Research Review Speaker Series™

Stroke prevention in atrial fibrillation

Making Education Easy

January 2013

Associate Professor Jonas Oldgren,

Uppsala University Hospital, Sweden

Dr Oldgren completed his studies in Medicine at Uppsala University, Sweden in 1989. In the following years he worked within the department of Cardiology, becoming a senior consultant and Head of the Coronary Care Unit (2002–2011). Currently he is the head of department of Cardiology at the University Hospital.

Prof. Oldgren's special interests include coagulation activity, inflammation, risk stratification and antithrombotic treatment in acute coronary syndromes and atrial fibrillation. He has published several papers in peer-reviewed journals in this field and has also been an investigator in several large-scale clinical trials, e.g. TRIM, FRISC II, ESTEEM, OASIS-5, OASIS-6, ExTRACT, APPRAISE, PLATO, TRACER, APPRAISE-2. He was the Swedish national co-ordinator and member of the Operations Committee of the phase III landmark RE-LY study, and International co-ordinating investigator in the multinational phase II RE-DEEM trial. He is also co-chairman in the global RE-LY AF registry.

This publication is a summary of a recent presentation by Dr Jonas Oldgren, Associate Professor in Cardiology at the Uppsala Clinical Research Center and Department of Cardiology, Uppsala University Hospital, Sweden. He spoke to medical professionals in Auckland in September 2012 about the novel oral anticoagulants and their uptake for the treatment of atrial fibrillation.

Atrial fibrillation (AF) is a common, sustained cardiac arrhythmia, responsible for 3 million strokes annually. Since their synthesis in the 1950s, vitamin K antagonists (VKAs) have proven to be highly effective for stroke prevention in patients with AF, reducing stroke by 67%. A meta-analysis has also shown a mortality reduction by 26% against placebo, which is seldom seen with oral anticoagulants (OACs), antiplatelets or any antithrombotic drug.[1] However, VKAs have numerous limitations (drug-drug interactions, food interactions, frequent dose adjustments, etc.), which have led to the development of novel anticoagulant therapies that would be safe and effective alternatives.[2-4]

The management of AF in clinical practice has been examined in three different patient cohorts prescribed VKAs:

- Medicare cohort, USA (n=23,657)[5]
- EuroHeart survey (n=5,333)[6]
- ATRIA cohort (managed care system, California, USA) (n=11,379)[7]

This and more recent data[8] have shown that warfarin is underutilised, with up to 60% left untreated.

Data for warfarin compared against the novel OACs (NOACs) have been provided by four different studies: RE-LY,[9,10] ROCKET,[11] AVERROES[12] and ARISTOTLE;[13] results from another major study will be presented in 2013. Figure 1 depicts the differences between these four studies:

	RE-LY[9,10]	**ROCKET**[11]	**AVERROES**[12]	**ARISTOTLE**[13]
	Dabigatran	Rivaroxaban	Apixaban	Apixaban
Inhibits clot factor	IIa	Xa	Xa	Xa
Renal excretion %	80	33	25	25
Randomized	18113	14171	5599	18201
Comparator	Warfarin open-label	Warfarin double-blind	Aspirin double-blind	Warfarin double-blind
Age (mean, median)	71.5	73	70	70
Males (%)	63	60	59	65
$CHADS_2$ score (mean)	2.1	3.5	2.1	2.1
Prior stroke/TIA	20	55	14	19
Prior MI (%)	17	17	?	14
CHF (%)	32	63	39	35
VKA naïve* (%)	50	62	39	43
TTR (mean %)	64	55	-	62

*various definitions

Figure 1. Inter-trial comparisons of RE-LY, ROCKET, AVERROES and ARISTOTLE.[9-13]

RE-LY[9,10]

The phase 3 multicentre, open-label RE-LY study was designed as a noninferiority study, with the rationale being at the time that no agent would ever prove superior to warfarin.[9,10] 18,113 patients with non-valvular AF at moderate-to-high risk of stroke or systemic embolism (≥1 high-risk factor) were randomised over a 2-year period to adjusted-dose warfarin with INR 2.0–3.0 (n=6,022), dabigatran etexilate 110 mg bid (n=6,015), or dabigatran etexilate 150 mg bid (n=6,076). The median follow-up was 2.0 years.

- Two doses dabigatran etexilate vs warfarin
- Dabigatran etexilate 150 mg bid significantly reduced stroke and systemic embolism versus warfarin
- Dabigatran etexilate 150 mg bid significantly reduced ischaemic stroke versus warfarin – is the only NOAC to show this
- Dabigatran etexilate 110 mg bid non-inferior to warfarin in reducing stroke and systemic embolism
- Dabigatran etexilate 150 mg bid associated with a significant 15% RRR in vascular mortality, whereas the reduction with dabigatran etexilate 110 mg bid was no different from warfarin
- A trend with borderline significance for a 12% reduction of all-cause mortality was seen with dabigatran etexilate 150 mg bid (p=0.051)
- Rates of life-threatening bleeding, intracranial haemorrhage (ICH), and major or minor bleeding were significantly higher with warfarin than with either dose of dabigatran etexilate
- Compared with dabigatran etexilate 110 mg bid, dabigatran etexilate 150 mg bid was associated with a trend toward an increased risk of major bleeding and also with increased risks of gastrointestinal, minor, and any bleeding
- The net clinical benefit (combined outcome of major vascular deaths, major bleeding, and death) was almost identical for the two doses of dabigatran etexilate
- All study arms were associated with low event rates of myocardial infarction (MI) but they were numerically lower with warfarin. Prof Oldgren commented that warfarin has previously been shown to be effective for prevention of MI and suggested that it might be that dabigatran etexilate is not as good as warfarin in MI prophylaxis.

All study arms were associated with low event rates of myocardial infarction (MI) but they were numerically lower with warfarin. Prof Oldgren commented that warfarin has previously been shown effective for prevention of MI and suggested that it might be that dabigatran etexilate is not as good as warfarin in MI prophylaxis.

ROCKET-AF[11]

The double-blind, double-dummy ROCKET study differs from RE-LY with the use of a once-daily OAC dose of rivaroxaban, despite the fact that the half-life for rixaroxaban is shorter than that for dabigatran etexilate.[11] Nevertheless, the results from ROCKET are important. The study involved 14,000 patients with higher stroke risk than patients in RE-LY or ARISTOTLE; ROCKET participants had AF and a $CHADS_2$ score ≥2 and were randomised to warfarin with an INR target of 2.5 (2.0–3.0 inclusive) or to rivaroxaban 20 mg daily (15 mg for severe renal impairment: CrCL 30–49 mL/min).

- In an on-treatment superiority comparison, rivaroxaban significantly reduced the risk of stroke and systemic embolism by 21% compared with warfarin
- Major and non-major clinically relevant bleeding rates were the same for rivaroxaban and warfarin

ICH rates were lower with rivaroxaban versus warfarin

AVERROES[12]

- Apixaban 5 mg bid vs aspirin in 5,599 patients with AF and ≥1 risk factor for stroke as well as demonstrated or expected unsuitability for VKAs[12]
- Trial stopped early due to a positive finding with apixiban - the risk of stroke or systemic embolic event (SEE) was significantly reduced by 55%
- Major bleeding was not increased with apixiban over that of aspirin

ARISTOTLE[13]

The double-blind, double-dummy ARISTOTLE study enrolled 18,201 AF patients with ≥1 additional risk factor for stroke.[13] Patients were randomised to receive oral apixaban 5 mg bid (2.5 mg bid in selected patients with a higher bleeding risk) or warfarin (target INR 2–3).

- The primary outcome of stroke or systemic embolism was significantly reduced with apixaban versus warfarin
- There was no reduction in ischaemic stroke rates with apixaban versus warfarin
- There was a significant reduction in all-cause mortality with apixaban over that of warfarin of 11%
- There was a significant reduction in major bleeding as well as ICH with apixaban versus warfarin

"Clinicians wishing to avoid intracranial bleeds in their patients should use a newer OAC."

Are the novel OACs comparable?

Several research groups have recently published meta-analyses, systematic analyses and reviews that have evaluated the comparative efficacy and safety of the NOACs in patients with AF.[14-19] The conclusions differ somewhat between the papers, with one stating: "An indirect comparison should be used only to generate hypotheses which need to be tested in a dedicated randomized trial directly comparing the three drugs."[18]

The various endpoints in these trials have also been compared, in an attempt to highlight equalities and differences between them. The superiority of rivaroxaban over warfarin for stroke/systemic embolism is questioned because the significant outcome is as a result of an on-treatment analysis, not an intention-to-treat analysis.

Prof. Oldgren advises caution when observing these comparisons, as it is difficult to make comparisons between different drugs in different study populations, throughout different countries worldwide and evaluated in different healthcare systems.

CHA_2DS_2-VASc

In 2010, the European Society of Cardiology (ESC) guidelines proposed a new risk stratification scheme – CHA_2DS_2-VASc – for the prediction of stroke in low-risk subjects.[20] The CHA_2DS_2-VASc score awards points for age:

+0 for <65 years old
+1 for 65–74 years old
+2 for ≥75 years old

Points are also added for:

Congestive heart failure history: Yes, +1
Hypertension history: Yes, +1
Stroke/transient ischaemic attack/thromboemolism history: Yes, +2
Vascular disease history: Yes, +1
Diabetes mellitus: Yes, +1
Female sex: Yes, +1

Thus, this acronym extends the $CHADS_2$ scheme by considering additional stroke risk factors that may influence a decision whether or not to anticoagulate.

Recently published Danish registry data reveal a better performance with the CHA_2DS_2-VASc score compared with the $CHADS_2$ in predicting 5-year event rates for death or hospitalisation for thromboembolism.[21] The study included 73,538 patients with AF not receiving VKA or heparin in Denmark during the period 1997–2006.

At 5 years' follow-up, the annual event rate (death or hospitalisation for thromboembolism) per 100 person-years in patients at "low risk" (score = 0) was 1.28 with $CHADS_2$ and 0.69 with CHA_2DS_2-VASc. In patients at "intermediate risk" (score = 1), the rates were 3.70 with $CHADS_2$ and 1.51 with CHA_2DS_2-VASc; corresponding rates were 5.58 with a $CHADS_2$ score of 2 and 3.01 with a CHA_2DS_2-VASc score of 2. Thus, the CHA_2DS_2-VASc score allows for better discrimination of the low-risk end of this scheme. Prof. Oldgren notes that the very low 5-year event rate for patients with a CHA_2DS_2-VASc score of 0 signifies that this population should not be treated with OACs. The risk increases with 1 risk factor and doubles with 2 risk factors on the CHA_2DS_2-VASc scheme. When patients were categorised into low-, intermediate-, and high-risk groups, *C* statistics at 10 years' follow-up were 0.812 (95% CI 0.796 to 0.827) with $CHADS_2$ and 0.888 (0.875 to 0.900) with CHA_2DS_2-VASc.

HAS-BLED score

Another bleeding risk score (from 0 to 9 points), HAS-BLED (hypertension, abnormal renal/liver function, stroke, bleeding history or predisposition, labile INR, elderly [age >65], drugs/alcohol concomitantly), has been derived from a 'real-world' cohort of 3,978 European patients with AF from the EuroHeart Survey.[20] Prof. Oldgren considers that the difficulty with this score is that some of the risk factors are the same; i.e., if the patient's risk is increased for stroke, the risk is also increased for bleeds. Nonetheless, he believes it is still important to have the HAS-BLED scheme, as it highlights the existence of hypertension which can subsequently be reduced.

HAS-BLED and CHA_2DS_2-VASc have been used in combination to calculate the risk of death, stroke and intracranial haemorrhage in 182,678 patients with AF in the Swedish Hospital Discharge Register.[22] As expected, in patients with a high risk for thromboembolic stroke and low risk for bleeding, OAC (warfarin in Sweden) is clearly superior to no OAC in the reduction of death, stroke and intracranial haemorrhage (a net clinical benefit) (see Fig. 2). Conversely, low stroke risk and a high bleed risk also benefited from OAC versus no OAC therapy. Prof. Oldgren noted that it depends on how the risk and benefit is calculated, as to what kinds of bleedings are being investigated. Clinical study data indicate a 2–3% risk for major bleeding. When considered with a stroke risk of ~1.2% or 2%, the net clinical benefit will *not* be in favour of OACs. However, with a net clinical outcome using intracranial haemorrhage (instead of all major bleeds), the Swedish registry data clearly demonstrate the superiority of OACs in patients with low stroke risk and high bleed risk. If a novel OAC is substituted for warfarin, the risk for intracranial bleeds will be further reduced and OAC therapy will be even more favourable in many patients. With only warfarin on the market, the Swedish registry data suggest that only 4% of the patients have no net benefit of OAC treatment.

Swedish registry data, n=182,678

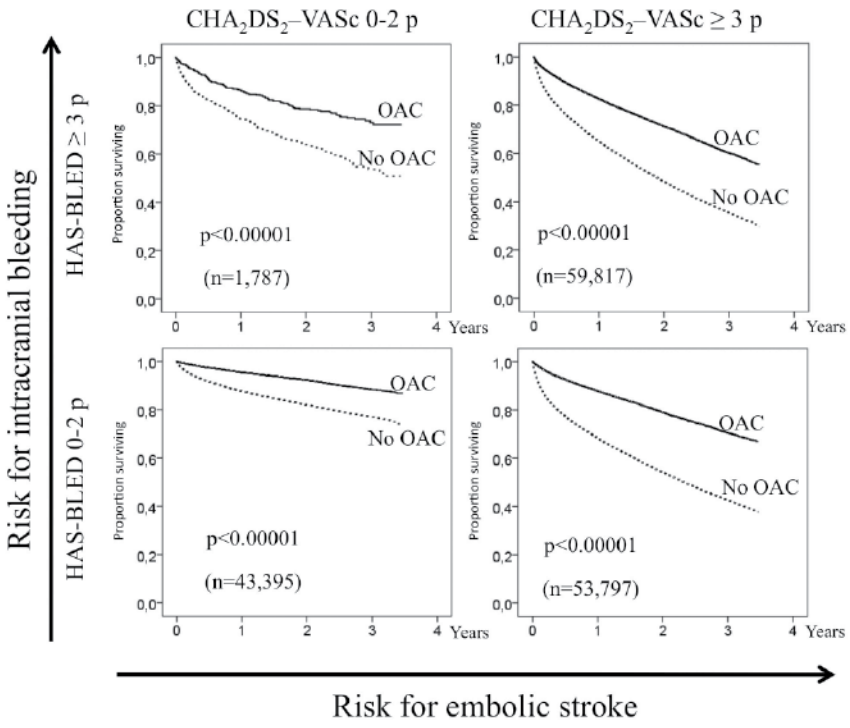

Figure 2. Death, stroke and intracranial haemorrhage.[22]

Novel or old OACs and clinical risk scores

Oldgren and colleagues used data from the RE-LY study to compare clinical risk scores for dabigatran etexilate and warfarin in stroke and systemic embolism, major and intracranial bleeding.[23] Event rates each increased in the warfarin and dabigatran etexilate groups as $CHADS_2$ score increased. The relative efficacy of dabigatran etexilate 110 mg compared to warfarin was the same, irrespective of the risk group; i.e., no interaction was observed. Dabigatran etexilate 150 mg was clearly more effective than warfarin, irrespective of the stroke risk for the patient. Thus, in both low- and high-risk patients, dabigatran etexilate 150 mg provides better stroke prevention than warfarin.

Similarly, no interaction was found for major bleeding, which indicates there is no difference according to the $CHADS_2$ scores. However, a small trend even in low-risk patients indicated that dabigatran etexilate 150 mg would be a better safety option with a lower major bleeding risk.

> "The analyses also revealed that warfarin increases the risk of intracranial bleeds, irrespective of the risk for each patient. Even in low-risk patients and more definitely in high-risk patients, dabigatran etexilate 110 mg or 150 mg was associated with a lower risk for intracranial bleeds compared with warfarin."

Guidelines on OAC and AF

Extensive, evidence-based clinical practice guidelines were released early in 2012 by the American College of Chest Physicians, providing recommendations for antithrombotic treatment based on net clinical benefit for patients with AF at varying levels of stroke risk and in a number of common clinical scenarios.[24]

In patients with atrial fibrillation (including paroxysmal) and:

- CHA_2DS_2-VASc = 0: no therapy other than antithrombotic therapy, and for patients choosing antithrombotic therapy, aspirin is suggested rather than OAC or combination therapy with aspirin and clopidogrel
- CHA_2DS_2-VASc = 1: OAC is recommended rather than no therapy, and OAC is suggested rather than aspirin or aspirin+clopidogrel
- CHA_2DS_2-VASc = ≥2: OAC is recommended rather than no therapy, aspirin, or aspirin+clopidogrel

"Clearly, the ACCP guidelines are in favour of OACs in almost all patients. They add that where recommendations or suggestions are in favour of OACs, dabigatran etexilate 150 mg bid is suggested, rather than VKAs."

This is the first guideline clearly stating that a novel OAC is preferable to VKA therapy. Prof. Oldgren noted that these guidelines can only consider the 150 mg dose of dabigatran etexilate, which has been granted FDA approval; the 110 mg dose of dabigatran etexilate is unavailable in the USA, as were rivaroxaban and apixaban at the time.

The 2010 ESC guidelines were recently updated and provide an antithrombotic treatment algorithm, as depicted in the adjacent figure.[25]

- CHA_2DS_2-VASc = 0: the guidelines recommend no antithrombotic therapy at all
- CHA_2DS_2-VASc = 1: the guidelines suggest an assessment of bleeding risk (HAS-BLED score), consider patient values and preferences
- Solid lines indicate best option treatment, which are stated to be the novel OACs
- Dashed lines indicate alternative options (VKAs)
- **CHA_2DS_2-VASc = ≥1: novel OACs are preferred over VKAs.**

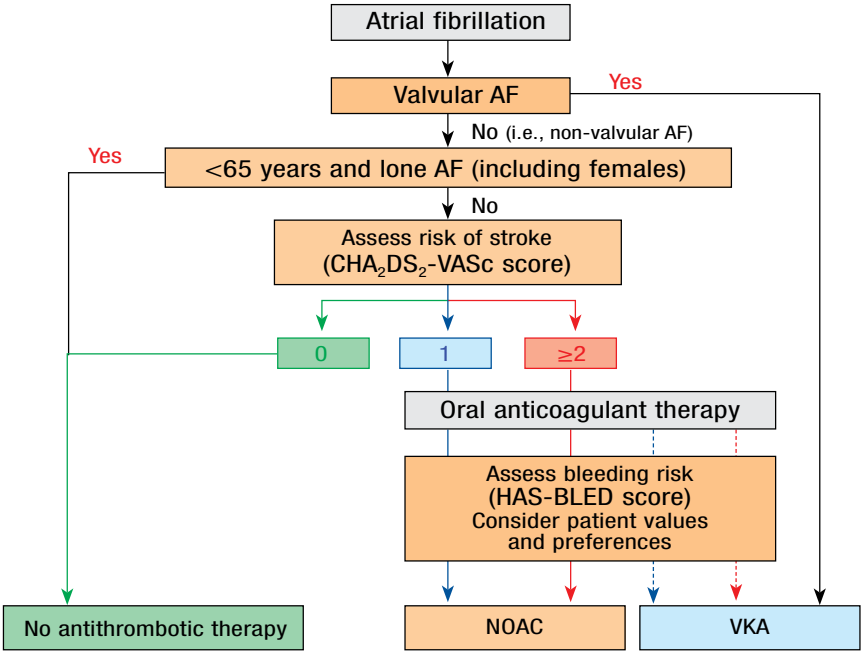

Figure 3. ESC AF guidelines update 2012: antithrombotic treatment algorithm.

References

1. Hart RG, et al. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146(12):857-67.
2. Ansell J, 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.
3. Nutescu EA, et al. New anticoagulant agents: direct thrombin inhibitors. Cardiol Clin 2008;26(2):169-87, v-vi.
4. Umer Usman MH, et al. Advancement in antithrombotics for stroke prevention in atrial fibrillation. J Interv Card Electrophysiol 2008;22(2):129-37.
5. Birman-Deych E, et al. Use and effectiveness of warfarin in Medicare beneficiaries with atrial fibrillation. Stroke 2006;37(4):1070-4.
6. Nieuwlaat R, et al. Atrial fibrillation management: a prospective survey in ESC member countries: the Euro Heart Survey on Atrial Fibrillation. Eur Heart J 2005;26(22):2422-34.
7. Go AS, et al. Anticoagulation therapy for stroke prevention in atrial fibrillation: how well do randomized trials translate into clinical practice? JAMA 2003;290(20):2685-92.
8. Friberg L, et al. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125(19):2298-307.
9. Ezekowitz MD, et al. Rationale and design of RE-LY: Randomized evaluation of long-term anticoagulant therapy, warfarin, compared with dabigatran. Am Heart J 2009;157(5): 805-10.e1-2.
10. Connolly SJ, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 2009;361(12):1139-51.
11. Patel MR, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 2011;365(10):883-91.
12. Connolly SJ, et al. Apixaban in patients with atrial fibrillation. N Engl J Med 2011;364(9): 806-17.
13. Granger CB, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 2011;365(11):981-92.
14. Schneeweiss S, et al. Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012;5(4):480-6.
15. Lip GY, et al. Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 2012;60(8):738-46.
16. Baker WL, Phung OJ. Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes 2012;5(5):711-9.
17. Harenberg J, et al. Comparison of efficacy and safety of dabigatran, rivaroxaban and apixaban in patients with atrial fibrillation using network meta-analysis. Int Angiol 2012;31(4):330-9.
18. Mantha S, Ansell J. An indirect comparison of dabigatran, rivaroxaban and apixaban for atrial fibrillation. Thromb Haemost 2012;108(3):476-84.
19. Miller CS, et al. Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 2012;110(3):453-60.
20. The Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Guidelines for the management of atrial fibrillation. Eur Heart J 2010;31(19):2369-429.
21. Olesen JB, et al. Validation of risk stratification schemes for predicting stroke and thromboembolism in patients with atrial fibrillation: nationwide cohort study. BMJ 2011;342:d124.
22. Friberg L, et al. Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 2012;125(19):2298-307.
23. Oldgren J, et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the $CHADS_2$ score: a subgroup analysis of the RE-LY trial. Ann Intern Med 2011;155(10):660-7.
24. You JJ, et al. Antithrombotic therapy for atrial fibrillation: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012;141(2 Suppl):e531S-75S.
25. Camm AJ, et al. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation. An update of the 2010 ESC Guidelines for the management of atrial fibrillation. Eur Heart J 2012;33:2719-47.

Boehringer Ingelheim

Dr Oldgren has been provided research support by and served in advisory boards on almost all pharmaceutical companies developing NOACs and he has been involved in their clinical trials. Boehringer Ingelheim provided Dr Oldgren with financial support to attend this educational meeting. The publication of this article was supported by an educational grant from Boehringer Ingelheim (NZ) Ltd. Content and opinions expressed in this publication are entirely independent of Boehringer Ingelheim. Products mentioned in the publication are prescription medicines and detailed prescribing information is available at www.medsafe.govt.nz. Treatment decisions based on these data are the full responsibility of the prescribing physician.