac Plug
Apixaban	Lifetech LAmbre™ device
ASA	

REFERENCES

1. Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation. 2013;127:e6-245.
2. Furie KL, Goldstein LB, Albers GW, Khatri P, Neyens R, Turakhia MP, et al. Oral antithrombotic agents for the prevention of stroke in nonvalvular atrial fibrillation: a science advisory for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2012;43:3442-53.
3. Connolly SJ, Pogue J, Eikelboom J, Flaker G, Commerford P, Franzosi MG, et al. Benefit of oral anticoagulant over antiplatelet therapy in atrial fibrillation depends on the quality of international normalized ratio control achieved by centers and countries as measured by time in therapeutic range. Circulation. 2008;118:2029-37.
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. Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med. 2012;172:397-402.
6. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91.
7. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92.
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.
9. 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. Ann Intern Med. 2011;154:1-11.
10. Shah SV, Gage BF. Cost-effectiveness of dabigatran for stroke prophylaxis in atrial fibrillation. Circulation. 2011;123:2562-70.
11. Kansal AR, Sorensen SV, Gani R, Robinson P, Pan F, Plumb JM, et al. Cost-effectiveness of dabigatran etexilate for the prevention of stroke and systemic embolism in UK patients with atrial fibrillation. Heart. 2012;98:573-8.
12. Pink J, Lane S, Pirmohamed 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:d6333.
13. Davidson T, Husberg M, Janzon M, Oldgren J, Levin LA. Cost-effectiveness of dabigatran compared with warfarin for patients with atrial fibrillation in Sweden. Eur Heart J. 2013;34:177-83.
14. González-Juanatey JR, Álvarez-Sabin J, Lobos JM, Martínez-Rubio A, Reverter JC, Oyagüez I, et al. Cost-effectiveness of dabigatran for stroke prevention in non-valvular atrial fibrillation in Spain. Rev Esp Cardiol (Engl Ed). 2012;65:901-10.
15. Kamel H, Johnston SC, Easton JD, Kim AS. Cost-effectiveness of dabigatran compared with warfarin for stroke prevention in patients with atrial fibrillation and prior stroke or transient ischemic attack. Stroke. 2012;43:881-3.
16. Langkilde LK, Bergholdt Asmussen M, Overgaard M. Cost-effectiveness of dabigatran etexilate for stroke prevention in non-valvular atrial fibrillation. Applying RE-LY to clinical practice in Denmark. J Med Econ. 2012;15:695-703.
17. You JH, Tsui KK, Wong RS, Cheng G. Cost-effectiveness of dabigatran versus genotype-guided management of warfarin therapy for stroke prevention in patients with atrial fibrillation. PLoS One. 2012;7:e39640.
18. Harrington AR, Armstrong EP, Nolan PEJ, Malone DC. Cost-effectiveness of apixaban, dabigatran, rivaroxaban, and warfarin for stroke prevention in atrial fibrillation. Stroke. 2013;44:1676-81.
19. Coyle D, Coyle K, Cameron C, Lee K, Kelly S, Steiner S, et al. Cost-effectiveness of new oral anticoagulants compared with warfarin in preventing stroke and other cardiovascular events in patients with atrial fibrillation. Value Health. 2013;16:498-506.
20. Lee S, Anglade MW, Pham D, Pisacane R, Kluger J, Coleman CI. Cost-effectiveness of rivaroxaban compared to warfarin for stroke prevention in atrial fibrillation. Am J Cardiol. 2012;110:845-51.
21. Lee S, Anglade MW, Meng J, Hagstrom K, Kluger J, Coleman CI. Cost-effectiveness of apixaban compared with aspirin for stroke prevention in atrial fibrillation among patients unsuitable for warfarin. Circ Cardiovasc Qual Outcomes. 2012;5:472-9.
22. Kamel H, Easton JD, Johnston SC, Kim AS. Cost-effectiveness of apixaban vs warfarin for secondary stroke prevention in atrial fibrillation. Neurology. 2012;79:1428-34.
23. Singh SM, Dukkipati SR, d'Avila A, Doshi SK, Reddy VY. Percutaneous left atrial appendage closure with an epicardial suture ligation approach: a prospective randomized pre-clinical feasibility study. Heart Rhythm. 2010;7:370-6.
24. Bruce CJ, Stanton CM, Asirvatham SJ, Danielsen AJ, Johnson SB, Packer DL, et al. Percutaneous epicardial left atrial appendage closure: intermediate-term results. J Cardiovasc Electrophysiol. 2011;22:64-70.
25. Bartus K, Bednarek J, Myc J, Kapelak B, Sadowski J, Lelakowski J, et al. Feasibility of closed-chest ligation of the left atrial appendage in humans. Heart Rhythm. 2011;8:188-93.
26. Park JW, Bethencourt A, Sievert H, Santoro G, Meier B, Walsh K, et al. Left atrial appendage closure with Amplatzer cardiac plug in atrial fibrillation: initial European experience. Catheter Cardiovasc Interv. 2011;77:700-6.
27. Sick PB, Schuler G, Hauptmann KE, Grube E, Yakubov S, Turi ZG, et al. Initial worldwide experience with the WATCHMAN left atrial appendage system for stroke prevention in atrial fibrillation. J Am Coll Cardiol. 2007;49:1490-5.
28. Reddy VY, Doshi SK, Sievert H, Buchbinder M, Neuzil P, Huber K, et al. Percutaneous left atrial appendage closure for stroke prophylaxis in patients with atrial fibrillation: 2.3-Year Follow-up of the PROTECT AF (Watchman Left Atrial Appendage System for Embolic Protection in Patients with Atrial Fibrillation) Trial. Circulation. 2013;127:720-9.
29. Alli O, Doshi S, Kar S, Reddy V, Sievert H, Mullin C, et al. Quality of life assessment in the randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) trial of patients at risk for stroke with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2013;61:1790-8.
30. Meerkin D, Butnaru A, Dratva D, Bertrand OF, Tzivoni D. Early safety of the Amplatzer Cardiac Plug for left atrial appendage occlusion. Int J Cardiol. 2013;doi:10.1016/j.ijcard.2013.06.062.
31. Urena M, Rodes-Cabau J, Freixa X, et al. Percutaneous left atrial appendage closure with the AMPLATZER cardiac plug device in patients with nonvalvular atrial fibrillation and contraindications to anticoagulation therapy. J Am Coll Cardiol. 2013;62(2):96-102.
32. Chun KJ, Bordignon S, Urban V, et al. Left atrial appendage closure followed by 6 weeks of antithrombotic therapy: A prospective single-center experience. Heart Rhythm. 2013;doi:10.1016/j.hrthm.2013.08.025.
33. Lam YY. A new left atrial appendage occluder (Lifetech LAmbre Device) for stroke prevention in atrial fibrillation. Cardiovasc. Revasc Med. 2013;14(3):134-6.