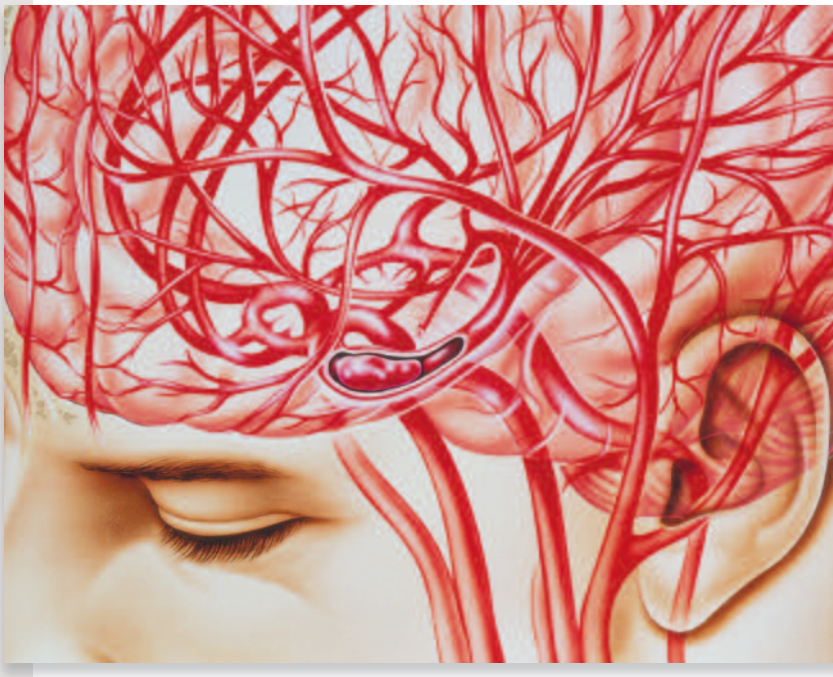
Dabigatran etexilate for preventing stroke and systemic embolism in atrial fibrillation



ALEX GALLUS MB BS, FRACP, FRCPA
JO JUDD MB BS, FRACP

Compared with warfarin in patients with nonvalvular atrial fibrillation, dabigatran at a dose of 150 mg twice daily is more effective for the prevention of stroke and systemic embolism with a similar risk of major bleeding, and at a dose of 110 mg twice daily has similar effectiveness with less major bleeding. The TGA recommends use of the higher dose except in patients aged over 75 years or with a high bleeding risk or with moderate renal impairment, where they suggest the lower dose should be used.

MedicineToday 2013; 14(3): 69-75

Professor Gallus is a Consultant Haematologist for SA Pathology at Flinders Medical Centre, and Professor of Haematology at Flinders University School of Medicine, Adelaide, SA. Dr Judd is a Cardiology Registrar completing an Echocardiography Fellowship at Flinders Medical Centre, Adelaide, SA.

Atrial fibrillation causes embolic stroke when thrombus formed in the nonfunctioning left atrial appendage detaches and lodges in a cerebral artery. The prevalence of atrial fibrillation rises with age, from less than 0.1% in people younger than 55 years to more than 10% in those older than 80 years. Atrial fibrillation accounts for 7% of ischaemic strokes in people aged between 50 and 59 years, rising to one-third in octogenarians. Embolic strokes are often severe, and 15 to 30% of survivors are left permanently disabled.[1,2]

Antithrombotic therapy is effective.[1,2] The vitamin K antagonist warfarin prevents about 65% of strokes in patients with atrial fibrillation and has twice the effectiveness of aspirin and is more likely to prevent severe stroke (Table 1). However, warfarin causes more major bleeding: 2.2% per annum compared with 1.3% with aspirin. This makes it essential to balance effectiveness with safety when recommending treatment. Almost 85% of people with newly diagnosed atrial fibrillation are candidates for antithrombotic therapy to prevent stroke.

Persistent and paroxysmal atrial fibrillation carry similar annual risks of a stroke developing, best estimated by using a clinical prediction rule. The $CHADS_2$ score allots two points for a previous stroke or transient ischaemic attack (S_2) and one point each for congestive heart failure or left ventricular systolic dysfunction (C), hypertension (H), age 75 years or older (A) and diabetes (D), as shown in Table 2.[3] The annual likelihood of stroke increases from about 2% to 18% as the $CHADS_2$ score rises from 0 to 6 (Table 3).

A more complicated scoring system (CHA_2DS_2-VASc) may improve prediction when the $CHADS_2$ score is 0 or 1.[4] CHA_2DS_2-VASc adds one point each for having vascular disease (V), age between 65 and 74 years (A) and being female (sex category, Sc), and age 75 years and older receives two points (A_2), as also shown in Table 2. A $CHADS_2$ score of 0 remains 'truly low risk' if the CHA_2DS_2-VASc score is 0, but escalates to 'at risk' if the CHA_2DS_2-VASc score is 2 or more (Table 3).

A major determinant of bleeding during warfarin therapy is an excessively high INR; the risk of bleeding increases exponentially with INR but is markedly raised once INR exceeds 6.[5] Patient-specific bleeding risk can be estimated using the HAS-BLED score. This scoring system gives points for nine clinical predictors, namely hypertension (H), abnormal renal or liver function (A), previous stroke (S), bleeding history or predisposition (B), labile INR (L), being elderly (over 65 years; E) and concomitant drug or alcohol use (D), with a score of 3 or more indicating closer clinical surveillance is required (Table 4).[6] The HAS-BLED system was developed and tested in the Euro Heart Survey on atrial fibrillation (Table 5).

Previous advice was to avoid antithrombotic therapy or take low-dose aspirin if the $CHADS_2$ score was 0, to take warfarin unless contraindicated if the score was 2 or more, and to choose warfarin or aspirin if the score was 1, depending on likely bleeding risk and personal preference. Present guidelines from the European Society of Cardiology recommend the use of an oral anticoagulant (warfarin or other) if the CHA_2DS_2-VASc score is 2 or more, use of an oral anticoagulant or aspirin if the score is 1 (with a preference for oral anticoagulant over aspirin), and preferably no antithrombotic therapy (i.e. no anticoagulant or aspirin) if the CHA_2DS_2-VASc score is 0.[7]

TABLE 1. STROKE IN PATIENTS WITH ATRIAL FIBRILLATION TREATED WITH A VITAMIN K ANTAGONIST OR ASPIRIN[1]*

	Strokes (% per annum)			Risk reduction (%)
	Placebo or untreated	Aspirin	Warfarin or another vitamin K antagonist	
Atrial Fibrillation Investigators, 1997	8.1	6.3		21
Atrial Fibrillation Investigators, 1994 (*Arch Intern Med* 1994; 154: 1449-1457)	4.5		1.4	68
Van Walraven et al, 2002 (*JAMA* 2002; 288: 2441–2448)		4.3	2.0	52

* Pooled analyses of randomised trials where baseline incidence varied with selection criteria for study entry.

TABLE 2. $CHADS_2$ AND CHA_2DS_2-VASC SCORES COMPARED[3,4]

	$CHADS_2$		CHA_2DS_2-VASc	
Risk factor		Points		Points
Congestive heart failure or left ventricular systolic dysfunction	C	1	C	1
Hypertension	H	1	H	1
Age 75 years or older	A	1	A_2	2
Diabetes mellitus	D	1	D	1
Prior stroke, transient ischaemic attack or thromboembolism	S_2	2	S_2	2
Vascular disease (prior peripheral artery disease, myocardial infarction, aortic plaque)			V	1
Age 65 to 74 years			A	1
Sex category (i.e. female)			Sc	1

NEW ORALLY ACTIVE ANTICOAGULANTS IN ATRIAL FIBRILLATION

Several new oral anticoagulants have undergone extensive clinical trials in atrial fibrillation and for other indications. These anticoagulants are direct inhibitors of single clotting factors (unlike warfarin, which inhibits the vitamin K-dependent synthesis of factors II, VII, IX and X and the natural anticoagulant proteins C and S). They include dabigatran etexilate, the orally absorbed precursor (prodrug) for dabigatran, which is a direct thrombin inhibitor, and rivaroxaban and apixaban,

which both inhibit factor Xa. This article will focus on dabigatran.

These new anticoagulants have a limited potential for drug–drug interactions and are given orally once or twice daily without laboratory monitoring. They are likely to prove much easier to use than warfarin with its complex pharmacology, unpredictable dose requirement, many drug interactions and need for close laboratory supervision.

Dabigatran etexilate, rivaroxaban and apixaban have been approved in the USA and the European Union for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.

The TGA approved dabigatran (150 mg twice daily) in April 2011 and rivaroxaban (20 mg once daily) in May 2012 for use in Australia for prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation and at least one additional risk factor for stroke. Rivaroxaban was also approved in May 2012 for the initial treatment of deep vein thrombosis (DVT) and to prevent recurrence of DVT and pulmonary embolism (15 mg twice daily for three weeks, then 20 mg once daily). Dabigatran (220 mg once daily), rivaroxaban (10 mg once daily) and apixaban (2.5 mg twice daily) are approved by the TGA and listed under the PBS for preventing venous thromboembolism after an elective hip or knee replacement.

The Pharmaceutical Benefits Advisory Committee has accepted that there is a place for dabigatran in the prevention of stroke in patients with nonvalvular atrial fibrillation. However, PBS listing of this drug has been delayed pending further modelling of value for money across the full spectrum of patients with atrial fibrillation.

The new oral anticoagulants invoke a paradox. By freeing patients from the need for coagulation testing, fixed-dose oral anticoagulants such as dabigatran bring the challenge of ensuring adherence without the spur of laboratory supervision.

TABLE 3. $CHADS_2$ AND CHA_2DS_2-VASC SCORES, AND ANNUAL RISK OF STROKE OR OTHER THROMBOEMBOLISM IN ATRIAL FIBRILLATION[3,4]*

$CHADS_2$ score	Annual risk of stroke (%)	CHA_2DS_2-VASc score	Annual risk of stroke (%)
0	1.9	0	0
		1	0.7
		2	1.9
1	2.8	3	4.7
		4	2.3
2	4.0	5	3.9
3	5.9	6	4.5
4	8.5	7	10.1
5	12.5	8	14.2
6	18.2		

* Rates adjusted for aspirin use (with the assumption that aspirin reduces annual rates by 22%).

DABIGATRAN ETEXILATE

Oral absorption of dabigatran etexilate is rapid, and the prodrug is converted to dabigatran in the plasma and liver. Simultaneous peaks of concentration and anticoagulant effect occur within two hours of dosing, and plasma concentrations then decline with an elimination half-life for the drug of 12 to 17 hours.[2] Almost all circulating dabigatran (80%) is cleared by the kidneys, so the drug should be used with care in the elderly and is contraindicated in patients with severe renal failure (creatinine clearance less than 30 mL/min). Oral bioavailability is about 6%.

TABLE 4. HAS-BLED SCORING SYSTEM[6]

HAS-BLED scoring clinical characteristic	Points
Hypertension (systolic above 160 mmHg)	1
Abnormal renal or liver function (1 point each)	1 or 2
Stroke in past	1
Bleeding	1
Labile INRs	1
Elderly (age over 65 years)	1
Drugs or alcohol (1 point each)	1 or 2

TABLE 5. BLEEDING RISK DURING WARFARIN TREATMENT FOR ATRIAL FIBRILLATION[6]*

HAS-BLED score	Bleeding rate per 100 years†
0	1.13
1	1.02
2	1.88
3	3.74
4	8.70
5	12.50
6	-
7	-
8	-
9	-

* Euro Heart Survey on atrial fibrillation.[6]
† Bleeding rates from the validation cohort.

TABLE 6. RESULTS OF THE RE-LY TRIAL OF DABIGATRAN VERSUS WARFARIN IN ATRIAL FIBRILLATION.[11,12]*

Treatment group	Dabigatran 110 mg twice daily	Dabigatran 150 mg twice daily	Warfarin	P relative to warfarin
Number of patients	6015	6076	6022	
Stroke or systemic embolism†	1.54%	1.11%	1.71%	110 mg: 'non-inferior' to warfarin (statistically no less effective)
Relative risk (95% CI)‡	0.90 (0.74–1.10)	0.65 (0.52–0.81)		150 mg: $p < 0.001$
Disabling or fatal stroke	0.94%	0.66%	1.00%	110 mg: $p = 0.005$ 150 mg: $p = 0.65$
Major bleeding†	2.87%	3.32%	3.57%	110 mg: $p = 0.003$
Relative risk (95% CI)	0.80 (0.70–0.93)	0.93 (0.81–1.07)		150 mg: $p = 0.32$
Intracranial bleeding	0.23%	0.30%	0.74%	110 mg: $p < 0.001$
Relative risk (95% CI)	0.31 (0.20–0.47)	0.40 (0.27–0.60)		150 mg: $p < 0.001$
Major gastrointestinal bleeding	1.12%	1.51%	1.02%	110 mg: $p = 0.43$ 150 mg: $p < 0.001$
Myocardial infarction†	0.82%	0.81%	0.64%	110 mg: $p = 0.09$
Relative risk (95% CI)	1.29 (0.96–1.75)	1.27 (0.96–1.75)		150 mg: $p = 0.12$
Death from any cause	3.75%	3.64%	4.13%	110 mg: $p = 0.13$ 150 mg: $p = 0.051$

ABBREVIATION: CI = confidence interval.

* Effectiveness and safety of dabigatran (110 mg or 150 mg twice daily) compared with warfarin (target INR, 2 to 3). Percentages refer to annual incidence of events.
† Results for stroke or systemic embolism, major bleeding and myocardial infarction are those after further analysis to include newly added events.[12]
‡ Relative risk is versus warfarin.

The main target for drug interactions is P-glycoprotein (P-gp), a gut cell efflux transporter molecule that controls absorption of the etexilate. Both drug absorption and drug levels are increased by strong P-gp inhibitors such as amiodarone, verapamil and systemic ketoconazole, and are reduced by strong P-gp inducers such as St John's wort and rifampicin. Concomitant use of dabigatran and ketoconazole is contraindicated, and concomitant use of P-gp inducers should generally be avoided.[8,9]

There is no specific antidote for dabigatran, unlike for warfarin (where vitamin K administration immediately reverses its anticoagulant effect).[10] However, it has a short half-life and so is excreted rapidly in patients with normal renal function.

Dabigatran and other thrombin inhibitors prolong the clotting times measured by common laboratory tests. The measurement of dabigatran concentration in cases of emergency is discussed later in this article.

Dabigatran etexilate and atrial fibrillation (the RE-LY trial)

The pivotal study of dabigatran etexilate in nonvalvular atrial fibrillation is the RE-LY (Randomised Evaluation of Long-term Anticoagulant Therapy) trial, a randomised study in which dabigatran at doses of 110 mg twice daily and 150 mg twice daily was compared with warfarin (target INR, 2 to 3) in 18,113 patients for a median follow-up period of two years, with the primary efficacy outcome of stroke or systemic embolism.[11,12] The dose of dabigatran was masked while warfarin treatment was unmasked (open label).

Patients entered the RE-LY trial with recently documented atrial fibrillation plus at least one other risk factor for systemic embolism (previous stroke or transient ischaemic attack, heart failure, age at least 75 years or age 65 to 74 plus diabetes, hypertension or coronary artery disease).[11] The main reasons for exclusion were high bleeding risk, creatinine clearance less than 30 mL/min (estimated using the Cockroft–Gault formula) and contraindications to warfarin use. Most patients had a moderate or high risk of embolism (the $CHADS_2$ score was 2 in 35.7% of study patients and 3 to 6 in 32.5%). Almost half the patients had taken a vitamin K antagonist for atrial fibrillation, and about 40% were taking aspirin before entering the study. Aspirin use was allowed during the trial (at a dose of less than 100 mg/day).

The RE-LY trial demonstrated that

efficacy and bleeding risk of dabigatran were dose-related. Patients taking warfarin had a 1.71% annual incidence of stroke or systemic embolism.[11,12] This compared with 1.11% in patients taking twice-daily 150 mg dabigatran (a significant reduction) and 1.54% in those taking twice-daily 110 mg dabigatran.[11,12] The incidences of disabling or fatal stroke were 1.00% per year in the warfarin group and 0.94% and 0.66% in the twice-daily 110 mg and 150 mg dabigatran groups, respectively.[11] Major bleeding was less frequent with twice-daily 110 mg dabigatran than with twice-daily 150 mg dabigatran or warfarin.[11] An important finding was significantly less intracranial bleeding with both dabigatran doses than with warfarin. These results are summarised in Table 6.

There were adverse effects associated with the use of dabigatran. Major gastrointestinal bleeding was more frequent with twice-daily 150 mg dabigatran than with twice-daily 110 mg or warfarin, and people who took dabigatran were more likely to report dyspepsia, and discontinue study therapy, than those taking open-label warfarin. In addition, the study noted a small excess of myocardial infarction in patients taking dabigatran (annual incidences, revised after further analysis, were 0.82% and 0.81% with twice-daily 110 mg and twice-daily 150 mg respectively, and 0.64% with warfarin; which was not a statistically significant difference).[12] All-cause mortality was unchanged (Table 6).

Subgroup analyses from the RE-LY trial

The quality of warfarin therapy is a critical question for all comparisons with new oral anticoagulants. The best current measure is the 'time in therapeutic range' (TTR), which is the average percentage of treatment time with an INR of 2 to 3. This was 64% in RE-LY, which compares well with similar studies and is above the usual TTR in community practice. In a substudy report, RE-LY patients were separated into quartiles depending on the TTR achieved by study centres: excellent (TTR, above 72.6%), good (TTR, 57.1 to 72.6%, or not so good (TTR, below 57.1%).[13] Where TTR was excellent, the rates of stroke, systemic embolism and major bleeding were similar across treatment groups, although both dabigatran doses retained their advantage of less intracranial bleeding. The TTR across Australian study centres was 74% – that is, in the excellent range.

A further subgroup analysis reported that risk of major bleeding increased in all treatment groups with advancing age.[14] Compared with warfarin, patients aged 75 years or older had less intracranial bleeding but more major gastrointestinal bleeding with dabigatran 150 mg or 110 mg twice daily, and more major bleeding outside the brain or gastrointestinal tract with 150 mg twice daily (Table 7). All treatment groups had more major bleeding if creatinine clearance was less than 50 mL/min or if patients took aspirin in addition to study drugs. Adding clopidogrel to aspirin increased the rates of major bleeding by 40 to 70%.

RE-LY trial findings were consistent with overall results in patients with a previous stroke or transient ischaemic attack, or newly diagnosed atrial fibrillation, or who took warfarin before they were enrolled.

TABLE 7. DABIGATRAN EFFECTIVENESS AND BLEEDING RELATED TO AGE, DOSE REGIMEN AND ASPIRIN CO-MEDICATION[14]

Subgroup	Dabigatran 110 mg twice daily (%/year)	Dabigatran 150 mg twice daily (%/year)	Warfarin (%/year)
Age under 75 years			
Stroke/embolism	1.32	0.90	1.43
Major bleeding	1.89	2.12	3.04
• Intracranial	0.14	0.26	0.61
• Extracranial	1.76	1.91	2.44
• Gastrointestinal	0.84	1.22	1.03
Age 75 years or older			
Stroke/embolism	1.89	1.43	2.14
Major bleeding	4.43	5.10	4.37
• Intracranial	0.37	0.41	1.00
• Extracranial	4.10	4.68	3.44
• Gastrointestinal	2.19	2.80	1.59
All age groups			
Major bleeding			
• Plus aspirin	3.65	4.08	4.32
• No aspirin	2.38	2.85	3.08

RIVAROXABAN AND APIXABAN IN ATRIAL FIBRILLATION

In a large trial that enrolled patients with atrial fibrillation and a high risk of stroke, rivaroxaban was no less (and probably more) effective than warfarin in preventing stroke or systemic embolism, with less intracranial bleeding but a similar total risk of major and non-major bleeding.[15]

Compared with warfarin in patients with atrial fibrillation, apixaban was more effective for the prevention of

CASE STUDY

A male patient with newly diagnosed atrial fibrillation is aged 90 years and weighs 83 kg. He is otherwise well and mentally acute but he has treated hypertension (blood pressure of 160/85 mmHg) and a serum creatinine level of 155 µmol/L. His derived creatinine clearance is 35 mL/min.

His $CHADS_2$ score is 2, indicating the likelihood of his having an embolic stroke is about 4% per annum. His HAS-BLED score is 3, indicating a likelihood of having major bleeding on warfarin treatment of about 3% per annum.

If the decision is to avoid an anticoagulant then an embolic stroke would carry a greater than 50% chance of resulting in serious long-term neurological deficit. If the decision is to accept an anticoagulant then the most likely site of major bleeding is from the gastrointestinal tract and the risk of intracranial bleeding is likely to be 0.5 to 1.0% per annum. In the case of gastrointestinal bleeding, this would require endoscopy and possible biopsy as part of immediate care.

Many cardiologists would advise an anticoagulant. However, this patient has a significant contraindication to dabigatran because its half-life is extended to 22 hours at his level of reduced renal clearance, which would complicate the management of any major bleeding.

stroke or systemic embolism, caused less haemorrhagic stroke and less major bleeding, and resulted in lower mortality.[16] Compared with aspirin, apixaban diminished the stroke rate by over half and significantly reduced mortality in patients thought to be not suitable for treatment with a vitamin K antagonist, without increasing the rates of intracranial or other major bleeding.[17]

DABIGATRAN FOR ATRIAL FIBRILLATION IN CLINICAL PRACTICE

The evaluation of two dabigatran dosing regimens (150 mg twice daily and 110 mg twice daily) in the RE-LY trial led to questions about which regimen should be preferred. The higher dose regimen was more effective than warfarin and had a similar risk of major bleeding, while the lower dose regimen had similar effectiveness to warfarin and less major bleeding; both dose levels reduced the chances of intracranial bleeding.

The TGA has approved both dabigatran regimens for use in prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation but recommends 150 mg twice daily except in patients aged over 75 years or with a high bleeding risk or moderate renal impairment (creatinine clearance, 30 to 50 mL/min), where they suggest the use of 110 mg twice daily should be considered.[8,9] This advice is consistent with the RE-LY trial subgroup analysis of results in people aged 75 years or older, in which the balance of efficacy for bleeding seemed better with the lower dose regimen.

When considering the use of dabigatran for patients with atrial fibrillation, it should be noted that the RE-LY trial excluded people with a contraindication to warfarin therapy or high bleeding risk. Severe renal failure was excluded because dabigatran excretion depends on renal function, so that half-life and drug levels increase with diminishing creatinine clearance. It seems prudent to consider dabigatran in people who would otherwise qualify for warfarin and whose estimated creatinine clearance is above the threshold level of 30 mL/min set by RE-LY (the eGFR routinely reported by laboratories tends to overestimate real creatinine clearance in people with a lower than average body weight, including many who are elderly, as it does not adjust for body surface area).

The RE-LY trial found the least difference between dabigatran and warfarin in the study centres that had excellent INR control, which suggests that patients taking well-controlled warfarin might prefer to stay with the drug they know. The reduced risk of intracranial bleeding with dabigatran should, however, be considered.[13]

A case study illustrating the assessment of a patient's suitability for dabigatran therapy is shown on this page.

More experience is needed with the new oral anticoagulants before there can be confidence about their safety in people who are elderly, have low body mass or have renal impairment. There may be a temptation to use dabigatran as an anticoagulant for certain 'off label' conditions such as valve replacement. This would be hazardous. Indeed, two recent trials of dabigatran in valve replacement were abandoned because dabigatran in this clinical setting was less effective than warfarin.

Managing bleeding

It remains uncertain how major bleeding or the need for urgent surgical intervention should best be managed in patients taking dabigatran or another new oral anticoagulant.

The first response to clinically important bleeding in a patient taking dabigatran should be the usual interventions (local measures and blood replacement) and the maintenance of diuresis to preserve renal dabigatran excretion, as the relatively short half-life of the drug ensures rapid excretion except in renal failure. Activated charcoal reduces further absorption if given soon after the most recent dabigatran dose. Albumin binding is low, and haemodialysis can remove most of the drug if usual measures fail to control major bleeding.

Although there is no direct supporting evidence, administration of a prothrombin complex concentrate or recombinant factor VIIa might help bypass

dabigatran-induced thrombin inhibition in people with life-threatening bleeding.[9]

Measuring dabigatran concentration in emergencies

Several laboratories have introduced the Hemoclot thrombin inhibitor assay to measure dabigatran concentration in patients who need urgent surgery or develop major bleeding or thromboembolism during therapy, or who may have overdosed with dabigatran.

As mentioned earlier, dabigatran prolongs clotting times measured by common laboratory tests such as the activated partial thromboplastin time (aPTT), INR and thrombin clotting time (TCT). Also, the TCT test is over-sensitive, the aPTT is prolonged only at high concentrations, and the INR is relatively insensitive to dabigatran. Test results peak soon after taking dabigatran and then diminish as the drug is cleared from the circulation.[10]

It is not known how the prolongation of a TCT, aPTT or INR may translate into bleeding risk or clotting risk, and there is no evidence for consideration of the use of these tests for dabigatran dose adjustment.

CONCLUSION

Of the several new oral anticoagulants now being introduced to clinical practice, dabigatran etexilate and rivaroxaban have been approved by the TGA for the prevention of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. Both these drugs and also apixaban have been approved for this use in the USA and the European Union. These new oral anticoagulants have a limited potential for drug–drug interactions and are given once or twice daily without laboratory monitoring.

Dabigatran at a dose of 150 mg twice daily is more effective than warfarin in patients with atrial fibrillation and has a similar risk of major bleeding, and at a dose of 110 mg twice daily has similar effectiveness to warfarin with less major bleeding. The TGA recommends use of the higher dose except in patients aged over 75 years or with a high bleeding risk or with moderate renal impairment, in whom it is suggested the lower dose be used. The Pharmaceutical Benefits Advisory Committee considers there is a place for dabigatran in the prevention of stroke in patients with nonvalvular atrial fibrillation but the listing of this drug on the PBS has been delayed while awaiting further analysis of benefit and cost across the full spectrum of patients with this condition.

The new oral anticoagulants also invoke a paradox. By freeing patients from the need for coagulation testing, fixed-dose oral anticoagulants such as dabigatran will bring the challenge of ensuring adherence without the spur of laboratory supervision. MT

REFERENCES

1. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th edn). Chest 2008; 133(6 Suppl): 546S-592S.
2. You JJ, Singer DE, Howard PA, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th edn: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012; 141(2 Suppl): e531s – e575s.
3. 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: 2864-2870.
4. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijns HJ. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest 2010; 137: 263-272.
5. Ansell J, Hirsh J, Hylek E, et al. Pharmacology and management of the vitamin K antagonists: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th Edition). Chest 2008; 133(6 Suppl): 160S-198S.
6. Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJ, Lip GY. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. Chest 2010; 138: 1093-1100.
7. Camm AJ, Lip GYH, De Caterina R, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012; 33: 2719-2747.
8. Boehringer-Ingelheim Pty Ltd. Pradaxa product information. Most recent amendment 13 November 2012.
9. TGA. Australian public assessment report for dabigatran etexilate mesilate. Canberra: Department of Health and Ageing, Australian Government; May 2011. Available online at: http://www.tga.gov.au/pdf/auspar/auspar-pradaxa.pdf (accessed December 2012).
10. van Ryn J, Stangier J, Haertter S, et al. Dabigatran etexilate – a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 2010; 103: 1116-1127.
11. Connolly SJ, Ezekowitz MD, Yusuf S, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009; 361: 1139-1151.
12. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L. Newly identified events in the RE-LY trial. [Letter.] N Engl J Med 2010; 363: 1875-1876.
13. Wallentin L, Yusuf S, Ezekowitz MD, et al. Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 2010; 376: 975-983.
14. Eikelboom JW, Wallentin L, Connolly SJ, et al. Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomised evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 2011; 123: 2363-2372.
15. Patel MR, Mahaffey KW, Garg J, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011; 365: 883-891.
16. Granger CB, Alexander JH, McMurray JJ, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011; 365: 981-992.
17. Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011; 364: 806-817.

COMPETING INTERESTS: Professor Gallus has been or is a steering committee member for Phase 3 clinical trials of apixaban (Bristol-Myers Squibb and Pfizer) and rivaroxaban (Bayer) for the prevention and treatment of venous thromboembolism and has contributed to these trials and studies of dabigatran (Boehringer-Ingelheim) as an investigator. He has contributed to Industry Advisory Boards on apixaban, rivaroxaban and dabigatran.