The management of venous thromboembolism: A practical tool for the front-line clinician

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Case

You are just about to finish your evening shift and close the pharmacy when Mr. James, a 57-year-old man who is well known to you, makes his way to the dispensary, favouring his right leg. He looks at you with a grimace on his face, and hands you 2 prescriptions, stating he just came from the local emergency department/health care centre. You look at the prescriptions and see that one is for pain management and the other is an anticoagulant. You note the anticoagulant is for only 3 days. Mr. James says, "I have to go back and get some sort of test done on my leg during normal business hours tomorrow."

Background

Venous thromboembolism (VTE), encompassing both deep vein thrombosis (DVT) and pulmonary embolism (PE), is common, affecting up to 5% of the population during their lifetime.¹ After more than half a century with no new therapies, 3 novel oral anticoagulants (NOACs) are now approved by Health Canada for the treatment of acute VTE and prevention of recurrent VTE.²⁻⁴ The NOACs offer many advantages over the traditional therapy of a parenteral anticoagulant transitioned to warfarin, and as a result, there is an increasing shift to treating many of these patients outside of a hospital setting.⁵ Given this shift in care, front-line clinicians must be aware of nuances with these newer treatment options. Herein, we highlight a case to feature a practice tool in the form of a pocket card that provides a systematic, 5-step approach for front-line clinicians to aid in the management of patients across the care continuum of VTE

(Figure 1). This pocket card is available in full as Appendix 1 in the online version of the article and from the Canadian Cardiovascular Pharmacists Network at www.ccpn.ca.

Process for management of acute VTE

Step 1: Determine your patient's likelihood of VTE and confirm diagnosis

DVT occurs quickly and results in acute changes to the affected limb.⁶⁻⁸ A typical red, warm swollen unilateral limb occurs below the location of the clot given the lack of venous return and resultant increased pressure in the venous system with extravasation of fluid into the leg (see Appendix 1, Table 1). Clinically, differentiation between proximal (above the knee, or clot location in the popliteal vein/more proximal) and distal DVTs is helpful, as proximal clots tend to be larger (occur in larger veins) and have an increased likelihood of embolization to the lungs (Figure 2).⁹ The extent of Mr. James's leg swelling is indicative of both the location and extensiveness (size) of the clot.¹⁰ While Mr. James's presentation may be typical of an acute DVT, the nonspecific presentation of DVT mandates objective diagnostic confirmation: Mr. James could also have cellulitis, a Baker's cyst, lymphedema, hematoma, muscle tear, and so on. To proceed with testing for acute DVT, probability scores may be used to discern the likelihood of a DVT (see Appendix 1, Table 2).^{11,12} Should Mr. James have a low probability of DVT, progression with a D-dimer (a simple blood test for fibrin degradation products [evidence of

FIGURE 1 Steps in care (brief summary)**step 1** Determine your patient's likelihood and confirm the diagnosis of VTE

- Assess signs and symptoms of VTE
- Determine probability of patient having a VTE event based on history, physical examination, and risk scoring (e.g., Wells)
- Perform applicable diagnostic testing

step 2 Determine treatment options for the Acute and Long-term treatment of VTE

Phase	Traditional	Apixaban	Dabigatran	Rivaroxaban
Acute	UFH/LMWH + Warfarin	10mg BID x 7 days	Parenteral Anticoagulant X 5-10 days	15mg BID x 21 days
Long-term	Warfarin INR 2.0-3.0	5mg BID	150mg BID (110mg BID)*	20mg daily

* Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110mg BID for those over the age of 80 years or 75 years of age or greater with a concomitant bleeding risk factor and to consider 110mg BID in those with CrCl between 30 and 50 mL/min.

step 3 Determine your patient's duration of therapy for the Long-term Phase

Category of VTE	Duration of Treatment
VTE Provoked by a transient risk factor†	3 months
First unprovoked VTE‡: Low to Moderate Bleed Risk High Bleed Risk	Suggest extending therapy beyond 3 months Suggest 3 months of therapy over extending therapy
Second Unprovoked VTE‡: Low to Moderate Bleed Risk High Bleed Risk	Suggest extending therapy beyond 3 months Suggest 3 months of therapy over extended therapy
Provoked Isolated distal DVT	3 months
Cancer associated VTE (regardless of bleed risk)	Minimum of 3-6 months of LMWH and then reassess duration and agent. Continue anticoagulation if active cancer (overt evidence of cancer) or continuing to receive anticancer therapy

* These decisions are sensitive to patient preference.

† Transient risk factors include surgical and non surgical factors. Nonsurgical provoking factors include pregnancy, estrogen therapy, fracture or plaster casting of lower limb (within 3 months) or hospitalization with confinement to bed (within 3 months), recent lower leg injuries or immobilization or history of prolonged travel (e.g., > 8 hours), within last 6-8 weeks.

‡ Absence of a transient risk factor or active cancer

step 4 Consider an Extended duration of therapy

Determine whether patients should be maintained on extended duration of therapy for secondary prevention. Consider risk of thrombosis recurrence, potential risk reduction with extended anticoagulant therapy, and the patient's individualized risk of bleeding. After discussing these factors with the patient, the patient's preference should be integrated into the treatment plan.

step 5 Pertinent information for patients and clinicians

Factor	Traditional Therapy	Apixaban	Dabigatran	Rivaroxaban
Acute Phase	Parenteral Anticoagulant + Warfarin, INR 2-3	10mg BID x 7 days	Parenteral Anticoagulant x 5-10 days	15mg BID x 21 days with food
Long-term Phase	Warfarin, INR 2-3	5mg BID	150mg BID‡	20mg daily with food
Extended Phase	Warfarin, INR 2-3	2.5mg BID***	150mg BID‡,§	20mg daily with food*
Administration	With or without food	With or without food	With or without food	With food‡
Side effect	Bleeding	Bleeding	Dyspepsia, Bleeding	Bleeding
Laboratory Monitoring	INR, Hgb, platelets	CrCl, Hgb	CrCl, Hgb, platelets§	CrCl, Hgb
General Information	<ul style="list-style-type: none"> • Do not stop your anticoagulant without consulting your healthcare professional • Consult your healthcare professional before taking any new medications • Inform all healthcare providers (dentists, doctors, etc.) you are taking an anticoagulant 			

* Clinical trials compared NOAC against placebo therefore clinical equipoise was assumed for continuation of therapy for the extended phase.

† Both a placebo (RE-SONATE) and warfarin controlled (RE-MEDY) trial have been completed.

‡ AUC decreased by 33% with empty stomach.

*** In trial, 5mg BID was also studied. The Canadian product monograph only lists 2.5mg BID for the prevention of recurrent VTE.

§ During run-in phase with heparin.

¶ Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110 mg BID for those over the age of 80 years or 75 years of age or greater with a concomitant bleeding risk factor and to consider 110 mg BID in those with CrCl between 30 and 50 mL/min.

clot breakdown]) may be done.¹³ The D-dimer is a very sensitive test with modest specificity; therefore, it is most useful if it is negative (below threshold), which enables the clinician to rule out acute DVT (as there is no evidence of clot [fibrin] breakdown). Should it be positive, progression to compression ultrasound is required.

Depending on the geographic location, the ability to perform compression ultrasound may be limited to certain days of the week or hours of the day. Mr. James was sent home from his local health care centre with the presumption that he may have a DVT, with the need to return during business hours to rule the diagnosis in or out through ultrasound confirmation. Most patients who are clinically stable with acute DVT may be managed on an ambulatory basis; historically, many emergency rooms have administered a therapeutic dose of low-molecular-weight heparin (LMWH) and had the patient return daily for their LMWH injection until the diagnosis was ruled in or out.⁵ With the NOACs, an oral option is now available that has the ability to further simplify care and negate the need for injections

and costly emergency room visits as well as extensive laboratory monitoring. Notably, if Mr. James presented to his physician's office with a moderate to high probability of DVT, it would be likely that progression to compression ultrasound would be done (performing a D-dimer is limited given the turnaround for community laboratories), with booking of an urgent ultrasound in the community and provision of anti-coagulant therapy in the interim.

Mr. James has taken his anticoagulant and now his ultrasound is complete. He returns to the pharmacy with his report and hands it to you, and you read, "extensive clot in the popliteal vein extending into the superficial femoral vein." While the pharmacist is not diagnosing the clot, it is important for him or her to understand that the clot burden, along with the cause of the clot, may have implications on therapy duration and occurrence of complications. While you have your laboratory system open, you would look for other testing for Mr. James, specifically renal function and complete blood count (CBC), as well as coagulation tests that may have been

FIGURE 2 Lower extremity vasculature⁸

performed. Mr. James then proceeds to hand you another prescription and states, “The doctor said the dose would change and that I’m to take this for at least 3 months.”

Step 2: Determine treatment options for the acute and long-term treatment of VTE

Three phases of care have been described for the management of VTE (Figure 3).¹⁴ First, an acute phase (day 0 to as long as day 21) encompasses the initial occurrence/diagnosis of the clot, where clot propagation is likely to occur without therapy. Therapy in this phase is often with higher doses of oral agents or parenteral therapy ($\pm$ warfarin) to treat the initial clot (see Appendix 1, Table 5¹⁵⁻¹⁹ and Table 6²⁻⁴). Second, a long-term active treatment phase (3 months to as long as 6 months) ensures the appropriate treatment of the initial clot with (typically) an oral anticoagulant agent (see Appendix 1, Table 6). Third, an extended phase (also known as secondary prevention) may follow for those having a high risk of clot recurrence, balancing this risk with that of major bleeding. This later extended phase must be informed by patients’ values and preferences. For each of these phases, clinical trials have been performed using varying oral

anticoagulant regimens, as outlined in Figure 3¹⁴ and Table 4²⁰⁻²⁴ of Appendix 1.

The goals of treatment (in the short term) for Mr. James are to use an anticoagulant to stabilize the existing clot to prevent clot extension or embolization and to allow his body to begin the process of breaking down the clot. Traditionally, Mr. James would have been limited to receiving only a parenteral anticoagulant (therapeutic doses of either LMWH or fondaparinux) with the intent of transitioning to warfarin therapy (target international normalized ratio [INR] of 2.0-3.0; see Appendix 1, Table 5).^{25,26} While very effective, use of this medication regimen on an ambulatory basis requires teaching patients to self-administer subcutaneous injections for a minimum of 5 days and obtainment of 2 consecutive days of therapeutic INRs (whichever is longer) with frequent laboratory testing. Several large-scale, noninferiority clinical trials have been conducted comparing the traditional standard of care (parenteral anticoagulant transitioned to warfarin) to each NOAC, and all have demonstrated that NOACs are noninferior to traditional therapy for the prevention of recurrent VTE and VTE-related death, with major bleeding rates similar or lower than that

FIGURE 3 VTE phases of care and clinical trials¹⁴

reported with traditional care (see Appendix 1, Table 4).²⁰⁻²⁴

Mr. James presents as a stable patient with a proximal DVT and is typical of the population represented in the NOAC clinical trials.²⁰⁻²⁴ You recall reviewing his renal function (CrCl ~75 mL/min) and noted his hemoglobin within his CBC was within normal limits, providing a benchmark should he have a hemorrhagic event. Given this, treatment with any of the applicable NOAC regimens (see Appendix 1, Table 6) would be appropriate for Mr. James,²⁻⁴ and the regimens are recommended as a preferential choice over warfarin by the current *Chest* guidelines.²⁷ It is important to note that clinical trials assessing the efficacy and safety of NOACs in the management of VTE fall into 2 general designs: apixaban and rivaroxaban studies have compared traditional therapy with an injectable anticoagulant transitioning to warfarin vs the NOAC monotherapy at a larger initiating dose moving to a maintenance dose (rivaroxaban, 15 mg twice daily [with food] must be administered for 21 days, then stepping down to 20 mg daily with food^{21,22}; apixaban, 10 mg twice daily for 7 days, followed by 5 mg twice daily with no dosage adjustment based on weight, renal function and serum creatinine).²⁰ In contrast, studies assessing dabigatran administered a parenteral anticoagulant for 5 to 10 days prior to the transition to dabigatran 150 mg twice daily.^{23,24}

For stroke prevention in atrial fibrillation, NOACs have varying dosage recommendations that are dependent on different variables for each agent, including renal dysfunction, advanced age (with or without accompanying bleeding risk factors) or low body weight. It is important to note that for the indication of acute VTE, provided the minimum renal function cutoff is met, no dosage adjustment was made in the clinical trials. Clinicians should avoid rivaroxaban and dabigatran in patients with CrCl <30 mL/min and apixaban if CrCl <25 mL/min, as these patients were excluded from the NOAC trials, and these agents accumulate in patients with significant renal dysfunction. Clinical trials also excluded patients having DVTs in atypical locations (e.g., splanchnic veins, hepatic veins, axillary veins, subclavian veins, etc.) or those having vena cava filters inserted. Moreover, within the population suffering a PE, those having massive clots requiring thrombolytic therapy or surgery or presenting with hemodynamic instability were excluded. Given the lack of data in these unique patient populations, most clinicians would elect to use traditional therapy at this time. Notably, a minority of patients having cancer were included in the NOAC trials. Current guidelines recommend LMWH therapy over oral anticoagulant options for cancer-associated thrombosis.²⁷ Should an oral anticoagulant be used in cancer-associated thrombosis, no preference for either

warfarin or a NOAC is given.²⁷ The front-line clinician should be aware of characteristics of the NOACs, including (but not limited to) quick onset, quick offset, extent of renal elimination, contraindications to use and drug-drug interactions (Table 1 and see Appendix 1, Table 8²⁸⁻³⁰).

Step 3: Determine your patient's duration of therapy for the long-term phase

One of the most clinically challenging areas in the management of VTE is establishing the duration of therapy. Guidelines suggest anticoagulating patients for a minimum of 3 months with reassessment to follow.²⁷ Patients who have a provoking, strong risk factor (such as surgery) require the shortest duration of therapy, while those having unprovoked clots have longer therapy durations, given that clot recurrence is more likely in a setting where no causative factor can be identified (and removed).²⁷ Regardless of the clinical scenario, it is helpful to pose, at therapy initiation, an anticipated duration of therapy to avoid having patients continue on long-term therapy unnecessarily as well as to minimize the probability of nonadherence due to lack of knowledge of intended duration. In determining the duration of therapy for the "long-term phase," your goal is to effectively treat the initial clot (see Appendix 1, Table 9). Reassessment of therapy at 3 months will typically reveal signs and symptoms of residual clot for patients having a more extensive clot burden or even complications from the initial clot. The most common complication from DVT is postthrombotic syndrome, occurring in 25% to 50%,³¹ whereas for PE, complications include compromise of the right ventricle and chronic thromboembolic pulmonary hypertension (occurring in ~5%).²⁷ Signs/symptoms that might suggest the need for extension of therapy for Mr. James's DVT may include affected limb continuing to be larger, limb swelling progressing with limb use, a pale or dusky colour to the limb, reporting of limitations with using the limb and a dull ache to the limb with continued use (e.g., postthrombotic syndrome). For those with PE, reports of ongoing pain, shortness of breath and limitations in activity prior to the clot are common. These patients should be treated longer, with plans for ongoing reassessment (every 3-6 months). Patients having VTE in the setting of cancer should be treated with LMWH for a minimum of 3 to 6 months.

Step 4: Consider an extended duration of therapy

Following the long-term treatment phase, the front-line clinician must, in conjunction with the patient, assess the need for ongoing therapy to prevent a recurrent VTE (i.e., extended or secondary prevention). This is one of the most clinically challenging areas in the management of VTE, given that we lack good prediction tools for the risk of recurrent VTE and risk of major bleeding and must strive to integrate patient values and preferences into the decisions made. Patients with transient provoking factors (e.g., surgery, hormone therapy) have the lowest risk of VTE recurrence and therefore would be expected to derive less benefit from extending therapy beyond 3 months (see Appendix 1, Table 10).^{27,32} In contrast, those having unprovoked VTEs have higher recurrence rates and thus may benefit more from extension therapy, provided the risk of major bleeding is not excessive and is minimized by removing factors that may predispose to bleeding (see Appendix 1, Table 11).²⁷ Notably, factors identified for the risk of major bleeding largely stem from data with traditional therapy (parenteral anticoagulant followed by warfarin), and given that we now have NOACs, these rates may be lower.

Several clinical trials have assessed NOACs for the extended phase of therapy (see Appendix 1, Table 12).^{21,33,34} Most of these trials have been placebo controlled, and the clinician must realize that clinical equipoise was evident for patients enrolled in these trials, given they had a 50% chance of receiving no ongoing therapy. In contrast, trials having a traditional care (namely, warfarin) control group would be expected to recruit patients for whom the clinician has made the decision that extended prevention is necessary and hence that recurrent VTE was more likely. All 3 placebo-controlled trials clearly showed efficacy for the NOAC to prevent recurrent VTE, with no statistically significant increase in major bleeding.^{21,33,34} Notably, the only dose of dabigatran studied in VTE is the 150 mg twice-daily dosing.^{23,24,34} Despite this, the product monograph suggests applying the lower 110 mg twice-daily dose for those patients fulfilling criteria for this dose for the indication of atrial fibrillation.³ The only NOAC having clinical trial data at a prophylactic dose for this extended phase is apixaban.³³ Notably, both doses of apixaban (5 mg twice

TABLE 1 Characteristics of the NOACs

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Mechanism of action	Direct thrombin inhibitor	Direct factor Xa inhibitor	
Pharmacokinetics			
t _{max}	0.5-2 hrs	2-4 hrs	3-4 hrs
T _{1/2}	12-14 hr	7-11 hrs	8.3 hrs
Elimination	Renal 80%	Renal 33% (active drug)	Renal 27%
Dosing for acute VTE treatment	After 5-10 days LMWH, dabigatran 150 mg BID (110 mg BID*)	Rivaroxaban 15 mg BID x 3 weeks, then rivaroxaban 20 mg daily	Apixaban 10 mg BID for 7 days, then apixaban 5 mg BID
Administration	Do not chew, break or open capsules Swallow capsule whole with or without food	Take with food (preferably main meals) Can be crushed and administered by NG	Take with or without food Can be crushed, suspended in water and administered by NG
Contraindications	Active bleeding; lesions at risk of clinically significant bleeding (e.g., hemorrhagic or ischemic stroke within 6 months [note: for apixaban—recent cerebral infarction], active peptic ulcer disease with recent bleeding)		
	Treatment with strong P-glycoprotein inhibitors or inducers (e.g., ketoconazole, rifampin)	Concomitant treatment with strong inhibitors of both CYP P450 3A4 and P-glycoprotein (e.g., ketoconazole, ritonavir); <i>strong inducers should also be avoided</i>	
	CrCl <30mL/min	Use in patients with CrCl <30mL/min is not recommended	Not recommended in patients with CrCl <15 mL/min, clinical data are very limited in patients with CrCl 15-24 mL/min
	Not recommended in patients with hepatic enzymes >3X upper limit of normal	Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and with clinically relevant bleeding risk <i>Use with caution in moderate hepatic impairment</i>	Not recommended in severe hepatic impairment or hepatic disease associated with coagulopathy and clinically relevant bleeding risk. <i>Use with caution in mild or moderate hepatic impairment</i>
	Contraindicated in patients with prosthetic heart valves requiring anticoagulation due to valvular status	Not recommended in patients with prosthetic heart valves	
	Dabigatran is contraindicated in nursing women. <i>Use in pregnancy is not recommended for rivaroxaban and apixaban.</i>		
Laboratory assessment and anticoagulation testing	Monitor CBC at baseline and with any change in health status that may impact hemoglobin, red blood cell count or platelets. Monitor CrCl at baseline and with any change in health status that may impact renal function and appropriateness of dose/continued use.		
	Routine anticoagulant monitoring is not required. The INR and aPTT do not quantitatively correlate with drug levels and should not be used for routine monitoring.		
	A calibrated TT* (Hemoclot assay) will provide dabigatran levels. In absence of Hemoclot assay availability, a normal TT rules out presence of clinically important dabigatran levels; aPTT may be used to reflect presence of drug, although a minority of patients (<2%) may have a normal aPTT just prior to their next dose while chronically taking dabigatran.	Rivaroxaban-calibrated anti-Xa levels reflect the pharmacodynamic effect in a dose-dependent fashion. In the absence of calibrated anti-Xa levels, PT (Neoplastin reagent) may be useful to reflect presence of drug.	Rotachrome Heparin Anti-Xa assay reflects the pharmacodynamic effect of apixaban in a linear, dose-related fashion. In the absence of calibrated anti-Xa levels, PT/INR is not effective for assessing apixaban.
Adverse effects	Dyspepsia, bleeding	Bleeding	Bleeding

(continued)

TABLE 1 (continued)

	Dabigatran (Pradaxa)	Rivaroxaban (Xarelto)	Apixaban (Eliquis)
Antidote	For dabigatran only, idarucizumab (Praxbind) has conditional notice of compliance for life-threatening or uncontrolled bleeding as well as emergency surgery/urgent procedures. Recommended dose is 5 g (administered as 2 consecutive boluses or infusions of the 2.5 g vials). Andexanet alpha is currently under study for reversal of anti-Xa inhibitors. Despite limited data, options may include activated prothrombin complex concentrates (PCCs), inactivated PCCs or rFVIIa. For dabigatran only, dialysis may be considered but may not be practical.		
Drug-drug interactions	Dabigatran etexilate is a substrate for the efflux P-gp transporter. Plasma concentrations are affected by strong P-gp inducers and P-gp inhibitors.	Elimination by CYP3A4 and P-glycoprotein (P-gp); concomitant strong inhibitors/inducers of both of these pathways will increase/decrease rivaroxaban and apixaban exposure, respectively.	

*Although not studied in the acute treatment of VTE, the manufacturer suggests aligning with the atrial fibrillation dosing strategy of 110 mg BID for those over the age of 80 years or 75 years or older with a concomitant bleeding risk factor and to consider 110 mg BID in those with a CrCl between 30-50 mL/min.

LMWH, low molecular weight heparin; BID, twice daily; TT, thrombin time; NG, nasogastric.

daily and 2.5 mg twice daily) had very similar rates of VTE recurrence, while the lower dose demonstrated less major bleeding. Given this, the apixaban product monograph recommends only the lower dose for this extension phase.² For rivaroxaban, the EINSTEIN-choice study is now under way, comparing rivaroxaban 20 mg daily, rivaroxaban 10 mg daily and acetylsalicylic acid (ASA) 100 mg daily and will offer important information about using the lower (prophylactic) dose of rivaroxaban.³⁵ Last, 2 trials (WARFASA and ASPIRE) assessed the use of ASA for secondary VTE prevention and reported an overall 30% reduction in recurrent VTE.^{36,37} While this appears good relative to placebo, one must realize that NOACs report (on average) an 80% risk reduction in the same setting, and most experts suggest that the use of ASA for long-term prophylaxis should be considered only when the use of an anticoagulant has been ruled out.

Step 5: Pertinent information for your patient

Patient education is paramount when using anticoagulants and should encompass the benefits and risks of therapy, emphasis on the need for adherence and dosing specific to the agent prescribed, as well as integration with ongoing monitoring and follow-up (e.g., therapy reassessment, renal function).³⁸

Summary

Pharmacists are well positioned and very accessible to the general public. As such, our role in ensuring optimal use of high-risk therapies such as anticoagulants that are relatively new in the marketplace is critical. As clinicians, we should be empowered to access diagnostic testing to allow both confirmation of the diagnosis and an ability to gauge the location and extent of the individual patient's clot burden (Step 1). Pharmacists must be informed of the varying pharmacologic regimens for the treatment of VTE, having first-hand knowledge of dosing to ensure patients are prescribed appropriate therapies as they transition through the 3 phases of therapy (Step 2). As patients return to the pharmacy for refills, the pharmacist should be attuned to the anticipated duration of therapy (Step 3), ensuring that at least annual reassessment occurs and that patients transitioned to the extended phase are prescribed the appropriate agent/dose (Step 4). Educating our patients to be proactive in their health care will optimize outcomes and must include information on the disease itself, the risk of therapy (major bleeding), and importance of adherence, knowing that 1 missed dose of a NOAC leaves the patient unprotected (Step 5). As therapy choices evolve, the complexities broaden, and the front-line pharmacist is well situated to optimize care and ensure good patient outcomes. ■

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Author Contributions: Both authors drafted, revised and approved the final version of this article.

Declaration of Conflicting Interests: T.J. Bungard has received honoraria from Bayer and Bristol Myers Squibb-Pfizer within the past 2 years. She has also received unrestricted grants from Pfizer and Bayer. W. Semchuk has received honoraria from Bayer, Pfizer, Bristol Myers Squibb and Boehringer Ingelheim within the past 2 years. He has served as a consultant or on an Advisory Board for Bayer and Pfizer/Bristol Myers Squibb in the past 2 years, and he has received a research grant from Pfizer in the past 2 years.

Funding: The authors received no financial support for the research, authorship and/or publication of this article.

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