Me, Active in Health Policy? Why?
Campbell et al.

CanMEDS Health Advocacy Curriculum for Residents
Sohi et al.
PRADAX (dabigatran etexilate) is indicated for the prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

PRADAX is contraindicated in patients with: severe renal impairment (CrCL <30 mL/min); hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of hemostasis; lesions at risk of clinically significant bleeding, e.g. extensive cerebral infarction (hemorrhagic or ischemic) within the last 6 months, active peptic ulcer disease with recent bleeding; concomitant treatment with the strong P-glycoprotein (P-gp) inhibitors, i.e. oral ketoconazole, and with known hypersensitivity to dabigatran, dabigatran etexilate or to any ingredient in the formulation or component of the container.

Bleeding is the most relevant side effect of PRADAX; bleeding of any type or severity occurred in 16.5% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism. As with all anticoagulants, PRADAX should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRADAX. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed PRADAX. Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially if risk factors are combined. Should severe bleeding occur, treatment with PRADAX must be discontinued and the source of bleeding investigated promptly. Patients who develop acute renal failure must discontinue PRADAX. In patients who are bleeding, an aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT >80 sec at trough, i.e. when the next dose is due, is associated with a higher risk of bleeding.

Agents that may enhance the risk of hemorrhage should not be administered concomitantly with PRADAX, or, if necessary, should only be administered with caution. Treatments that should NOT be administered concomitantly with PRADAX due to increase in bleeding risk include: unfractionated heparin and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, bivalirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, sulfinpyrazone and vitamin K antagonists such as warfarin.

The concomitant use of PRADAX with the following treatments has not been studied and may increase the risk of bleeding: rivaroxaban, prasugrel and the strong P-gp inhibitors itraconazole, tacrolimus, cyclosporine, rifabutin, tipranavir, nelfinavir and saquinavir. Unfractionated heparin may be administered at doses necessary to maintain a patent central venous or arterial catheter. In patients with atrial fibrillation treated for the prevention of stroke and systemic embolism, the co-administration of oral anti-platelet (including ASA and clopidogrel) and NSAID therapies increases the risk of bleeding by about two-fold (see ACTION and CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic interactions). If necessary, co-administration of low-dose ASA, i.e. ≤100 mg daily with PRADAX may be considered for other indications than stroke prevention in atrial fibrillation. The concomitant use of PRADAX with the strong P-gp inducer, rifampicin, reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John's Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution.

The most common adverse events observed in ≥1% of PRADAX 150 mg BID patients and 110 mg BID patients was anemia (1.6%, 1.2%), epistaxis (1.1%, 1.1%), gastrointestinal hemorrhage (4.6%, 3.3%), urogenital hemorrhage (1.4%, 1.1%), abdominal pain (2.2%, 2.3%), diarrhea (1.2%, 1.3%), dyspepsia (3.9%, 4.2%) and nausea (1.2%, 1.0%), respectively. Gastrointestinal adverse reactions occurred more often with dabigatran etexilate than warfarin. These were related to dyspepsia (including upper abdominal pain, abdominal pain, abdominal discomfort, epigastric discomfort) or gastritis-like symptoms (including GERD, esophagitis, erosive gastritis, gastric hemorrhage, hemorrhagic gastritis, hemorrhagic erosive gastritis and gastrointestinal ulcer). Gastrointestinal hemorrhage occurred at a higher frequency with PRADAX 150 mg BID and 110 mg BID (4.6%, 3.3%, respectively) compared to warfarin (2.6%). The underlying mechanism of the increased rate of GI bleeding has not been established.

Allergic reactions or drug hypersensitivity including urticaria, bronchospasm, rash and pruritus have been reported in patients who received dabigatran etexilate. Rare cases of anaphylactic reactions have also been reported.

For complete prescribing information, please refer to the Product Monograph.


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ABOUT THE COVER
This photo was taken by Rene Ehrhardt, a freelance photographer based in London, United Kingdom, who
specializes in wedding, portraiture, and event photography (www.ehrhardt-photography.com). In his spare time, he
is a keen traveller and photographs land, sea and city scapes, architecture, interiors, and exteriors. He captured this
photo of Notre-Dame Basilica in 2008 while on vacation in Montreal, Quebec.

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- Reduce the risk of nonfatal stroke
- Reduce the risk of coronary artery revascularization

CRESTOR is also indicated as an adjunct to diet, at least equivalent to the Adult Treatment Panel III (ATP III TLC diet), for the reduction of elevated total cholesterol (Total-C), LDL-C, ApoB, the Total-C/HDL-C ratio and triglycerides (TG) and for increasing HDL-C in hyperlipidemic and dyslipidemic conditions, when response to diet and exercise alone has been inadequate, including: primary hypercholesterolemia (Type IIa including heterozygous familial hypercholesterolemia and severe nonfamilial hypercholesterolemia); combined (mixed) dyslipidemia (Type IIb); or homozygous familial hypercholesterolemia where CRESTOR is used either alone or as an adjunct to diet and other lipid-lowering treatment such as apheresis.

In the JUPITER trial, there were no statistically significant treatment differences between the CRESTOR and placebo groups for death due to cardiovascular causes or hospitalizations for unstable angina. The majority of patients are controlled at the 10 mg dose.

A dose of 20 mg once daily has been found to reduce the risk of major cardiovascular events. CRESTOR is contraindicated in patients who are hypersensitive to any component of this medication; in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal; in pregnant and nursing mothers and in patients using concomitant cyclosporine. CRESTOR 40 mg is contraindicated in patients with predisposing factors for myopathy/ rhabdomyolysis and in Asian patients.

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In the JUPITER trial, CRESTOR 20 mg was observed to increase plasma glucose levels, which were sufficient to shift some prediabetic subjects to the diabetes mellitus status.

Most commonly reported adverse events in hypercholesterolemia vs. placebo were headache (1.4% vs. 2.2%), abdominal pain (1.7% vs. 2.2%), flatulence (1.6% vs. 2.7%) and nausea (2.2% vs. 1.6%).

Most commonly reported adverse events in prevention of major cardiovascular events vs. placebo were urinary tract infection (6.1% vs. 8.6%), nasopharyngitis (1.6% vs. 2.2%), back pain (1.6% vs. 6.6%) and myalgia (1.6% vs. 6.6%).

See the Product Monograph for full contraindications, warnings, precautions, dosing and administration.


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In Search of Shakespeareans

Finlay McAlister MD

About the Author
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The Royal College Committee on Specialties approved the motion to recognize general internal medicine (GIM) as a subspecialty of medicine on October 29, 2010. This was a major hurdle on the path to recognition, but we still need the approval of the Royal College Education Committee, the Executive of Council, and ultimately the Royal College Council. All going well, I hope we will thus have Royal College recognition of GIM by late February 2011. Recognition by the Royal College will mark only the start of our journey. The onus will then be on all of us to attract trainees into careers in GIM. At our Annual Scientific Meeting in Vancouver, Dr. Bill Coke pointed out that whereas 2% of medical subspecialists are older than 65 years, 23% of general internists in the Canadian Medical Association 2009 Masterfile are older than 65 years. Clearly, if we want our specialty to continue to exist, we need to attract trainees to follow in our footsteps!

We also heard from both community- and university-based general internists at the Provincial Roundtable, and the message was the same from both groups: we are desperately short of general internists. In the coming months, there will be discussion of the issues surrounding 4 and 5 years of training in GIM. But we should not lose our focus – we need to train both community and university internists. The flexibility proposed by Dr. Brian O’Brien and the GIM Program directors for a 2-year GIM training program will meet the goals of both of our key constituencies – academic GIM trainees will have more time to pursue MSc degrees in research or education, and community GIM trainees will obtain clinical, procedural, and management skills appropriate to their chosen community of practice.

Although the popularity of GIM training has increased recently, we are still training only about half of the number of general internists required to maintain the status quo. Dr. Coke presented data, drawn from the CMA Masterfile and CAPER, that showed the scope of the problem. Among an average retirement age of 70 years, we need to produce 463 new general internists by 2013 just to produce 463 new general internists by 2013 just to maintain the current GIM workforce. We anticipate graduating only 239 GIM specialists by that date. In fact, GIM and geriatrics are the only two medical specialties that have fewer trainees than needed to replace anticipated retirements. Thus, unless we can drive a rapid upswing in GIM training positions, the situation, both for community and academic GIM, is going to get worse in the short term.

How can we increase the popularity of GIM as a career choice? While the traditional role modelling and mentoring of trainees will clearly remain the foundations of our recruitment efforts, better pay for general internists will help too. As many readers know, several provinces have modified fee codes to enhance remuneration for comprehensive care of patients with multi-system disease. Many of these billing codes benefit those of us in GIM preferentially and reflect government recognition of the need for more general internists. We should explicitly acknowledge that economics does play a role in career choice, particularly as our trainees are now graduating with higher levels of debt than at any time in the past. As the pendulum swings to reimbursing cognitive skills as much (or more) than procedural skills, I think we will see a decline in the popularity of some of the more procedurally based subspecialties in medicine.

Another important factor working in our favour is the increasing prevalence of multi-system disease and co-morbidities in the Canadian population. A 2003 study from the Saguenay region of Quebec found that the average number of chronic conditions in patients aged 45–64 was 4.1 (men) and 4.8 (women), and in patients aged over 65 it was 6.3 (men) and 6.6 (women). In the words of the authors of that report, “Patients with multimorbidity … represent the rule rather than the exception.” Surely internists, specialists in complex adult medicine, will be best suited to help our primary care colleagues deal with these increasingly challenging patients.

Finally, the strongest factor working in our favour for recruitment is the sheer diversity of patients we, as general internists, meet. In an earlier message (April 2010), I had opined that no 2 days, and no two patients, are ever the same for general internists and that that was what drove me to choose GIM. Dr. Tinsley Harrison said it better in his introduction to the first edition of his Principles of Internal Medicine, when he stated that the best physicians must have “a Shakespearean breadth of interest.” The task for all of us is to continue to find the budding Shakespeareans among our trainees.

References
En quête d’émules de Shakespeare

Finlay McAlister MD

Au sujet de l’auteur
Finlay McAlister est membre de la Division de médecine interne générale de l’Université de l’Alberta à Edmonton. Prière d’adresser la correspondance à Finlay.McAlister@ualberta.ca.

Le 29 octobre 2010, le Comité des spécialités du Collège royal a adopté la motion voulant que la médecine interne générale soit reconnue au titre de surspécialité médicale. Voici que nous venons de franchir une haie de taille dans ce parcours de la reconnaissance, mais il nous faut encore obtenir l’approbation du Comité de l’éducation, du Comité de direction du Conseil et, au bout du compte, du Conseil d’administration du Collège royal. Si tout se déroule sans heurts, j’espère bien que le Collège royal donnera son aval à la reconnaissance de la médecine interne générale à la fin de février 2011.

Cette reconnaissance du Collège royal marquera le début de l’aventure. Il nous incombera alors d’attirer des médecins résidents vers notre surspécialité. Au dernier congrès scientifique à Vancouver, le docteur Bill Coke a fait remarquer que 2 % des médecins surspécialistes sont âgés de plus de 65 ans, tandis que 23 % des internistes généralistes dont le nom figure dans le fichier central de l’Association médicale canadienne (AMC) en 2009 ont plus de 65 ans. À l’évidence, nous devons recruter des médecins résidents pour assurer la viabilité de notre spécialité.

Des internistes généralistes des milieux communautaires comme des milieux universitaires ont exprimé leur opinion lors de la table ronde provinciale, et les deux groupes ont transmis le même message : la pénurie d’internistes généralistes est criante. Dans les prochains mois, la discussion s’attardera aux questions ayant trait aux 4e et 5e années de la formation en médecine interne générale. Mais gardons-nous de perdre de vue notre but, celui de former des internistes de pratique communautaire et des internistes de pratique universitaire. Grâce à sa souplesse, la proposition du docteur Brian O’Brien et des directeurs de programme de formation de se doter d’un programme de formation de deux ans satura répondre aux besoins des deux milieux de pratique : les médecins résidents qui se destinent au milieu universitaire auront amplement le loisir d’entreprendre une maîtrise en recherche ou en éducation et les médecins résidents qui s’orientent vers la pratique communautaire acquerront les aptitudes cliniques et techniques et les compétences en gestion nécessaires à leur mode de pratique.

Bien que la formation en médecine interne générale ait gagné en popularité dernièrement, nous ne formons que la moitié environ des internistes généralistes qu’il faudrait pour que la situation reste telle quelle. Le docteur Coke a illustré l’ampleur du problème par des données issues du fichier central de l’AMC et du Système informatisé sur les stigmates post-M.D. en formation clinique (CAPER). En supposant que l’âge moyen de la retraite est de 70 ans, nous devrions former 463 nouveaux internistes généralistes d’ici 2013 juste pour compenser les départs à la retraite et maintenir l’effectif tel qu’il est en ce moment. Cependant, nous prévoyons que seulement 239 internistes généralistes frais émulons seront entrés en fonction d’ici là. De fait, la médecine interne générale et la gériatrie sont les deux seules spécialités médicales où les résidents ne sont pas assez nombreux pour remplacer les médecins qui prendront leur retraite. Aussi, à moins que nous puissions faire grimper rapidement le nombre de postes de formation en médecine interne générale, la situation, tant en pratique communautaire qu’en pratique universitaire, ira de mal en pis à brève échéance.

Que faire pour que la médecine interne générale devienne un choix de carrière prisé ? Manifestement, l’exercice du modèle de rôle et du mentorat demeurera l’assise du recrutement, mais celui-ci s’en trouverait facilité si l’on haussait la rémunération de l’interniste généraliste. Vous êtes nombreux à savoir que plusieurs provinces ont modifié leur barème d’honoraires pour rehausser la rémunération des médecins qui produisent des soins globaux aux patients atteints d’une maladie multisystémique. Nombre de ces nouveaux codes de facturation sont avantageux d’abord pour nous autres en médecine interne générale, sans compter qu’ils traduisent le fait que les administrations publiques se rendent compte de la nécessité d’augmenter le nombre d’internistes généralistes. Nous devrions admettre en toute franchise que les aspects financiers entrent en jeu dans le choix d’une carrière, d’autant plus que les médecins résidents terminent leur formation à un niveau d’endettement plus élevé que jamais auparavant. Au moment où le pendule se dirige vers la rétribution des compétences cognitives et des habiletés techniques à égale mesure (si ce n’est plus pour les premières), je prévois que certaines surspécialités médicales à forte composante opératoire deviendront de moins en moins attrayantes.

La prévalence croissante des troubles multisystémiques et de la comorbidité dans la population canadienne est un autre facteur important qui nous est favorable. Une étude effectuée en 2003 au Saguenay (Québec) révèle que le nombre moyen d’affections chroniques chez les patients âgés de 45 à 64 ans était de 4,1 chez les hommes et de 4,8 chez les femmes à ce moment-là et qu’il était de 6,3 chez les hommes et de 6,6 chez les femmes dans le groupe de patients de plus de 65 ans. Pour reprendre le mot de l’un des auteurs du rapport : « Les patients présentant une multimorbidité…sont la règle, non pas l’exception ». Dans un tel contexte, l’interniste, spécialiste de la médecine complexe de l’adulte, est certes le mieux placé pour prêter main-forte à ses collègues de première ligne dans la prise en charge de ces cas de plus en plus difficiles.

Enfin, la diversité des cas qui sont le lot de la médecine interne générale est sans doute l’argument le plus convaincant aux fins de recrutement. J’ai déjà dit qu’il n’y a pas deux jours ni deux patients pareils dans la vie de l’interniste généraliste et que c’est ce qui m’a motivé dans le choix de cette carrière. Le docteur Tinsley Harrison le dit avec plus d’élégance dans son introduction à la première édition de ses Principles of Internal Medicine lorsqu’il affirme que le meilleur médecin est celui qui a un « champ d’intérêt shakespearien ». La tâche qui nous attend est d’identifier ces émules de Shakespeare parmi les médecins résidents.

Références
Congratulations

The Canadian Society of Internal Medicine congratulates the following winners and presenters from its Annual Scientific Meeting, held on October 27–30, 2010, in Vancouver.

Osler Awards
Dr. Howard Abrams, Toronto, Ontario
Dr. Donald Echenberg, Sherbrooke, Quebec

CSIM/Royal College Osler Lecture
Dr. Samuel Benaroya, Montreal, Quebec
“Great Expectations: Challenges and Leadership in Canadian Medical Faculties”

Hui Lee Health Promotion Scholarship
Dr. Andrea Kermack, McGill University

Ted Giles Clinical Vignettes
First Place – Dr. Samantha Halman, University of Ottawa
“A Modern Case of Scurvy: Gastrointestinal Hemorrhage in a Hemodialysis Patient”

Second Place – Dr. Lindsay Crabbe, McMaster University
“A Breathtaking Presentation of Metastatic Renal Cell Carcinoma”

Third Place – Dr. Erin Kelly, University of Ottawa
“Master of Disguises – An Interesting Case of CNS Pseudovasculitis”

CSIM/CAPM Awards for Post-Graduate Research
Research Oral Competition
First Place – Dr. Karmon Helmle, University of Calgary
“Basal Bolus Insulin Therapy: A ‘BBIT’ of Change in Hospital Diabetes Management”

Second Place – Dr. Leena Amin, University of Toronto
“Impact of Gender and Socioeconomic Status on Lower Extremity Amputation Rates in Individuals with Diabetes”

Third Place – Dr. Ngan Lam, University of Western Ontario
“Hospital Admissions for Hyperkalemia with Trimethoprim-Sulfamethoxazole”

Research Poster Competition
First Place – Dr. Geneviève Beaujieu-Boire, Sherbrooke University
“MUSIC Project: Musicotherapy at the Intensive Care Unit”

Second Place – Dr. Alexandre Lafleur, Université Laval
“Atorvastatin Increases Intestinal Expression of NPC1L1 in Hyperlipidemic Men”

Third Place – Dr. Ben John Wilson, University of Calgary
“Pulse Oximeter Accuracy in Intensive Care Unit Patients with Severe Sepsis: A Retrospective Cohort Study”

Dr. David Sackett Senior Investigator Award
Dr. Jack Tu, Toronto, Ontario
“Canadian Cardiovascular Outcomes Research Team: Lessons Learned” (to appear in Volume 6, Issue 1)

New Investigator Award
Dr. John You, McMaster University
“Achieving a Peaceful Death: The Internist’s Role in Advance Care Planning” (see p. 174)

CSIM Annual Scientific Meeting
October 12–15, 2011
Halifax, Nova Scotia

Information: csim@royalcollege.ca/613-730-6244

Please watch for the call for abstracts and award submissions.
Most Canadians are physically inactive and eat an unhealthy diet. The consequences are hypertension, obesity, diabetes mellitus (type 2), dyslipidemia, cardiovascular disease, and several types of cancer. These changes are occurring throughout the industrialized world and, sadly, it has been predicted that the next generation after ours will be the first since industrialization where the life expectancy is anticipated to be shorter than the previous one. Note that the greatest impact of these chronic non-communicable diseases is in the developing world. As internists, a large proportion of our patients have these health risks and diseases. However, it is important to note that much of the death and disability caused by health risks are below the thresholds we traditionally use in clinical medicine. For example, about 50% of blood pressure–related disease occurs in individuals who are considered to have normal blood pressure. Population-based approaches to lower risk can prevent disease in those with clinical risk as well as those who we perceive are not at risk: for example, lowering blood pressure on a population-wide basis reduces the risk of stroke in both hypertensive and normotensive groups. Improved population health often requires strategic implementation of health policy initiatives.

Internists can play an important role in advocating for policy changes to reduce risk and prevent disease. In recent years, Canadian health care professionals have helped by advocating for health policy changes to reduce smoking and intake of dietary trans fats and sodium, which have the potential to markedly improve the well-being of Canadians. Hypertension, like most other prevalent health risks, is largely preventable. Unhealthy diets high in sodium and saturated fats and low in fresh fruits and vegetables; physical inactivity and weight gain; coupled with excess alcohol consumption and smoking cause many of our current health risks. In Canada, more than 70% of the adult population have at least one or more traditional health risk factor. It is estimated that about 95% of those living an average lifespan will become hypertensive: almost half of Canadians over the age of 60 are on medications for hypertension. Changing lifestyle is very difficult in our social environment where an unhealthy diet is easy, fast, and inexpensive. Nearly all of our communities encourage driving, rather than an alternative mode of transport that involves some degree of daily physical activity. The government policies required to facilitate healthy choices have been outlined by many public health organizations and expert groups – but rarely implemented. This lack of political action is likely a consequence of a failure of health care professionals (and their representative organizations) to engage public opinion. On some health issues (tobacco use, dietary trans fats, and sodium intake), there has been modest success in modifying outcomes.

Our government does not intervene to limit the provision of unhealthy food in many of our schools, to our military, or to patients and visitors in our hospitals. Municipal, provincial, and federal buildings are often unhealthy. The food industry, which claims to be self-regulating, continues to heavily market unhealthy food items to children. As a result, childhood obesity is on the rise. Physicians have sat on the sidelines, waiting for some other group or person to act.

In New York City, a food procurement policy is being developed to ensure that government buildings buy and sell only healthy food. The Quebec provincial government, in response to health advocates, has banned advertising of foods that might contribute to childhood obesity. In Finland, warning food labels alert consumers to high sodium content. In the United Kingdom, colour-coded packaging labels have been developed to indicate which foods to avoid (red), be cautious of (orange), or consider safe to eat (green) – based on their sodium, saturated fat, and simple sugar contents. When this easy-to-understand food label was considered for use in Europe, the food sector reportedly spent $1 billion in a successful lobby to block its use – while the health sector was largely silent. The Canadian Society for Internal Medicine’s Health Promotion Committee will endorse policies and actions that promote health and prevent disease. Every internist in Canada has a potential role and responsibility to engage in public advocacy, and we encourage your active participation. By aligning health care professionals, their organizations, and various levels of government to work on a common policy agenda, we can make substantive progress toward improving the health of Canadians, now and in the future.

Reference/Référence

Moi, agir à l’échelon de la politique de la santé? Pourquoi?

Norm Campbell MD, Bert Govig MD, Don Echenberg MD, au nom du Comité de promotion de la santé de la Société canadienne de médecine interne

La majeure partie de la population du pays est inactive et ne mange pas de façon équilibrée. Un tel mode de vie a des conséquences : hypertension, obésité, diabète de type 2, dyslipidémie, maladie cardiovasculaire et cancers de toute sorte. Cette situation se répand dans tout le monde industrialisé, et l’on prévoit, hélas, que la génération qui nous suit sera la première depuis l’industrialisation dont l’espérance de vie sera moindre que celle de la précédente. A souligner que ces maladies chroniques non transmissibles ont un effet dévastateur dans les pays développés surtout. Un grand nombre de nos patients, à nous internistes, sont aux prises avec ces risques pour la santé et ces maladies. Il faut savoir toutefois que la mortalité et l’incapacité découlant de ces risques pour la santé se produisent pour beaucoup en deçà des seuils généralement admis en pratique clinique. Ainsi, dans près de 50 % des cas de maladie liée à la pression artérielle, celle-ci se situe dans les valeurs normales. La stratégie de masse destinée à réduire ces risques aurait le potentiel de prévenir la maladie tant dans les groupes présentant un risque clinique que dans les groupes qui ne sont pas à risque apparemment : par exemple, la campagne de diminution de la pression artérielle à l’échelle de la population aurait pour effet de réduire le risque d’accident vasculaire cérébral dans les groupes hypertendus comme dans les groupes normotendus. L’amélioration de la santé de la population repose souvent sur la mise en œuvre d’initiatives stratégiques en matière de politiques de santé. L’interniste est en mesure d’exercer de l’influence dans ce domaine en militant pour des changements de fond dans le but de réduire les risques pour la santé et de prévenir la maladie. Les dernières années ont vu des professionnels de la santé du pays promouvoir de tels changements dans les politiques de la santé afin de favoriser l’abandon du tabac, de prévenir la maladie. Les dernières années ont vu des professionnels de la santé du pays promouvoir de tels changements dans les politiques de la santé afin de favoriser l’abandon du tabac et la réduction de l’obésité chez les enfants en réaction aux pressions exercées par des promoteurs de la santé. L’interniste est en mesure de déterminer leur valeur nutritive. L’industrie alimentaire, qui prétend s’autoréglementer, inonde le marché d’aliments à calories vides destinés aux enfants. Et c’est ainsi que l’obésité est à la hausse dans ce groupe de la population. Les médecins se sont tenus en retrait, attendant que d’autres groupes ou personnes agissent. La Ville de New York prépare une directive sur l’approvisionnement alimentaire qui fera en sorte que les immeubles gouvernementaux n’achèteront et ne vendront que des aliments sains 1. Le gouvernement du Québec a banni la publicité d’aliments susceptibles de contribuer à l’obésité chez les enfants en réaction aux pressions exercées par des promoteurs de la santé. En Finlande, les aliments riches en sodium portent une étiquette mettant en garde le consommateur. Le Royaume-Uni a conçu un code de couleurs pour l’étiquetage des aliments selon leur contenu en sodium, en graisses saturées et en sucre simple; le rouge désigne les aliments à éviter, l’orange commande la circonspection et le vert s’applique aux aliments sûrs. Lorsque l’Europe a envisagé d’adopter ce système d’étiquetage simple, le secteur alimentaire a investi un milliard de dollars dans une campagne de lobbying pour bloquer sa mise en œuvre, tandis que le secteur de la santé se tenait coi.

Le Comité de promotion de la santé de la Société canadienne de médecine interne appuiera les politiques et les actions destinées à promouvoir la santé et à prévenir la maladie. L’interniste est bien placé pour exercer de l’influence dans ce sens et défendre les intérêts publics, et je souhaite qu’il s’engage activement dans cette voie. En mobilisant les professionnels de la santé, les associations qui les représentent et les divers ordres de gouvernement dans le cadre d’un programme d’action commun, nous pouvons réussir à améliorer la santé des Canadiens et des Canadiennes, aujourd’hui et à l’avenir.
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In the last issue (Volume 5, Issue 3), we reviewed the EKGs shown in Figures 1 and 2, recorded in an 80-year-old woman with a history of rapid palpitations. She has sinus rhythm with non-conducted atrial bigeminy (see Figure 1), and sinus rhythm with conducted atrial bigeminy (see Figure 2). No abnormalities of sinus node function are apparent on these EKGs, and she had no symptoms of bradycardia, even though her effective ventricular rate during non-conducted atrial bigeminy was only 40 bpm, so there is no obvious indication for a pacemaker. A pacemaker could still be indicated if she had asymptomatic advanced His-Purkinje disease. In this regard, when atrial bigeminal beats conduct, they do so with right bundle branch block (RBBB; see Figure 2), so the question left dangling at the end of this column in the preceding edition was, does this patient have asymptomatic advanced His-Purkinje disease that might require a pacemaker?

Figure 1. Sinus bradycardia with non-conducted atrial bigeminy. The premature atrial contractions are marked with black arrows on the rhythm strip.
Figure 2. Sinus bradycardia with atrial bigeminy. The premature atrial contractions (PACs) are marked with black arrows on the rhythm strip. Why do the PACs conduct with right bundle branch block? Is this a sign of His-Purkinje disease?

Figure 3. As the ladder diagram shows, the rate at which the His-Purkinje (HP) network is stimulated alternates during atrial bigeminy with long (green arrows) and short (brown arrows) sequences. When the premature atrial contraction (PAC) occurs, the preceding long sequence lengthens the refractory period of the HP network so that the right bundle (which usually has a slightly longer refractory period than the left bundle) hasn’t completely recovered. Accordingly, the premature atrial beat conducts aberrantly with right bundle branch block: a classic case of Ashman’s phenomenon, which is purely physiological. AVN = atrioventricular node; SN = sinus node.
Discussion
As mentioned above, the rhythm on display in the EKG shown in Figure 2 is sinus rhythm with atrial bigeminy. That is, after every sinus beat, there is a premature atrial contraction (PAC) that conducts through the AV conduction system. In contrast, in the EKG shown in Figure 1, the PACs that occur after every sinus beat are so premature that they cannot conduct through the AV conduction system. In Figure 1, the PACs block in the AV conduction system for purely physiological reasons: the AV conduction system simply hasn’t had sufficient time to recover from having just conducted the preceding sinus beat.

The refractory period of the His-Purkinje network is rate dependent. As the rate at which the His-Purkinje network is stimulated increases, the refractory period of the His-Purkinje network decreases. This makes good physiological sense: at fast heart rates, one would want the His-Purkinje network to recover more quickly to ensure, as much as physiologically possible, that it will be ready to be depolarized when the next heartbeat occurs. Changes in His-Purkinje network refactoriness occur quickly, on a beat-to-beat basis. Accordingly, the refractory period of the His-Purkinje network is proportional to the duration of the preceding R–R interval. If the preceding R–R interval is short, the refractory period of the His-Purkinje network is relatively short; whereas if the preceding R–R interval is relatively long, the refractory period of the His-Purkinje network is longer.

At the time that a PAC occurs and conducts to the AV conduction system, the refractory period of the His-Purkinje will have been determined by the preceding, comparatively slower rate. Accordingly, at the time that the PAC occurs, the His-Purkinje network has a relatively long refractory period. In addition, the refractory period of the right bundle is usually slightly longer than that of the left bundle. Thus, when the PAC occurs, the right bundle simply hasn’t had enough time to recover for purely physiological reasons. This phenomenon, aberrant His-Purkinje conduction associated with a premature beat (usually RBBB but can be left bundle branch block too), is known as Ashman’s phenomenon (Figure 3).

Gouaux and Ashman first described this phenomenon in 1947, noting the variable R–R intervals that can be seen during conducted atrial fibrillation. They noticed that after a long R–R interval, when the next beat has a relatively short R–R interval, that QRS complex often has the typical morphology of RBBB. These beats are frequently confused with premature ventricular contractions because they are wide complex. With no apparent abnormalities of sinus node or AV conduction system function, and no symptomatic bradycardia, this patient has no obvious indication for a pacemaker.

Reference
Carotid Atherosclerosis: Technological Evolution of Ultrasonic Imaging

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Stroke represents a major health problem and is an important cause of death and long-term disability in several developed countries. In Canada, 15,000 deaths are attributed to stroke each year. In the United States, at least 500,000 persons suffer new or recurrent stroke annually, and stroke is a contributing factor in 150,000 deaths each year. Mortality from stroke ranges between 10 and 30%, and its survivors remain at a high annual risk of recurrent ischemic events and mortality, both from myocardial infarction and recurrent stroke.

Internal carotid artery (ICA) stenosis due to the formation of atherosclerotic plaques is one of the main etiological factors known to cause cerebrovascular events—stroke, transient ischemic attack (TIA), and amaurosis fugax. The atherosclerotic plaque is a dynamic structure that undergoes continuous remodelling of the extracellular matrix on which its structural integrity depends. Unstable atherosclerotic plaques (also known as high-risk or vulnerable plaques) are at high risk of rupture, which might lead to severe and potentially life-threatening cerebrovascular events. Scientific efforts to identify patients at high risk of cerebrovascular events early are numerous, but applications ready for implementation in clinical practice are few.

Imaging and Image Analysis
Several invasive and non-invasive imaging techniques have been used to identify arterial atherosclerosis (e.g., high-resolution ultrasonography, computed tomography angiography [CTA], and magnetic resonance angiography [MRA]). Among these techniques, high-resolution ultrasonography has been the most widely used method to assess atherosclerotic disease. For the diagnosis of high-grade stenosis, ultrasonography has a pooled sensitivity and specificity of 86% and 87%, respectively, when compared with digital subtraction angiography (the “gold standard”), while for occlusion its sensitivity and specificity is 96% and 100%, respectively. Moreover, ultrasonography allows for real-time in vivo imaging, and it is a non-invasive, reliable, safe, and relatively inexpensive modality that in experienced hands can facilitate the study not only of the lumen (as digital subtraction angiography does) but also of the intima-media thickness and atherosclerotic plaques, both hemodynamically and morphologically. The degree of carotid stenosis is a well-established risk factor of plaque instability and rupture. Natural history studies have demonstrated that the risk of developing ipsilateral hemispheric symptoms grows with increasing severity of ICA stenosis. Specifically, the risk of stroke in asymptomatic patients is low (0.1–1.6%/y) for stenosis <75–80% (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria) and higher (2.0–3.3%/y) with greater degrees of stenosis. However, many high-grade stenoses remain stable and asymptomatic, whereas other plaques that cause moderate stenoses rupture and induce symptoms. It is increasingly recognized that, in addition to the degree of stenosis, plaque morphology and surface characteristics play an important role in plaque instability. In fact, Saam et al. evaluating the American Heart Association (AHA) histological lesion type in patients who underwent carotid endarterectomy noted that 29.8% of AHA type VI lesions (most advanced type) occurred in patients who had ≤50% carotid stenosis. This indicates that a large proportion of vulnerable plaques produce low-grade stenoses. Therefore, it is critical to identify unstable plaques based not only on the degree of stenosis but also on plaque morphology using advanced technology and imaging modalities that are simple, reliable, and non-invasive, such as ultrasonography.

Visual Classification
Several visual classifications have been proposed to characterize the morphology of ultrasonic plaques; the most widely used consists of five plaque types (Geroulakos classification): type 1, completely echolucent (homogeneous, appears black on ultrasonograms); type 2, predominantly echolucent (heterogeneous, mostly black); type 3, predominantly echogenic (heterogeneous, mostly white on ultrasonograms); type 4, completely echogenic (homogeneous, white); and type 5, calcified plaque with acoustic shadow. Numerous studies have demonstrated that unstable plaques are typically characterized on ultrasonograms by high-grade stenosis, ulceration, and intraplaque hemorrhage, appearing echolucent with irregular borders (types 1 and 2). There is evidence suggesting that plaque echolucency is associated with histologically advanced atherosclerosis. Furthermore, plaque echolucency is associated with hemispheric symptomatology. In a study of symptomatic patients, the relative risk (RR) of ipsilateral ischemic stroke for echolucent versus echogenic plaques was 3.1 (95% confidence interval [CI] 1.3–7.3), whereas for 80–99% versus 50–79% stenosis, the RR was only 1.4 (95% CI 0.7–3.0). The Asymptomatic Carotid Stenosis and Risk of Stroke (ACRS) study, a natural history, multi-centre prospective study of symptomatic patients designed by the authors’ group in the United Kingdom, showed that for stenosis 50–99% (North American Symptomatic Carotid Endarterectomy Trial [NASCET] criteria), the RR for those with echolucent plaques versus those with echogenic plaques was 11.7 (95% CI 1.63–84.5). This shows that plaque echolucency is an important determinant for the risk of stroke and has additional prognostic value when added to stenosis. Although it is well known that echolucent plaques are more unstable than echogenic plaques, visual classification is a qualitative, subjective method with low reproducibility; for example, a wide variability in the classification of type...
Computer-Assisted Methods of Plaque Morphology

The need for a quantitative assessment of ultrasonic images led to computer-assisted methods to characterize plaque morphology. In this process, the median of the frequency distribution of grey values of the pixels within the plaque (grey-scale median [GSM]) ranges from 0 to 255; 0 = black and 255 = white) was used to quantify pixels within the plaque (grey-scale median [GSM] ranges from 0 to 255; higher the macrophage infiltration on histological examination of carotid specimens. Furthermore, a low GSM is strongly associated with hemispheric symptomatology; for example, it was shown that echolucent plaques with a GSM <32 had a fivefold increase in the prevalence of silent brain infarctions on CT brain scans. It quickly became apparent that ultrasonic image normalization was necessary, so that images captured under different instrument settings, from different scanners, by different operators, and through different peripherals, such as digital video disc (DVD), video, and magneto-optical disc could be compared. Images of plaques are normalized to two reference points, the blood (GSM = 0) and adventitia (GSM = 190), using commercially available software. Image normalization in the ACSRS study resulted in 60% of plaques being reclassified.

The Need for Further Technological Advancement

There is controversy about the role of heterogeneity in plaque instability; some studies suggest that plaques with a heterogeneous texture (mixture of echolucent and echogenic areas) are more unstable, while others suggest that homogeneous (predominantly echolucent) plaques are more unstable. However, assessments of heterogeneity have been performed visually.

Although previous studies advanced our knowledge on plaque echomorphology, they have limitations. Either they are subjective (visual classification) or they only assess the overall brightness of a plaque (median of the grey tone values), failing to provide important information about its heterogeneity. For example, a plaque with a GSM of 40 can be heterogeneous (median value 40 of black parts with a low GSM and white parts with a high GSM) or homogeneous (with all parts having a GSM of approximately 40). These limitations stimulated research to generate more sophisticated computer-assisted methods of plaque characterization, such as digital image analysis.

Digital Image Analysis

Digital image analysis can provide an accurate measurement of the morphology of a plaque, including not only the echodensity (the overall brightness of the plaque, measured by GSM) but also the texture (heterogeneity, measured by texture analysis) of the plaque. Measuring plaque texture provides quantitative information about its morphology, that is, if the plaque is homogeneous or heterogeneous. Digital image analysis is a well-established method initially developed by electrical and electronic engineers. Past studies have confirmed reliability, reproducibility, and validity of the digital image analysis method in ultrasonic studies of solid organs. In the ACSRS study, the combination of measures of heterogeneity with GSM significantly (p = .02) improved the value of GSM alone in distinguishing embolic from non-embolic CT brain infarctions; the area under the curve increased from 0.62 (GSM) to 0.81 (combination). Not only can texture analysis discriminate between symptomatic and asymptomatic carotid plaques, it can further discriminate between carotid plaques obtained from patients with different hemispheric symptomatology, significantly improving the diagnostic value of GSM alone. Furthermore, in the ACSRS study, heterogeneous plaques carried a significantly higher risk (odds ratio [OR] 5, p = .0001) of stroke in comparison with homogeneous plaques during a mean follow-up of 37 months. Furthermore, heterogeneous plaques were at a particularly increased risk of progression (OR 5.2, p = .0001).

Three-Dimensional Reconstruction

Three-dimensional reconstruction of ultrasonic plaques is another recent advancement that enables more accurate and reproducible quantification of plaque volume/size and plaque surface characteristics (e.g., ulceration) when compared with two-dimensional ultrasonography or angiography.

Expected Contributions

With more than 70,000 myocardial infarctions, 50,000 strokes, and 15,000 TIs in Canada each year, atherosclerosis causes a deep burden on the Canadian health care system; $22.2 billion per year is spent as a result of these life-threatening events. Additionally, the impact of stroke is devastating: 20% of stroke patients die, 11% go to long-term care, and even many people who are able to return home have functional limitations, severely compromising quality of life. Early identification of plaque instability will result in appropriate management of carotid atherosclerosis and prevention of stroke, with direct benefit at the individual and the health services levels.

Advanced imaging technologies are now available and can be used to monitor patients with carotid atherosclerotic plaques and identify early when plaques become unstable and at risk to rupture (when prevention is still possible). These advanced technologies will challenge the current paradigm of managing carotid atherosclerotic disease in clinical practice. Currently, recommendations for surgical interventions are based on only the degree of carotid stenosis. Using these novel methods of plaque characterization could lead to the refining of guidelines for carotid atherosclerosis beyond carotid stenosis to include plaque morphology. In this context, carotid intervention will be reserved for patients with high-risk plaques, while those at low risk will be spared an unnecessary, potentially dangerous, and expensive intervention.

Furthermore, currently pharmacological treatments focus on target therapeutic values (e.g., blood pressure, glucose, cholesterol levels) as evidence of therapeutic efficacy. These advanced methods of plaque characterization will stimulate future research aimed at expanding the focus to include not only target values but also the target tissue, namely the stabilization of atherosclerotic plaques. In this concept, old and new anti-atherosclerotic medication will have to prove their efficacy in stabilization or even the reversal of the progression of atherosclerosis. Medicine needs to take advantage of the extensive technological advances that are already available, and implement them in the everyday clinical practice in order to achieve more accurate diagnosis, better monitoring, improved treatment, and more effective prevention of atherosclerosis.
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Tumour in the Kidneys: Have You Considered a Genetic Syndrome?

Dawna M. Gilchrist MD

Case Report
A 48-year-old female presented to her family doctor complaining of flank discomfort. An abdominal ultrasonogram showed multiple bilateral tumours of the kidneys without other abnormality. A referral to urology was made, and surgery followed. Frozen section showed the tumours were oncocytomas, and limited resection was done to preserve kidney function. Post-surgical pathology confirmed the findings with no evidence of malignancy. The patient has normal kidney function post-operatively. The patient was referred to genetics. There was no contributory personal or family history. A detailed physical examination was unremarkable. Based on the pathology of oncocytomas, genetic testing was requested for succinate dehydrogenase B (SDHB) and Birt-Hogg-Dubé (BHD) syndrome. The test for SDHB was negative, but a mutation was found in the BHD gene. At-risk family members have been offered testing for the BHD mutation.

When to Consider a Genetic Cause for Tumour of the Kidney
Approximately 2% of cancer is kidney cancer, with 80–85% of that being renal cell (also known as clear cell) cancer, followed by transitional cell cancer at 8%. The contribution of genetic factors to kidney cancer is still undetermined but is likely higher than the traditionally quoted 5–10%. A hereditary syndrome should be particularly considered when the following are present:

- Young age of onset <40 years
- Bilateral tumours
- Personal or family history of manifestations of a genetic syndrome known to include kidney tumours
- Pathological type (Table 1)

In patients with an onset of kidney tumour under the age of 40, there is a 1,800% increased risk for development of bilateral tumours. The genetic syndromes associated with kidney cancers are all inherited as autosomal dominant conditions. These syndromes exhibit incomplete penetrance, that is, not all individuals with a mutation have manifestations. There is also variable expressivity, meaning that individuals with the same mutation do not always present with the same manifestations or at the same age, or have the same response to therapy.

### Table 1. Correlations of Pathological Type to Syndrome

<table>
<thead>
<tr>
<th>Pathological Type</th>
<th>Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal cell</td>
<td>VHL, BHD, TS, SDHB, HRCC</td>
</tr>
<tr>
<td>Papillary cell</td>
<td>HPCC, HL+PCC, SDHB</td>
</tr>
<tr>
<td>Oncocytoma</td>
<td>BHD, SDHB, TS</td>
</tr>
<tr>
<td>Chromophobe</td>
<td>BHD, SDHB</td>
</tr>
<tr>
<td>Hybrid</td>
<td>BHD</td>
</tr>
<tr>
<td>Angiolipoma</td>
<td>TS</td>
</tr>
<tr>
<td>Transitional cell</td>
<td>Lynch</td>
</tr>
<tr>
<td>Cysts</td>
<td>VHL, BHD, HL+PCC, TS/polycystic kidney disease overlap</td>
</tr>
</tbody>
</table>

BHD = Birt-Hogg-Dubé; HL+PCC = hereditary leiomyomatosis (skin and uterus) and papillary cell carcinoma of the kidney; HPCC = hereditary papillary cell carcinoma of the kidney; HRCC = hereditary renal cell carcinoma; SDHB = succinate dehydrogenase B; TS = tuberous sclerosis; VHL = Von Hippel–Lindau disease.

Source: Adapted from Linehan.

### Von Hippel–Lindau Disease
Von Hippel–Lindau disease (VHL) is a multisystem disorder with both central nervous system and visceral manifestations. The best known of these are cerebellar hemangioblastoma, retinal angiodysplasia, and pheochromocytoma. Clear cell kidney cancers occur in approximately 35–45% of patients with VHL. Kidney cysts and cancers are usually multifocal and often bilateral. Mutation analysis of the VHL gene has a sensitivity of 99%.

### Lynch Syndrome
Lynch syndrome, also known as hereditary non-polyposis colon cancer (HNPPC), accounts for approximately 5% of colon cancer. Cancer can potentially occur in most organs in the abdomino-pelvic cavity, with urinary collection system cancer in approximately 10% of patients. The pathological type is transitional cell. These tumours are likely to be unifocal and unilateral. There are four genes known to be associated with Lynch syndrome. Most genetic laboratories test for mutations in MLH1 and MSH2, which account for about 80% of Lynch syndrome cases. Mutations in MSH6 account for 10% of Lynch syndrome cases. Mutation analysis of these genes has a sensitivity of 96–98%.

### Tuberous Sclerosis
Tuberous sclerosis (TS) is a multisystem disorder that has a wide variety of presentations. Severe cases are likely due to sporadic new mutations; mild TS is underdiagnosed in the population and often familial. The common renal manifestations are cysts and angiolipomas. Approximately 1% of patients with TS have oncocytomas of the kidney and 3% have renal cell cancer. Genetic testing in TSCI and TSC2 reveals the mutation in 70–
Tumour in the Kidneys: Have You Considered a Genetic Syndrome?

75% of cases. The diagnosis is better made on clinical grounds following published criteria.4

Birt-Hogg-Dubé Syndrome
BHD is a syndrome with manifestations of skin, kidneys, and lung. Of the multiple skin findings, fibrofolliculomas are the most specific; dermatological pathology is usually necessary. Lung cysts are similar to those produced by emphysema and are usually multiple and bilateral. They may lead to spontaneous pneumothorax. The kidney tumours are bilateral and usually slow growing, with an unusual pathology of oncocytoma, chromophobe, or a hybrid of the two. There is a single gene associated with BHD called FLCN, and current testing has 88% sensitivity.

Other Syndromes
There are other rare syndromes of kidney cell tumours that are defined by their pathology and genetic etiology:

- Hereditary papillary cell carcinoma of the kidney (HPCC) – MET gene
- Hereditary leiomyomatosis (skin and uterus) and papillary cell carcinoma of the kidney – (HL+PCC) – FH gene
- SDHB – more usually associated with paragangliomas and pheochromocytomas
- Hereditary renal cell carcinoma (HRCC) – gene(s) unknown

Identifying Kidney Tumour Syndromes
A genetic cause for kidney tumour should always be considered but especially when the patient is young, the pathology is unusual, and/or the tumours are multifocal or bilateral. A thorough exploration of the patient’s personal and family histories is necessary, and attention should be paid to potential manifestations outside of the urinary tract. Physical examination may be helpful in terms of the skin manifestations of BHD and TS (for the latter, a black light may be necessary). Pathology of the tumour can be extremely helpful, and correlations are found in Table 1.5 Should suspicion for a genetic cause be significantly raised, referral of the affected individual to a medical genetics clinic is recommended. Identification of a specific syndrome will offer better prognostic information and monitoring recommendations for the patient. If a specific gene mutation is found, pre-symptomatic predictive testing should be offered to at-risk individuals, that is, all first-degree adult relatives of the affected individuals. In some instances, testing of children is also recommended (for VHL, SDHB, and possibly TS).

Summary
Patients with kidney tumour(s) are common in internal medicine practices. It is worthwhile to consider potential genetic syndromes as their diagnosis can be to the benefit of the patients and their family.

References
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Development and Implementation of CanMEDS Health Advocacy Curriculum for Internal Medicine Residents

Davedeep Sohi MD, Anson Li MD, Roger Y. Wong MD

The health advocate role and the related competencies are part of the formal educational and assessment requirements in Canadian residency training within the CanMEDS framework (Table 1). Since the adoption of CanMEDS by residency programs nationwide, it has become apparent that the role of health advocate is one of the most difficult to teach and assess. A 2006 survey of Canadian general internal medicine graduates identified the role of health advocate as being an area of particular weakness. Although this role has been highlighted as an area of deficiency in residency training, there is a paucity of data in the literature to explore this issue. The broad scope of health advocacy, insufficient resident and staff time, an inadequate definition of advocacy, a lack of remuneration, a lack of resident awareness, and the absence of a structured curriculum are some of the barriers identified in the literature explaining the difficulty in teaching the role of health advocate.

In this article, we address some of these obstacles by providing an outline of our innovative health advocacy curriculum at the University of British Columbia (UBC) internal medicine residency program. The curriculum is resident driven, experiential, flexible, and community responsive, and it includes an assessment tool. To our knowledge, this is the first report of a structured health advocacy curriculum in a Canadian internal medicine residency program.

Table 1. Definition and Competencies of the CanMEDS Health Advocate Role

Definition of the Health Advocate Role
As health advocates, physicians responsibly use their expertise and influence to advance the health and well-being of individual patients, communities, and populations.

Competencies
Physicians will:
- respond to individual patient health needs and issues as part of patient care;
- respond to the health needs of the communities that they serve;
- identify the determinants of health of the populations that they serve; and
- promote the health of individual patients, communities, and populations.

Source: Adapted from Frank.

Table 2. Advocacy Topics Covered in Interactive Lecture Format during Academic Half-Days and Annual Retreat Sessions

Health disparities and advocacy
Emergency preparedness for natural disaster
International health advocacy initiatives
Advocacy issues in patient care
Local community health resources
Insights on advocacy from local internists
Infectious diseases and health advocacy
The bulk of the UBC health advocacy curriculum involves experiential learning whereby residents are required to participate in at least one self-selected, applied advocacy activity during their 3 years of training. To create opportunities for residents, we began by identifying faculty members who are active in health advocacy activities. These faculty members have spearheaded a variety of projects including dementia awareness sessions with culturally sensitive lectures and blood pressure checks targeting the local Chinese immigrant population. Another faculty-led project is an international health initiative that sends teams of faculty and residents to a resource-poor area of South Africa to not only care for patients but also educate local healthcare providers.

Creating a culture among faculty that nurtures health advocacy led to a number of resident-driven projects. Since 2008, residents used their medical expertise to promote health and well-being throughout the greater Vancouver area via a number of initiatives (Table 3). These individual initiatives have evolved into a Health Advocacy Network (HAN). The HAN is a partnership between community-based health advocacy groups and UBC internal medicine residents. It uses existing community channels to advertise the availability and interest of our residents to work with local groups on health promotion. The HAN streamlines the ability of our residents to provide educational talks on a variety of topics for local groups that represent a diversity of ethnicities, languages, and lifestyle choices.

The curriculum also includes two assessment and feedback tools. The first is a reflection survey that residents fill in after participating in health advocacy events. This not only gives residents a chance to reflect on the health advocate role but also provides feedback on the event itself. For example, one resident remarked, “Based on the experience of this advocacy event, I am motivated to actively identify and participate in outreach projects in the community in the future.” Essentially, such reflections become part of the residents' learning portfolios. An additional tool we have used is an online photo blog. This is a password-protected, online forum where residents can post pictures from advocacy events. Residents can also add their online reflections, which again become part of their portfolios. These tools are added to a log of advocacy events in which residents participated; when combined with other relevant letters or media exposure, residents have constructed their individual health advocacy portfolios.

Discussion
The UBC health advocacy curriculum is an innovative approach to teaching the CanMEDS role of health advocate. This is the first reported curriculum of its kind in Canada that targets internal medicine residents. We have combined a small number of classroom-based sessions with a greater emphasis on practical, community-based, health advocacy experiences. Throughout the development process, we have adhered to the five principles outlined below that make our curriculum unique: experiential, resident driven, community networking, flexibility, and assessment.

Experiential
Our advocacy curriculum is predominantly experiential. Hands-on health advocacy is challenging because it demands competency in many of the CanMEDS roles. Because it is so demanding, experience in health advocacy is also highly educational and richly rewarding. Experience-based learning equips residents with the motivation and the skill set to be highly effective health advocates as practising internists.

Resident Driven
We strived to involve our residents in curriculum development and implementation. Supported by faculty role models, residents have demonstrated a keen interest in both the process of curriculum development and in health advocacy itself. In addition, collaborating with staff on advocacy initiatives gave residents another opportunity to seek out mentors within our faculty.

Community Networking
One particularly unique aspect of the curriculum is community networking. Work done in the pediatric population has shown that community-driven advocacy events lead to increased positive attitude and higher self-perceived competency for residents. The need to partner with established community groups that serve as a voice for marginalized, underserved populations has also been endorsed by other authors as an effective means of practising health advocacy. The emergence of the HAN allows our residents to be truly community responsive in their activities by targeting populations most in need of health promotion. In addition, community groups share the work involved in organizing health promotion events. This helps overcome resident time constraints, which has been reported as being a barrier to involvement in health advocacy.

Flexibility
We have encouraged residents to be creative in their health advocacy endeavours and embrace their subspecialty interests within internal medicine. Although we do have a mandatory community-based activity for all residents, the target population, topic, and form of involvement are entirely flexible. By giving residents choice in their advocacy training, we encourage greater involvement and a more rewarding experience. This is reflected in the diversity of topics chosen by residents (see Table 3).

Assessment
In order to assess learning of health advocacy, an assessment tool is required. Other Canadian schools have incorporated in-training evaluation records for documentation as well as self-evaluation methods in the form of logs, portfolios, or essays. Here at UBC, an individualized resident advocacy portfolio is composed of feedback surveys, photo blogs, and a record of advocacy activities. This form of assessment allows for residents to reflect on their progress in mastering the CanMEDS competencies for the health advocate role. In addition, it gives our faculty the opportunity to track each resident’s development with respect to health advocacy.

Barriers and Limitations
There were a number of obstacles in the development and implementation of this curriculum. First, there is a paucity of peer-reviewed literature to guide health advocacy training at the resident level. Therefore, we often relied on faculty and resident opinion to design the curriculum. Second, it was difficult to identify and recruit faculty to

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### Table 3. Summary of Community-Based Health Advocacy Initiatives

<table>
<thead>
<tr>
<th>Topic</th>
<th>Description</th>
<th>Led by F or R</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Addictions</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking Cessation Strategies*</td>
<td>Residents talk to the public to increase awareness on smoking cessation</td>
<td>R</td>
</tr>
<tr>
<td>Tours of Community Resources</td>
<td>Residents are oriented to health facilities in Vancouver’s downtown east side to better understand barriers to health faced by marginalized population</td>
<td>F</td>
</tr>
<tr>
<td><strong>Cardiology</strong></td>
<td></td>
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<tr>
<td>Optimizing Cardiovascular Health*</td>
<td>Residents give educational sessions to ambulatory patients regarding cardiac health and risk factor modification, the deleterious effects of substance abuse, and gender-specific heart health</td>
<td>R</td>
</tr>
<tr>
<td>Substance Abuse and Heart Disease*</td>
<td></td>
<td>R</td>
</tr>
<tr>
<td>Women and Heart Disease*</td>
<td></td>
<td>R</td>
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<tr>
<td><strong>Endocrinology</strong></td>
<td></td>
<td></td>
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<tr>
<td>Diabetes Education*</td>
<td>Residents give educational sessions to diabetic outpatients regarding diabetes mellitus</td>
<td>R</td>
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<tr>
<td><strong>Geriatrics</strong></td>
<td></td>
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<tr>
<td>Dementia Awareness Workshop for Caregivers</td>
<td>Residents participate in this annual outreach program targeting at-risk Asian seniors in Chinatown, and they check blood pressure for seniors and advise them of the benefits of blood pressure control in preventing dementia</td>
<td>F</td>
</tr>
<tr>
<td>Osteoporosis*</td>
<td>Residents give educational sessions to the public regarding osteoporosis</td>
<td>R</td>
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<tr>
<td><strong>Immigrant/Language Issues</strong></td>
<td></td>
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</tr>
<tr>
<td>Medical Cantonese Lessons for Health Providers</td>
<td>Residents participate in several peer-teaching sessions to learn the basics of medical Cantonese, which help residents to more effectively communicate with their Cantonese-speaking patients</td>
<td>R</td>
</tr>
<tr>
<td>Medical Punjabi Lessons for Health Providers</td>
<td>Residents participate in several peer-teaching sessions to learn the basics of medical Punjabi, which help residents to more effectively communicate with their Punjabi-speaking patients</td>
<td>R</td>
</tr>
<tr>
<td>Visit to Refugee Shelter</td>
<td>Residents are oriented to refugee shelter to better understand health challenges faced by marginalized population</td>
<td>R</td>
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<tr>
<td><strong>Infectious Diseases</strong></td>
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<td></td>
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<tr>
<td>HIV/Hepatitis C Education*</td>
<td>Residents give educational sessions to the public regarding common infections and their prevention</td>
<td>R</td>
</tr>
<tr>
<td>Influenza Education*</td>
<td></td>
<td>R</td>
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<tr>
<td><strong>International Focus</strong></td>
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<tr>
<td>Establishment of South Africa Medical Elective for Residents</td>
<td>Residents spend 1 month in a community hospital in South Africa, which helps them gain insight into marginalized population and challenges in system changes to improve overall health delivery</td>
<td>F</td>
</tr>
<tr>
<td><strong>Oncology</strong></td>
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<tr>
<td>Cancer Screening*</td>
<td>Residents attend informal barbeque to promote cancer awareness and screening; residents give educational sessions to the public regarding common cancers and their prevention</td>
<td>R</td>
</tr>
<tr>
<td>Leukemia Education*</td>
<td></td>
<td>R</td>
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<tr>
<td>Pancreatic Cancer Education*</td>
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<td>R</td>
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<tr>
<td><strong>Organ Donation</strong></td>
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<td></td>
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<tr>
<td>Public Awareness Initiative</td>
<td>This initiative is organized by BC Transplant and aims to educate the public about the importance of organ donation; residents are trained in a short session and then paired with a transplant recipient to hold public education sessions in the community</td>
<td>R</td>
</tr>
</tbody>
</table>

* = Health promotion talks delivered in the community via the Health Advocacy Network.

F = faculty members; HIV = human immunodeficiency virus; R = residents.
mentor residents and serve as local champions for health advocacy. The reasons for this are numerous and include those identified in the literature, such as lack of time, a perception of advocacy as charity work, and inadequate training. Overcoming these obstacles requires a sustained effort at both the local and national levels to change the perception of health advocacy and equip faculty with the tools necessary to teach residents. Finally, residents often felt burdened from existing educational obligations and thus were hesitant to engage in formal health advocacy training. We feel that our curriculum is community driven and yet minimizes the time requirements of the residents.

There are also notable limitations to this descriptive report. Foremost is the fact that this curriculum was deployed at a single institution and it therefore requires tailoring when implemented at other institutions, although we believe the curriculum is generalizable. Also, it would be ideal to develop additional measures of objective learning outcomes to augment our current assessment tools. To remedy this problem, we are currently developing tools to enable web-based, multi-source feedback of resident community health promotion activities.

Conclusion
There is a need to improve teaching of the health advocate role among residency programs nationwide. We believe the UBC health advocacy curriculum is an engaging, structured curriculum that empowers residents to learn health advocacy through participating in community-based health promotion initiatives.

References
Misrepresentation by Trainees: A Serious Threat to Professionalism

Alexander A.C. Leung MD

Background
It has been suggested that the medical culture, which rewards clinical achievements and academic scholarship, may ironically promote dishonest behaviour among trainees who may choose to lie and deceive in order to excel, produce, publish, and gain recognition. Although honesty is a valued and essential component of the medical profession, deceit and misrepresentation may be alarmingly more common than previously thought. However, deceptive practices can jeopardize trust and irreparably tarnish the credibility of the medical profession.

Misrepresentation on Multiple Levels
The iterative and competitive selection process to enter medical schools, postgraduate training programs, and even positions of faculty appointment may reward candidates who embellish their achievements. Consequently, identifying dishonest practices during these particular milestones has been a subject of considerable interest.

The application to medical schools and most residency training programs is perceived to be a competitive process. Deans of admission and program directors typically look at many factors when selecting students and residents, which may include academic records, research experience, scientific publications, extracurricular involvement, volunteer experience, advanced degrees, and letters of reference. Many of these areas are provided by self-report and the accuracy based solely on the “honour system.” Unfortunately, to gain a competitive advantage, some applicants may be tempted to falsify credentials or exaggerate their accomplishments. The fabrication of academic accomplishments appears to be more common than most would believe. The Association of American Medical Colleges reported that over a period of a decade, nearly a thousand irregular cases were investigated, and fraudulent transcripts, unauthentic letters of recommendation, inaccurate and incomplete credentials, applications under assumed identities, and irregular examination behaviour were exposed among applicants to medical schools.

Erroneous claims of authorship by medical students applying for residency training have been well documented in various fields including medical, psychiatric, surgical, and diagnostic imaging specialties. Estimates of publication misrepresentation are consistently between 10 and 30% across studies, mostly involving the reporting of non-existent articles or non-existent journals.

Furthermore, the falsification of credentials, inaccurate reporting of advanced degrees, and fabrication of previous employment history are common, estimated to occur in as many as a quarter to half of applications. Shockingly, case reports exist of individuals entering residency programs without successful completion of medical school, and even con artists who never attended medical school at all.

One study of applicants to family medicine residency across 150 programs in the United States estimated that deception (defined as “the active misrepresentation or omission of facts about one’s qualifications, background, or abilities”) may occur in up to half of all applications. Of these, acts of deception relating to personal statements accounted for 56% of cases, and inaccurate reporting of graduation status from a qualified medical school accounted for 13%. Other acts of deception included candidates misrepresenting their specialty choice, the purposeful omission of information from application materials, misrepresentation of past experiences, and the submission of falsified documents. Very rarely, some applicants were discovered to have undisclosed criminal backgrounds or previous positive drug screens.

Interestingly, the pattern of misrepresentation is not unique to medical trainees but has also been noted in physicians in practice. A study of eight academic institutions in the United States (with specialty representation from emergency medicine, internal medicine, ophthalmology, pediatrics, radiology, and surgery) found that 15.6% of applicants to faculty positions had misrepresented their bibliographies, with journal citations being the most frequent source of misrepresentation. Many of these discrepancies were likely intentional, with rearrangement of authorship order with advancements, claiming authorship for another’s material, and outright fabrication of non-existent articles. Physicians may also falsify credentials. An audit of physicians listed in the Yellow Pages found that 12% of those advertising as “specialists” were not board certified in any specialty.

Another audit found that 5% of physicians provided false clinical credentials when applying for ambulatory staff privileges.

Reinforcing Dishonest Behaviour
Dishonesty may have become institutionalized into our medical training. Despite an apparently careful admission process to medical schools, education in medical ethics, and professional mentoring, trainees still appear to misrepresent themselves to gain a competitive edge. When selecting applicants for medical schools, residency programs, and faculty positions, we should reconsider the value of solely using academic merit to discriminate between candidates. Although it is unrealistic to completely eliminate conventional selection criteria (i.e., academic transcripts, educational experience, scientific contributions, publications, and awards), perhaps greater emphasis can be placed on other important qualities such as compassion, integrity, honesty, humanity, collaboration, and altruism, which may be presently undervalued.

Moreover, academic success is often measured by publications, resulting in unfortunate adages like “publish or perish.” Given these expectations and the competitive academic climate, it is not surprising that some people give in to the temptation to embellish their achievements, even among physicians.
in practice and those applying for academic and clinical appointments. It is disturbing that societal acceptance of lying and deceit may also be shifting. For example, a faculty member at the University of Chicago suggested that “a limited form of résumé embellishment is morally permissible (and perhaps required)” on the basis of relativity, arguing that as it is certain that some résumés are embellished, it is better that all résumés are embellished for fair comparison.13 Disappointingly, if these ideas also fairly represent changing societal norms, intentional misrepresentation is likely to become more rampant over time.

Possible Solutions

Dishonesty is a serious threat to our medical profession, and those who demonstrate a pattern of deceit during their training may go on to be dishonest in their dealings with colleagues and patients in the future. As such, it is paramount to identify solutions to deter the widespread use of deceptive practices. One possible strategy is to educate trainees, increase surveillance to detect dishonest behaviour, instate a common standard for the reporting of achievements and activities, and enforce strict disciplinary measures for those who are caught breaching the rules. First, the purpose of education should be to educate trainees on ethical standards and principles, and to promote accurate documentation practices. While it is impossible to know with certainty if some inaccuracies are deliberate (as that is a question of motivation), some discrepancies such as erroneous authorship claims or factitious declarations of certification are most likely intentional fabrications, whereas other errors are likely the result of unintentional mistake (i.e., typographical errors). Consequently, it is quite possible that some of the “misrepresentation” reported by existing studies may be a result of “sloppy referencing,” thus resulting in the reporting of publications or activities that could not be confirmed by reviewers. Teaching better documentation practices is a simple remedy. Second, there is evidence that deceptive practices are more likely to be detected when formal verification processes are instituted to review applications.9 Complete verification of all claims made on applications to medical schools, residency programs, faculty appointments, and hospital positions will likely never be instituted because this would be a prohibitively costly and time-consuming endeavour. Nonetheless, with the wide accessibility of electronic databases, primary verification of publications (as a surrogate marker of application accuracy) can be a simple tool that can be employed universally. Random audits by confirming the authenticity of letters of reference or employment can also be considered on a case-by-case basis. Third, addressing the common finding of misrepresentation of authorship, some authorities have proposed that all cited publications should be accompanied by photocopies or reprints of cover pages; articles listed as “in press” should be accompanied by a letter of acceptance from the journal’s editor; and the listing of articles “in preparation/in progress” or “in review/submitted for publication” should be discouraged.14 Instating specific citation guidelines may help reduce innocent errors and dissuade intentional misrepresentation. Finally, upholding high ethical standards should be a criterion for employment. When misrepresentation is found, it must be treated seriously. If intentional, the applicant breaches the professional code of ethics and breaks the rules that govern the formal application process to medical training programs. A concerted effort is required by training institutions and professional regulatory bodies to discipline those found guilty. For example, the American Board of Internal Medicine has developed a standard method of handling confirmed cases of misrepresentation involving revocation of board eligibility and certification, and notification of state disciplinary boards.15 A similar formalized process does not yet exist in Canada but should be considered.

Conclusions

The profession of medicine is held to a high standard. The physician-patient and physician-physician relationships are built on trust and honesty. Lamentably, ethical compromises and deceit appear to be disturbingly common among trainees and even among physicians in practice. Falsification of credentials or self-misrepresentation is clearly undesirable in our profession. Promoting awareness of this problem and creating systematic checks to dissuade deceit are necessary to prevent unscrupulous behaviour from those who are in positions of trust and authority.

References

Atrial fibrillation (AF) is the most common form of sustained cardiac arrhythmia, especially among older adults, and contributes to significant morbidity and mortality. Between the years 2000 and 2005, deaths reported as resulting from AF or atrial flutter totalled 7,911 in Canada. Two treatment strategies currently exist for the management of AF – rate control and rhythm control. In the AFFIRM study (expansion provided in Appendix 1), neither method was found to be superior in reducing all-cause mortality in patients at risk for recurrent AF. The decision to pursue rate versus rhythm control should therefore be individualized according to patient symptoms and preference. The rhythm control strategy may be preferred in patients who present with their first AF episode, those with disabling symptoms of AF, or those remaining symptomatic despite rate control therapy. The most recent American College of Cardiology/American Heart Association/European Society of Cardiology (ACC/AHA/ESC) guidelines recommend class Ic and class III anti-arrhythmic agents as first-line therapy for the maintenance of sinus rhythm in AF patients. While amiodarone is one of the most commonly prescribed anti-arrhythmic agents, it is associated with significant potential long-term, multi-organ toxicity, including skin photosensitivity and discoloration (blue-grey), pulmonary fibrosis, hypothyroidism (common), hyperthyroidism (rare), corneal micro-deposits, and non-alcoholic steatohepatitis. Dronedarone is a non-iodinated benzofuran derivative of amiodarone that has been developed to retain the efficacy of amiodarone while improving its safety profile. This review evaluates the current evidence regarding the efficacy and safety of dronedarone in the chronic management of AF.

Rationale for the Use of Dronedarone
In August 2009, Health Canada approved dronedarone for the treatment of patients with a history of or current AF to reduce the risk of cardiovascular (CV)-related hospitalization. Like amiodarone, dronedarone exhibits electrophysiological properties that span all four Vaughan-Williams classes. However, the deletion of the iodine moiety from this new agent is thought to eliminate harmful effects on the thyroid gland, and the addition of a methane sulphonyl group renders the compound less lipophilic. These pharmacological modifications decrease the elimination half-life of dronedarone to 24–31 hours (compared with 58 days for amiodarone), thereby reducing the total tissue drug accumulation and potentially long-term drug toxicities. In addition, the shorter half-life negates the need for the use of a loading dose during the initiation of therapy.

Efficacy of Dronedarone
To date, there are published six placebo-controlled trials and one trial that directly compared dronedarone to amiodarone in the chronic management of AF (see Appendix 1). A detailed summary of these clinical trials is presented in Table 1. No clinical trials have yet evaluated dronedarone for acute pharmacological cardioversion.

Recurrent AF
Recurrent AF constitutes the majority of cases of AF in clinical practice and is defined by the ACC/AHA as the occurrence of two or more AF episodes. Three large, multi-national randomized controlled trials (EURIDIS, ADONIS, and ATHENA) were conducted to compare the efficacy and safety of dronedarone versus placebo in patients with recurrent AF. All patients were in sinus rhythm at the time of randomization. In the ATHENA trial, treatment with dronedarone significantly reduced the primary composite end point of first CV-related hospitalization and all-cause mortality compared with placebo (HR 0.76, 95% confidence interval [CI] 0.69–0.84). Notably, this result was primarily driven by a reduction in CV-related hospitalization since the end point of all-cause mortality alone demonstrated a non-significant reduction. In post hoc analyses, both the EURIDIS and ADONIS studies showed a similar reduction in the composite outcome of first CV-related hospitalization and all-cause mortality (HR 0.73, 95% CI 0.57–0.93). In the EURIDIS and ADONIS studies, patients treated with dronedarone were also observed to have derived other benefits: (1) a longer time to their first recurrence of AF (median time of 116 days compared with 53 days in the placebo group); (2) an 8.3% reduction in the symptomatic recurrence of AF at 12 months (HR 0.91, 95% CI 0.61–0.86); and (3) a decrease in their mean ventricular response rate of 13.7 beats per minute (bpm). In comparison, previous trials have shown that amiodarone reduced recurrent AF episodes by 40.7% but did not demonstrate a mortality benefit relative to placebo.

Persistent AF
It is estimated that approximately 10% of patients with AF progress to persistent AF. While a rate control strategy may suffice for many of these patients in reducing symptoms, some will remain symptomatic despite heart rate control. There are two placebo-controlled trials (ATHENA and DAFNE) and one comparator-controlled trial (DIONYSOS) with amiodarone that evaluated patients with persistent AF. These studies defined persistent AF as episodes lasting longer than 72 hours. This definition deviates from the ACC/AHA clinical definition for persistent AF, which is AF lasting longer than 7 days.
### Table 1. Summary of Results of Dronedarone Clinical Trials

<table>
<thead>
<tr>
<th>Study*</th>
<th>N</th>
<th>Patient Characteristics</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EURIDIS</td>
<td>612</td>
<td>≥21 yo, recurrent AF</td>
<td>Placebo (n = 201) Dronedarone 400 mg PO bid (n = 411)</td>
<td>Mean time to first AF recurrence: 41 d (P) vs. 96 d (D) AF recurrence rate at 12 mo: 77.5% (P) vs. 67.1% (D) (p = .01) Mean ventricular rate at first AF recurrence: 117.5 ± 29.1 bpm (P) vs. 102.3 ± 24.7 (D) (p &lt; .001) Hospitalization or death: 32.0% (P) vs. 21.2% (D) (p = .02)</td>
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<tr>
<td>ADONIS</td>
<td>625</td>
<td>See EURIDIS</td>
<td>Placebo (n = 208) Dronedarone 400 mg PO bid (n = 417)</td>
<td>Mean time to first AF recurrence: 59 d (P) vs. 158 d (D) AF recurrence rate at 12 mo: 72.8% (P) vs. 61.1% (D) (p = .002) Mean ventricular rate at first AF recurrence: 116.6 ± 31.9 bpm (P) vs. 104.6 ± 27.1 (D) (p &lt; .001) Hospitalization or death: 29.8% (P) vs. 24.5% (D) (p = .22)</td>
</tr>
<tr>
<td>ATHENA</td>
<td>4,628</td>
<td>≥70 yo, paroxysmal or persistent AF, LVEF &lt;40%</td>
<td>Placebo (n = 2,327) Dronedarone 400 mg PO bid (n = 2,301)</td>
<td>Composite of first CV hospitalization/all-cause mortality: 39.4% (P) vs. 31.9% (D) (p &lt; .001) First CV hospitalization: 36.9% (P) vs. 29.3% (D) (p &lt; .001) All-cause mortality: 6.0% (P) vs. 5.0% (D) (p = .18) Any serious treatment-emergent adverse events: 21.1% (P) vs. 19.9% (D) (p = .31) Discontinuation of drug due to adverse events: 8.1% (P) vs. 12.7% (D) (p &lt; .001)</td>
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<tr>
<td>DAFNE*</td>
<td>199</td>
<td>21-85 yo, persistent AF scheduled for elective cardioversion</td>
<td>Placebo (n = 48) Dronedarone 400 mg PO bid (n = 54)</td>
<td>Median time to first AF recurrence: 5.3 d (P) vs. 60 d (D) (p &lt; .001) Spontaneous cardioversion rates: 3.1% (P) vs. 5.8% (D) (p = .001) Adverse event: 0% (P) vs. 3.9% (D) vs. 7.6% (D) vs. 22.6% (D)</td>
</tr>
<tr>
<td>DIONYSUS*</td>
<td>504</td>
<td>Persistent AF Amiodarone naive</td>
<td>Amiodarone 600 mg PO daily × 28 d, then 200 mg PO daily thereafter Dronedarone 400 mg PO bid</td>
<td>Composite of AF recurrence or premature study discontinuation: 58.8% (A) vs. 75.1% (D) (p &lt; .001) AF recurrence after electrical cardioversion: 24.3% (A) vs. 36.5% (D) Premature drug discontinuation: 34 patients (A) vs. 26 patients (D) Adverse events: 107 patients (A) vs. 83 patients (D) (p = .13) Bradycardia: 22 patients (A) vs. 8 patients (D) Pronounced QTc prolongation: 52 patients (A) vs. 27 patients (D)</td>
</tr>
<tr>
<td>ERATO*</td>
<td>174</td>
<td>≥21 yo, symptomatic permanent AF for which cardioversion was not an option</td>
<td>Placebo (n = 89) Dronedarone 400 mg PO bid (n = 85)</td>
<td>Mean 24 h ∆ in ventricular rate at 4 mo: –1.3 bpm (P) vs. –10.1 bpm (D) (p &lt; .001); results remained significant after adjusting for concomitant rate-controlling agents Mean 24 h ∆ in ventricular rate during sub-maximal exercise: –2.2 bpm (P) vs. –25.6 bpm (D) (p &lt; .0001) Mean 24 h ∆ in ventricular rate during maximal exercise: –2.9 bpm (P) vs. –27.4 bpm (D) (p &lt; .0001) Bradycardia: 22 patients (A) vs. 8 patients (D) (p = .13) Discontinuation of drug due to adverse events: 10% (P) vs. 15% (D)</td>
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<tr>
<td>ANDROMEDA*</td>
<td>627</td>
<td>&gt; 18 yo, hospitalized for symptomatic CHF NYHA class III–IV, LVEF &lt;35%</td>
<td>Placebo (n = 310) Dronedarone 400 mg PO bid (n = 317)</td>
<td>Composite of all-cause mortality/hospitalization for worsening HF: 12.6% (P) vs. 17.1% (D) (p = .12) Mortality at median of 2 mo: 3.8% (P) vs. 8.1% (D) (p = .03) Hospitalization for worsening HF: 60.0% (P) vs. 49.3% (D) (p = not reported)</td>
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</table>

A = amiodarone; AF = atrial fibrillation; AFL = atrial flutter; AICD = automated implantable cardioverter defibrillator; bpm = beats per minute; CHF = congestive heart failure; D = dronedarone; GFR = glomerular filtration rate; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NSD = no significant difference; NSR = normal sinus rhythm; NYHA = New York Heart Association; P = placebo; QTc = QT interval corrected for heart rate; SCr = serum creatinine; UA = unstable angina; WPW – Wolff-Parkinson-White; yo = years old.

*See Appendix 1 for study acronym expansions.
Results for the ATHENA trial are presented above. The DAFNE trial was the first randomized controlled trial to exclusively evaluate patients with persistent AF where cardioversion was indicated.\(^5\) In this placebo-controlled trial, patients treated with dronedarone had a significantly longer time to first AF recurrence (median 60 days versus 5.3 days). At 6 months, 35% of patients on dronedarone remained in normal sinus rhythm (NSR) compared with only 10% with placebo. All patients who did not return to NSR after 5–7 days underwent electrical cardioversion. DAFNE was also a dose-finding study, and it evaluated dronedarone 400 mg bid, 600 mg bid, 800 mg bid, and placebo. Of note, only dronedarone 400 mg bid dosing was superior to placebo in delaying time to first AF recurrence. Higher doses failed to demonstrate significant benefit but resulted in significantly higher rates of study discontinuation due to adverse drug effects (3.9% with 400 mg bid versus 7.6% with 600 mg bid versus 22.6% with 800 mg bid).

The DIONYSOS trial was the first randomized controlled trial to compare dronedarone against an active comparator, amiodarone, in the management of AF.\(^\text{6}\) Patients were randomized to dronedarone 400 mg bid and amiodarone 600 mg daily for 28 days, followed by 200 mg daily. Dronedarone was shown to be inferior to amiodarone in reducing the composite end point of AF recurrence or premature study discontinuation at 12 months (75.1 versus 58.8%; HR 1.59, 95% CI 1.28–1.98; \(p = .0001\)). This result was driven by the increased rate of AF recurrence in patients treated with dronedarone (63.5 versus 42.0%). The main safety end point, defined as the occurrence of thyroid, hepatic, pulmonary, neurological, skin, eye, or gastrointestinal specific event, or premature study drug discontinuation following an adverse event, showed a non-significant reduction among patients treated with dronedarone (39.3 versus 44.5% at 12 months; HR = 0.80, 95% CI 0.60–1.07; \(p = .129\)).

Permanent AF

The ERATO study was the only double-blind randomized controlled trial that exclusively enrolled patients with symptomatic permanent AF.\(^\text{10}\) Permanent AF was defined as AF persisting for more than 6 months where electrical cardioversion was not indicated. The primary outcome in this study was the mean change in ventricular heart rate at 14 days. Secondary outcomes included reduction in heart rate during exercise, exercise duration, and adverse effects. Although more than 50% of the study population were prescribed concomitant negative chronotropic agents (i.e., beta-blockers, calcium channel blockers, digoxin), the primary outcome of mean change in ventricular heart rate at 14 days was superior in the dronedarone group (mean decrease of 11 bpm versus mean increase by 0.7 bpm in the placebo group). This benefit was sustained at 4 months. Dronedarone also significantly reduced heart rate during exercise compared with placebo but failed to significantly increase patients’ ability to exercise for a longer duration. Unfortunately, the ERATO study enrolled only 174 patients and was not adequately powered to evaluate clinically meaningful end points, such as all-cause mortality, CV mortality, and CV-related hospitalization.\(^\text{10}\) Although previous studies (EURIDIS, ADONIS, and ATHENA) evaluated these end points, patients with permanent AF were excluded from enrollment.\(^\text{5,7}\) Therefore, it is not possible to extrapolate these trial results to patients with permanent AF. Another limitation to the ERATO trial was that it failed to address whether further heart rate reduction resulted in decreased patient symptoms.

**AF Associated with Heart Failure**

Heart failure (HF) is a common comorbidity and often a direct complication of AF. Historically, only HF patients with mild to moderate symptoms have been included in AF clinical trials while those with severe disease have often been excluded. Therefore, efficacy data in this population were largely derived from post hoc analyses. Similarly, the majority of studies evaluating dronedarone excluded patients with severe HF. ANDROMEDA was the only clinical trial that included patients with class III and IV HF (57% and 4.1%, respectively).\(^\text{11}\) Importantly, this trial was terminated prematurely due to increased mortality in the dronedarone-treated group compared with the placebo-treated group. At 7 months, patients randomized to dronedarone had a significantly higher rate of all-cause mortality (8.1% versus 3.8%; HR = 2.13; 95% CI 1.07–4.25; \(p = .03\)) and more hospitalizations for acute CV causes (22.9% versus 15.8%, \(p = .02\)). Progressive HF accounted for much of the excess in all-cause mortality (3.2 versus 0.6%) and rate of hospitalization for CV causes (11.3 versus 9.5%) attributed to dronedarone. In a subgroup analysis, the risk of death associated with dronedarone was shown to be increased among patients who had a lower wall-motion index. The unexpected findings in the ANDROMEDA trial remain the subject of significant debate and speculation. Nevertheless, this study has caused dronedarone to receive a “black box warning,” with a contraindication for use in patients with New York Heart Association (NYHA) class IV HF, or NYHA class II–III HF with a recent decompensation requiring hospitalization or referral to a specialized HF clinic.\(^\text{11}\)

**Safety and Tolerability of Dronedarone**

Common adverse effects reported for dronedarone include gastrointestinal symptoms (i.e., nausea, vomiting, and diarrhea), a rise in serum creatinine, bradycardia, and QT prolongation.\(^\text{6,10}\) Serum creatinine generally increased but does not appear to correlate with a reduction in the glomerular filtration rate. In the DIONYSOS trial, significantly fewer patients randomized to dronedarone discontinued the study medication secondary to adverse effects as compared with amiodarone.\(^\text{6}\) Although more patients on dronedarone complained of gastrointestinal symptoms, fewer patients reported thyroid, neurological, bradycardic, and QT prolonging effects.

**Place in Therapy**

Dronedarone is the first novel anti-arrhythmic agent to reach the market in over a decade. As a structurally modified version of amiodarone, it holds the potential to retain the favourable efficacy characteristics of amiodarone while minimizing the long-term toxicities that may contribute to significant morbidity. Clinical trials have shown that dronedarone delays the time to first AF recurrence and reduces overall recurrences compared with placebo in patients with recurrent, persistent, and permanent AF. It also exerts negative chronotropic effects and lowers CV-related hospitalization, but has not yet demonstrated any mortality benefits. In direct comparison to amiodarone, dronedarone demonstrated inferior efficacy but superior short-term tolerability. It is important to keep in mind that the current studies are too short in duration to evaluate dronedarone’s long-term toxicity profile—a property that will likely determine its future place in the management of AF. Therefore, ongoing post-marketing surveillance will be critical to evaluate the long-term safety.
of dronedarone. Until long-term safety data are ascertained, it is premature to conclude whether dronedarone is a safer alternative to amiodarone. Since there are currently a number of anti-arrhythmic agents indicated for the maintenance of sinus rhythm in patients with AF, it may be more prudent to select these agents for patients at risk for amiodarone-induced toxicity when a rhythm control strategy is being pursued. When clinicians are considering dronedarone in appropriately selected patients, they must consider the fact that there are no cost-effectiveness data that compare it to other marketed anti-arrhythmic agents, such as amiodarone, which is available as a generic. Recently, the Canadian Expert Drug Advisory Committee completed the common drug review of dronedarone and concluded that it should not be listed for coverage in participating provincial and other drug plans across Canada. This decision was based on the clinical trial evidence available for dronedarone to date and its excess (~fourfold) cost over the most appropriate comparator, amiodarone.

Conclusion
Current evidence with dronedarone demonstrates that is a reasonable option for the management of AF in select patients. It appears to have an improved tolerability in the short term, at the expense of decreased efficacy when compared with amiodarone. Dronedarone is not appropriate for use in patients with NYHA class IV HF or class II–III HF with a recent decompensation. The lack of cost-effectiveness data and potential of non-coverage by provincial formulary programs may limit the clinical use of this new agent.

Appendix 1. Clinical Trial Acronym Definitions
Below are the expansions for trial acronyms discussed in this article:

ADONIS: American–Australian–African trial with DrONedarone In atrial fibrillation or flutter patients for the maintenance of Sinus rhythm
AFFIRM: Atrial Fibrillation Follow-up Investigation of Rhythm Management
ANDROMEDA: ANtiarrhythmic trial with DRONedarone in Moderate to severe CHF Evaluating morbidity DecreASe
ATHENA: A placebo-controlled, double-blind, parallel arm Trial to assess the efficacy of dronedarone 400 mg bid for the prevention of cardiovascular Hospitalization or death from any cause in patiENts with Atrial fibrillation/atrial flutter
DAFNE: Dronedarone Atrial FibrillationN study after Electrical cardioversion
DIOMYSOS: randomized, Double-blind trial to evaluate the efficacy and safety of dRonedarone [400 mg bid] versus amiodarone [600 mg qd for 28 dAYs, then 200 mg qd thereafter] for at least 6 mOnths for the maintenance of sinus rhythm in patients with AF
ERATO: Efficacy and safety of dRonedarone for The cOntrol of ventricular rate during atrial fibrillation
EURIDIS: EUropean trial In atrial fibrillation or flutter patients receiving Dronedarone for the maintenance of Sinus rhythm

References
Achieving a Peaceful Death: The Internist’s Role In Advance Care Planning

John J. You MD

Do not go gentle into that good night,
Old age should burn and rage at close of day;
Rage, rage against the dying of the light.
– Dylan Thomas

Written for his dying father, these words evoke helplessness, the fear of losing a loved one, and a desperate plea for his father to fight on. The will, courage, and audacity to survive and the refusal to let go of life comprise a visceral human instinct. Expressions such as, “He was a real fighter,” or, “I’m a cancer survivor,” glorify the struggle to stay alive. Medical science has given us the tools to push the frontiers of human survival to new limits and has increased our ability to rescue ourselves from deeper and deeper out of the jaws of death. We celebrate these innovations and modern miracles, and rightly so. But, as Atul Gawande aptly puts it, how should our patients decide “when to switch from fighting for time to fighting for the other things that people value?”

A general internist colleague of mine once told me, “Everyone comes to visit me before they die.” Those of us who practise in-patient general medicine agree that we regularly come face to face with death. The reality of death in Canada is that over 250,000 individuals die each year, projected to reach nearly half a million individuals per year by 2035, and that 70% of these deaths occur in hospital. There is also evidence suggesting that the general medical ward is home to the highest number of deaths compared with any other service in hospital.

My own experiences on the clinical teaching unit confirm that death on the medical ward is common. But more importantly, my experiences indicate that there are a much larger number of patients who actually do not die in hospital but who are reaching the end of the road. For these people, who are at the end stages of chronic illness, there is often little that we can do to change the overall trajectory of their disease. Should we throw up our hands in despair? Ironically, I think that it is among this group of patients where we as internists have an opportunity to make a huge difference in their life and in the lives of their families. Some might argue that we should fight until the very end. That would be no problem if that is the experience that patients truly desired. However, when directly asked, many patients and their families identify the following elements as important aspects of high-quality end-of-life care: feelings of peace, assessment and treatment of emotional problems, trust in the doctors looking after them, avoidance of life support when there is little hope for a meaningful recovery, honest communication of information about their disease, and preparation for life’s end. Each time I attend on the general medicine teaching unit, there is at least one and usually more patients who die while under my care. Unfortunately, “peaceful” is not one of the words I would typically use to describe their death. Instead, a slow deterioration punctuated by invasive procedures, life support, multiple tests, innumerable complications of their underlying disease and their treatments, and overworked health care staff with little time to attend to the basic needs of patients describes a commonplace scenario for many of my patients at the end of life. The family members, thrust unprepared into their role as substitute decision makers, are forced into the uncomfortable situation of making decisions about treatment for their loved one without any prior knowledge of their values or preferences for care at the end of life.

In these situations, it is too late. We are left to struggle through and to do our best to guide the family through the series of decisions that lie ahead. However, for the much larger group of patients we care for on the medical ward who do not die during their hospital stay but who are at high risk of dying in the coming year, there is a captive moment. The hospitalization can be an opportune time for us to start conversations about advance care planning for many reasons: the acute change in the patient’s condition may increase the relevance of having these kinds of conversations; family members, who will typically become the surrogate decision makers, are often present; a multidisciplinary health care team is present; and the target population – the patient at high risk of dying – are concentrated in one physical location (the in-patient medical ward).

There are, however, important barriers to initiating advance care planning in this setting. First, talking about death can be uncomfortable, and with more pressing demands for our time it is all too easy to push these discussions to the bottom of our priority list. Second, many of us do not follow up with these patients in the community after discharge, creating problems for continuity of any discussions that might get started in hospital. Third, some of us may feel inadequately trained to have these conversations or may believe that it is simply not our job to address these issues and that the physicians who know the patients the best (i.e., the primary care physicians or specialists who provide longitudinal care) are the most appropriate care providers to be starting these conversations.

Finally, difficulties in estimating survival may be an important barrier. In contrast to the patient with newly diagnosed metastatic cancer, many of our patients have non-malignant disease, and it can be harder to define a group of patients who are at high risk of dying within the coming 6–12 months. Although prognostic scores have been published, none are simple to use at the bedside. Also, these scoring systems only provide estimates of survival at a given point in time, for example, the proportion of patients alive at 6 months, when median life expectancy (or 90th percentile life expectancy – the time within which 90% of similar patients would be dead) would likely be more meaningful and understandable for most
patients. Heyland et al. have used what may be a more practical approach in their work in end-of-life care to define patients at high risk of dying in, and their criteria appear to identify a group of patients with an average mortality of 50% at 6 months (patients age 55 years or older with end-stage congestive heart failure, chronic obstructive pulmonary disease, cirrhosis, metastatic cancer, or dementia, or any patients age 80 years or older admitted to hospital from the community for an acute medical condition).\textsuperscript{5,6}

Even if we were to overcome these barriers, is there any evidence that advance care planning actually works? SUPPORT (the Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) was a landmark randomized clinical trial to improve end-of-life care and advance care planning in critically ill patients, but the intensive intervention failed to make any meaningful difference in important outcomes, including the timing of a written do not resuscitate order before death, patient and physician agreement on preferences to withhold resuscitation, days spent in an intensive care unit before death, frequency or severity of pain, and hospital resource use before death.\textsuperscript{9}

Despite these sobering results, there is still reason for optimism. A recent randomized clinical trial of an advance care planning intervention delivered by a trained facilitator versus usual care in medical in-patients aged 80 years or more showed that, of the participants who died during follow-up, end-of-life wishes were much more likely to be known and followed in patients who received the study intervention.\textsuperscript{10}

As internists, we can each get involved and make a difference. We each invest our time differently into research, education, and patient care. For those of us who do research, there are huge opportunities to conduct research that aims to improve care in this area. For those of us who are educators, there are tremendous opportunities to develop educational interventions, curricula, and programs that provide our undergraduate and postgraduate trainees and our colleagues (through continuing medical education) with the skills they need to provide high-quality end-of-life care. For all of us who see patients, we are called by our profession not to treat disease entities and normalize aberrant physiology, but to heal people. Patients want to be heard, to receive honest information about their disease and prognosis, and to have their spiritual and emotional needs addressed. We either need to develop the skills to do these ourselves or to work out practical and innovative ways to deliver care in a way that can meet these needs. This is what our patients want. I think we can stand to do a whole lot better, so what are we waiting for?

References

A balanced and nutritive diet has long been recognized as the cornerstone of health. Hippocrates observed, “Our food should be our medicine and our medicine should be our food.” Maimonides echoed this, and advised, “Let nothing which can be treated by diet be treated by other means.” More recently Thomas Edison predicted that “the doctor of the future will give no medications, but will interest his patients in the care of the human frame, diet and in the cause and prevention of disease.”

His contemporary, Abraham Flexner, a major architect of modern medical education, concurred – “the physician’s function is fast becoming social and preventative, rather than individual and curative.” Despite a strong narrative that runs throughout 2,000 years of healing traditions, modern clinicians fail to routinely diagnose and address their patients’ nutrition needs. In the twentieth century explosion of medical sub-specialization and technological advances in pharmacology, immunology, genetics, medical devices, etc., nutrition issues seem to have been pushed to the back burner.

Clinical neglect aside, healthy nutrition is threatened by a multitude of cultural and societal developments within the past half-century. These include changes in school lunch programs, a general decline of traditional family meals, and transformations in the agricultural and food-processing industries. The link between the land (in theory where food comes from) and what we put on our table has become hard to trace, and in some cases it is difficult to identify at the most basic levels the origins of “food” items, that is, animal, mineral, vegetable, or … chemical?

On a positive note, nutritional epidemiologists have made tremendous strides toward understanding the relationships between diet and health. A growing body of epidemiological literature supports the conclusion that a plant-based diet rich in fruits, vegetables, legumes, and whole grains is associated with positive health outcomes.1–4 Dietary analysis of the INTERHEART study observed that patients observing a “prudent” diet, largely as defined above, had half the risk of myocardial infarction as did “less prudent” patients (odds ratio comparing extreme quartiles = 1.92; 95% confidence interval [CI] 1.74–2.11),7 and estimated that 30% of the myocardial infarction in the studied population was attributable to diet.

From a therapeutic perspective, the DASH diet trials demonstrated that a diet rich in fruits, vegetables, and low-fat dairy products, as well as reduced saturated and total fats, was associated with a 5.5 and 3.0 mm Hg reduction in systolic and diastolic blood pressures8– similar or greater than would be expected with many antihypertensive drugs.

Whom to Screen

In today’s evidence-driven medical culture, addressing nutrition is no longer an option. The first clinical dilemma is whom do we screen? Survey studies from the United States suggest that 77% of Americans eat less than five fruits and vegetables per day.8 Canadian practices may be marginally different, but among lifestyle-related risk factors, nutrition ranks high. The HOPER study,9 published in this journal, observed the following risk-related behaviours in a sample of emergency room outpatients: smoking 27%, overweight 51%, sedentary behaviour 65%, and unhealthy nutrition 83%. Such data are alarming, and yet the screen that was used to identify unhealthy nutrition was extremely simple – less than five fruits and vegetables per day – and is likely to underestimate the incidence of “at risk” nutrition. A decade ago, one might have been tempted to limit nutrition screening to the population with overt nutrition-related complications, such as obesity, cachexia, or frank vascular disease. Yet, ignoring nutrition-related risk because a patient has normal body weight is the equivalent of ignoring smoking because pulmonary function is preserved. The clear, albeit somewhat depressing, conclusion is that almost all of our patients with a life expectancy of a decade or more merit consideration for nutrition screening.

How to Screen

The second and more challenging clinical dilemma is how to screen this large segment of the population. Over the past 30 years, epidemiologists have developed and standardized methods to identify nutrient-related risk, and much of our understanding of nutrition-related risk comes from the use of these food frequency questionnaires (FFQs). Unfortunately, they are unwieldy to use in clinical practice, and many of the lessons culled from the epidemiological research are not easily translated into clinical practice. For example, a recommendation to eat more selenium is not very useful to most patients. Nutrition researchers recognize that people buy, cook, and eat food not nutrients, and over the past decade food-based patterns of healthy nutrition have been identified. It is no surprise that there are many eating patterns that are associated with health, and some of the mainstream ones that are becoming a part of the nutrition vernacular are the Mediterranean Diet, the DASH Diet, and the Prudent Diet.

These dietary patterns are the intellectual offspring of epidemiological studies, and some of them still require the use of FFQs for implementation. This relates them to the research arena, and there is an ongoing need for clinical screening tools that can be implemented at the bedside, in the clinics, or, even better, by patients in their own homes. In 2008, a group, of which I was part, published one such tool – the Eating Assessment Table (EAT).10 This is a self-administered nutrition screening tool that asks patients what they eat for breakfast, lunch, dinner, snacks, and any special occasions during the past week. A score of 3 or more is considered to have nutritional risk, and further evaluation is then indicated.

A growing body of evidence demonstrates that nutrition screening can usefully identify patients at risk for heart disease, diabetes, stroke, and other chronic diseases. Nutrition screening can be easily implemented in clinical practice, and it enables us to “let nothing which can be treated by diet be treated by other means.”

Bert Govig MD, MPH

About the Author

Bert Govig is with the Departments of Internal Medicine at CSSS Les Eskers de L’Abitibi, Amos, and at McGill University, Montréal, Québec, and is physician in chief with Coalition pour L’Acquisition de Saines Habitudes. Correspondence may be directed to Bert@govig.ca.
tool that can be completed by most patients in 15 minutes or less. This was well received by the research community and by many clinicians who were quick to recognize that they did not have 15 minutes to administer a screening questionnaire to even a fraction of their patients. Two years of experience with this tool have taught us that busy clinicians also lack the time to correct, tabulate, and score even this simple questionnaire; therefore, we built an online version that validates data entry, tabulates the data, creates a score on a scale of 0–100, creates a computer-generated report based on the patient data, and makes recommendations seeking to guide patients toward a change process. This online tool, currently in a Beta version, is freely available to patients and clinicians and can be accessed under the tools tab of the website www.soundhabits.org. Readers of this journal are invited to use this tool and submit any feedback through the website.

Conclusion
The links between nutrition and health constitute nothing less than ancient knowledge, and nutrition’s role in today’s health problems is probably even greater than in the past. The evidence base for this conclusion grows stronger by the year, and yet, paradoxically, it has become perhaps the most prevalent and at the same time the most neglected risk factor for chronic disease. Arguably, almost all patients should be screened for nutrition issues in the same way that we screen for blood pressure and ask about tobacco use. Until recently, such screening was labour and resource intensive and simply not achievable on a large-scale basis. However, emerging Internet-based technologies promise to dramatically reduce the barriers to nutrition screening and to shift the burden of work to patients who are most likely to benefit from the procedure. As with tobacco use, clinicians can exert great influence on their patients’ nutrition through the use of focused, time-limited interventions. Our job is not to conduct the screen, but to promote it. Health care workers who believe in the links between lifestyles and health can make critical contributions to healthy lifestyle promotion, and collectively we may achieve Abraham Flexner’s 100-year-old vision of clinician-led, population-based medicine.

References
9. MMWR 2001;September 7.
**Pradaxa**
dabigatran etexilate

Dabigatran Etxeinate 110mg and 150mg Capsules

### Prescribing Summary

This is a condensed version of the Product Monograph. For complete information please refer to the Product Monograph available at www.boehringer-ingelheim.ca or by contacting Boehringer Ingelheim (Canada) Ltd., 5180 South Service Road, Burlington, Ontario, L7L 5H4.

### Patient Selection Criteria

**THERAPEUTIC CLASSIFICATION:** Anticoagulant

**INDICATIONS AND CLINICAL USE**

- Prevention of stroke and systemic embolism in patients with atrial fibrillation, in whom anticoagulation is appropriate.

**Geriatrics (>65 years of age):** Clinical studies have been conducted in patients with a mean age >65 years. Safety and efficacy data are available (see CLINICAL TRIALS).

Pharmacokinetic studies in older subjects demonstrate an increase in exposure to dabigatran in most of those patients, usually in association with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Renal Impairment).

**Pediatrics (<18 years of age):** The safety and efficacy of PRADAX have not been established in children less than 18 years of age. Therefore, PRADAX is not recommended in this patient population.

**CONTRAINDICATIONS**

- Severe renal impairment (CrCl <30mL/min)
- Hemorrhagic manifestations, bleeding diathesis, or patients with spontaneous or pharmacological impairment of hemostasis
- Lesions at risk of clinically significant bleeding, e.g., extensive cerebral infarction (hemorrhagic or ischemic) within the last 6 months, or active peptic ulcer disease with recent bleeding
- Concomitant treatment with strong P-glycoprotein (P-gp) inhibitors, i.e., oral ketoconazole (see DRUG INTERACTIONS)
- Known hypersensitivity to dabigatran or dabigatran etexilate or to any ingredient in the formulation or component of the container. For a complete listing, see the DOSAGE FORMS, COMPOSITION AND PACKAGING section of the Product Monograph.

### Safety Information

**WARNINGS AND PRECAUTIONS**

The following Warnings and Precautions are listed in alphabetical order.

### Bleeding

As with all anticoagulants, PRADAX should be used with caution in circumstances associated with an increased risk of bleeding. Bleeding can occur at any site during therapy with PRADAX. An unexplained fall in hemoglobin and/or hematocrit or blood pressure should lead to a search for a bleeding site. Patients at high risk of bleeding should not be prescribed PRADAX (see CONTRAINDICATIONS).

Close clinical surveillance (looking for signs of bleeding or anemia) is recommended throughout the treatment period, especially if risk factors are combined.

**Table 1: Factors which increase hemorrhagic risk, as identified in clinical studies**

<table>
<thead>
<tr>
<th>Factors increasing dabigatran plasma levels</th>
<th>Moderate renal impairment (30-50 mL/min CrCl)</th>
<th>P-glycoprotein inhibitor combination</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pharmacodynamic interactions</td>
<td>Acetylsalicylic acid</td>
<td>NSAID</td>
</tr>
<tr>
<td></td>
<td>Clopidogrel</td>
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</tr>
<tr>
<td>Diseases/procedures with special hemorrhagic risks</td>
<td>Congenital or acquired coagulation disorders</td>
<td>Thrombolytic or functional platelet defects</td>
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<td></td>
<td>Active atrial fibrillation</td>
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<tr>
<td></td>
<td>Recent gastrointestinal bleeding</td>
<td>Recent major trauma</td>
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<tr>
<td></td>
<td>Recent intracranial hemorrhage</td>
<td>Brain, spinal or ophthalmic surgery</td>
</tr>
<tr>
<td>Others</td>
<td>Age &lt;75 years</td>
<td>Bacterial endocarditis</td>
</tr>
</tbody>
</table>

The measurement of dabigatran-related anticoagulation may be helpful to avoid excessive high exposure to dabigatran in the presence of additional risk factors. In patients who are bleeding, an aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT >80 sec at trough, i.e., when the next dose is due, is associated with a higher risk of bleeding (see Monitoring and Laboratory Tests).

**Should severe bleeding occur, treatment with PRADAX must be discontinued and the source of bleeding investigated promptly.** Agents that may enhance the risk of hemorrhage should not be administered concomitantly with PRADAX, or, if necessary, should only be administered with caution (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetic Interactions in the Product Monograph).

**Treatments that should NOT be administered concomitantly with PRADAX due to increase in bleeding risk include: unfractonated heparin and heparin derivatives, low molecular weight heparins (LMWH), fondaparinux, bivalirudin, thrombolytic agents, GPIIb/IIIa receptor antagonists, ticlopidine, sulfonpyrazone, and vitamin K antagonists such as warfarin.** The concomitant use of PRADAX with the following treatments has not been studied and may increase the risk of bleeding: rivaroxaban, prasugrel, and the strong P-gp inhibitors itraconazole, tacrolimus, cyclosporine, ritonavir, tipranavir, neflinavir and saquinavir.

Unfractionated heparin may be administered at doses necessary to maintain a patent central venous or arterial catheter. In patients with atrial fibrillation treated for the prevention of stroke and systemic embolism, the co-administration of oral anti-platelet (including aspirin and clopidogrel) and NSAID therapies increases the risk of bleeding by about two-fold (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic Interactions). If necessary, co-administration of low-dose ASA, i.e., ≤100 mg daily with PRADAX may be considered for other indications than stroke prevention in atrial fibrillation. Note that in the RELY trial, there is no evidence that the addition of ASA or clopidogrel to dabigatran, or its comparator warfarin, improved outcomes in respect to stroke (see CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation).

**Treatment initiation with verapamil should be avoided in patients following orthopedic surgery who are already treated with PRADAX. Simultaneous initiation of treatment with PRADAX and verapamil should also be avoided at any time (see DRUG INTERACTIONS, P-glycoprotein inhibitors).**

**Interaction with P-gp inducers**

The concomitant use of PRADAX with the strong P-gp inducer, rifampin, reduces dabigatran plasma concentrations. Other P-gp inducers such as St. John’s Wort or carbamazepine are also expected to reduce dabigatran plasma concentrations, and should be co-administered with caution (see DRUG INTERACTIONS and Special Populations).

**Surgery/Procedural Interventions**

Patients on PRADAX who undergo surgery or invasive procedures are at increased risk for bleeding. In these circumstances, temporary discontinuation of PRADAX may be required.

**Pre-operative Phase**

In advance of invasive or surgical procedures PRADAX should be stopped temporarily due to an increased risk of bleeding. If possible, PRADAX should be discontinued at least 24 hours before invasive or surgical procedures. In patients at higher risk of bleeding (see DOSAGE AND ADMINISTRATION) or in major surgery where complete hemostasis may be required, consider stopping PRADAX 2-4 days before surgery. Clearance of dabigatran in patients with renal insufficiency may take longer (see DOSAGE AND ADMINISTRATION, Renal). This should be considered in advance of any procedures.

**PRADAX is contraindicated in patients with**
severe renal dysfunction (CrCl <30 mL/min). Should acute renal failure occur before surgery is required, PRADAX should generally be stopped at least 5 days before major surgery. If acute intervention is required, PRADAX should be temporarily discontinued, due to increased risk of bleeding. Surgery or procedural interventions should be delayed if possible until at least 12 hours after the last dose of PRADAX, with risk of bleeding weighed against the urgency of the needed intervention.

**Peri-Operative Spinal/Epidural Anesthesia, Lumbar Puncture**

Procedures such as spinal anesthesia may require complete hemostatic function. In patients treated with PRADAX for VTE prevention following major orthopedic surgery and who undergo spinal or epidural anesthesia, or in whom lumbar puncture is performed in follow-up to surgery, the formation of spinal or epidural hematomas that may result in long-term or permanent paralysis cannot be excluded.

In the case of these peri-spinal procedures, administration of the first dose of PRADAX should occur after hemostasis has been obtained and no sooner than 2 hours following puncture or removal of catheters related to these procedures.

**The risk of these rare events may be higher with post-operative use of indwelling epidural catheters or the concomitant use of other products affecting hemostasis.** Accordingly, the use of PRADAX is not recommended in patients undergoing anesthesia with post-operative indwelling epidural catheters.

**Post-Procedural Period**

Resume treatment with PRADAX as soon as complete hemostasis is achieved.

**Renal**

PRADAX is contraindicated in cases of severe renal impairment (CrCl <30 mL/min). Patients who develop acute renal failure while on PRADAX should discontinue such treatment.

- **Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:** Since no dose adjustment is necessary for most atrial fibrillation patients with moderate renal impairment (CrCl 30-50 mL/min), a standard daily dose of 300 mg, taken orally as one 150 mg capsule twice daily is recommended (see DOSAGE AND ADMINISTRATION, Renal Impairment).

**Special Populations**

**Pregnant Women:** Since there are no studies of PRADAX in pregnant women, the potential risk in these patients is unknown. Animal reproductive studies did not show any adverse effects on fertility or postnatal development of the neonate.

Women of child-bearing potential should avoid pregnancy during treatment with PRADAX and when pregnant, women should not be treated with PRADAX unless the expected benefit is greater than the risk.

**Nursing Women:** Breast-feeding during treatment with PRADAX is not recommended. There are no clinical data available on the excretion of dabigatran into breast milk.

**Geriatrics (>65 years of age):**

Pharmacokinetic studies in older subjects demonstrate an increase in drug exposure, especially in those patients with age-related decline of renal function (see WARNINGS AND PRECAUTIONS, Renal, and DOSAGE AND ADMINISTRATION, Renal Impairment).

- **Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:** Patients aged 80 years and above should be treated with a daily dose of 220 mg taken orally as one 110 mg capsule twice daily. This alternate dosing may also be considered for other geriatric patients (see DOSAGE AND ADMINISTRATION, Elderly). Use with caution.

**Pediatrics (<18 years of age):** The safety and efficacy of PRADAX have not been established in children less than 18 years of age. Therefore, PRADAX is not recommended in this patient population.

**Patients of low body weight (<50 kg):** Since limited data are available in these patients, PRADAX should be used with caution.

**Monitoring and Laboratory Tests**

At recommended doses of PRADAX, dabigatran prolongs coagulation time as measured by the activated partial thromboplastin time (aPTT), thrombin time (TT) and ecarin clotting time (ECT). In patients who are bleeding due to excess activity of dabigatran, these coagulation tests would be expected to be elevated and may be helpful in assessing anticoagulant activity of dabigatran, if necessary (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics). The aPTT is generally less sensitive to anticoagulant activity than either TT or ECT (see DRUG INTERACTIONS, Drug-Laboratory Interactions).

However, the aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding. In circumstances where there is no excess of anticoagulant activity, the utility of aPTT is limited in monitoring anticoagulant status of patients taking PRADAX.

**ADVERSE REACTIONS**

The safety of PRADAX has been evaluated overall in 22,126 patients. A total of 10,084 patients were exposed to at least one dose of dabigatran as study medication in four active-controlled clinical trials conducted to evaluate the safety and effectiveness of dabigatran etexilate in the prevention of venous thromboembolic events (VTE) following major elective orthopedic surgery. Of these, 5,419 were treated with 150 mg or 220 mg daily of PRADAX, while 389 received doses of less than 150 mg daily, and 1,168 received doses in excess of 220 mg daily.

In the RELY trial investigating the prevention of stroke and systemic embolism in patients with atrial fibrillation, a total of 12,042 patients were exposed to PRADAX. Of these, 6,059 were treated with 150 mg twice daily of dabigatran etexilate, while 5,983 received doses of 110 mg twice daily.

About 21% of patients with atrial fibrillation treated with dabigatran and about 16% of patients treated with warfarin for the prevention of stroke and systemic embolism (long-term treatment for up to 3 years) experienced adverse events considered related to treatment.

**Bleeding**

Bleeding is the most relevant side effect of PRADAX. Bleeding of any type or severity occurred in approximately 14% of patients treated short-term for elective hip or knee replacement surgery and in long-term treatment in 16.5% of patients with atrial fibrillation treated for the prevention of stroke and systemic embolism.

Although rare in frequency in clinical trials, major or severe bleeding may occur and, regardless of location, may lead to disabling, life-threatening or even fatal outcomes.

A summary description of major and total bleeding is provided in Table 2. Table 2 shows the number of patients experiencing major and total bleeding event rates during the treatment period in the RELY study, conducted in patients with atrial fibrillation. In Table 2, the category of major bleeds includes both life-threatening and non-life threatening bleeds. Within life-threatening, intracranial bleeds is a subcategory of life-threatening bleeds. Intracranial bleeds include intracerebral (hemorrhagic stroke), subarachnoid and subdural bleeds. For this reason, these events may be counted in multiple categories.
Clinical Trial Adverse Drug Reactions:

- **Laboratory abnormalities**: hematology, chemistry
- **Hematological disorders**: anemia
- **Other adverse drug reactions**: fatigue, influenza

**Investigator-reported bleeding events**

- **Major bleeding events (INR)**: 84 (1.3), 61 (1.3), 47 (0.8)
- **Minor bleeding events**: 325 (5.5), 290 (4.9), 262 (4.4)
- **Any bleeding events**: 536 (9.2), 503 (8.3), 488 (8.5)

**Adverse drug reactions**

- **Gastrointestinal disorders**: epistaxis, rash, pruritus
- **Allergic reactions or drug hypersensitivity**: urticaria, bronchospasm
- **Musculoskeletal and connective tissue disorders**: hemarthrosis

**Concomitant use of PRADAX with other anticoagulants** has not been adequately studied and is not recommended.

In the RELY trial, conducted in patients with atrial fibrillation, a two-fold increase in major bleeding was seen in both dabigatran study treatment arms, as well as that of the comparator, warfarin, when ASA was administered concomitantly (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic Interactions in the Product Monograph; CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation; and DOSAGE AND ADMINISTRATION).

**Drug-Drug Interactions**

**Transporter interactions**: Dabigatran etexilate, but not dabigatran, is a substrate with moderate affinity for the efflux P-glycoprotein (P-gp) transporter. Therefore, potent P-glycoprotein inducers or inhibitors may be expected to impact exposure to dabigatran.

**P-glycoprotein inhibitors**: P-gp inhibitors like verapamil, quinidine and amiodarone may be expected to increase systemic exposure to dabigatran, see Table 4 below. The strong P-glycoprotein inhibitor ketoconazole, when administered orally, is contraindicated (see CONTRAINDICATIONS). If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anemia), along with a sense of caution is required when dabigatran is co-administered with strong P-glycoprotein inhibitors.

**P-glycoprotein substrates**: Dabigatran etexilate is not expected to have a clinically meaningful interaction with P-glycoprotein substrates that do not also act as inhibitors or inducers of P-gp.

---

**Table 3: Common Adverse Reactions observed in ≥1% of dabigatran-treated patients with atrial fibrillation in the active-controlled trial, RELY**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Dabigatran etexilate 110 mg bid</th>
<th>Dabigatran etexilate 150 mg bid</th>
<th>Warfarin</th>
<th>N (%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients randomized</td>
<td>5,983 (100)</td>
<td>6,059 (100)</td>
<td>5,998 (100)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patients-years</td>
<td>747 (12.3)</td>
<td>805 (13.3)</td>
<td>825 (14.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding event (INR)*</td>
<td>0.80 (0.79, 0.81)</td>
<td>0.83 (0.82, 0.84)</td>
<td>0.77 (0.76, 0.78)</td>
<td>&lt;0.0001</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>p-value</td>
<td>0.0006</td>
<td>0.0006</td>
<td>0.0006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening MBE</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td>3 (0.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding event (INR)**</td>
<td>0.78 (0.73, 0.83)</td>
<td>0.81 (0.75, 0.86)</td>
<td>0.77 (0.72, 0.82)</td>
<td>&gt;0.05</td>
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<td>p-value</td>
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</tr>
</tbody>
</table>

**Adverse drug reactions**

- **Common Clinical Trial Adverse Drug Reactions**: chest pain, dyspnea
- **More Common Clinical Trial Adverse Drug Reactions**: constipation, diarrhea
- **Less Common Clinical Trial Adverse Drug Reactions**: thrombocytopenia

**Drug Interactions**

Based on *in vitro* evaluation, neither dabigatran etexilate nor its active moiety, dabigatran, have been shown to be metabolized by the human cytochrome P450 system, nor did they exhibit effects on human CYP P450 isozymes. Concomitant use of PRADAX with treatments that interfere with hemostasis or coagulation increases bleeding risk (see WARNINGS AND PRECAUTIONS, Bleeding). Co-administration of PRADAX with other anticoagulants has not been adequately studied and is not recommended.

In the RELY trial, conducted in patients with atrial fibrillation, a two-fold increase in major bleeding was seen in both dabigatran study treatment arms, as well as that of the comparator, warfarin, when ASA was administered concomitantly (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic Interactions in the Product Monograph; CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation; and DOSAGE AND ADMINISTRATION).

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**P-glycoprotein inhibitors**: P-gp inhibitors like verapamil, quinidine and amiodarone may be expected to increase systemic exposure to dabigatran, see Table 4 below. The strong P-glycoprotein inhibitor ketoconazole, when administered orally, is contraindicated (see CONTRAINDICATIONS). If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anemia), along with a sense of caution is required when dabigatran is co-administered with strong P-glycoprotein inhibitors.

**P-glycoprotein substrates**: Dabigatran etexilate is not expected to have a clinically meaningful interaction with P-glycoprotein substrates that do not also act as inhibitors or inducers of P-gp.

---

**Table 2: Frequency and annualized event rate (%) of bleeding events from the RELY trial**

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In the RELY trial, conducted in patients with atrial fibrillation, a two-fold increase in major bleeding was seen in both dabigatran study treatment arms, as well as that of the comparator, warfarin, when ASA was administered concomitantly (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic Interactions in the Product Monograph; CLINICAL TRIALS, Stroke Prevention in Atrial Fibrillation; and DOSAGE AND ADMINISTRATION).

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**P-glycoprotein inhibitors**: P-gp inhibitors like verapamil, quinidine and amiodarone may be expected to increase systemic exposure to dabigatran, see Table 4 below. The strong P-glycoprotein inhibitor ketoconazole, when administered orally, is contraindicated (see CONTRAINDICATIONS). If not otherwise specifically described, close clinical surveillance (looking for signs of bleeding or anemia), along with a sense of caution is required when dabigatran is co-administered with strong P-glycoprotein inhibitors.

**P-glycoprotein substrates**: Dabigatran etexilate is not expected to have a clinically meaningful interaction with P-glycoprotein substrates that do not also act as inhibitors or inducers of P-gp.
Drug-Food Interactions

Food does not affect the bioavailability of PRADAX but delays the time-to-peak plasma concentrations by 2 hours.

Drug-Herb Interactions

Drug-herb interactions have not been investigated. Potent P-gp inducers such as St. John’s Wort (Hypericum perforatum) may be expected to affect systemic exposure of dabigatran. Co-administration of these products is not recommended.

Drug-Laboratory Interactions

No single test (aPTT, TT, ECT) is adequate to reliably assess the anticoagulant activity of dabigatran following PRADAX administration. At therapeutic levels of dabigatran, thrombin time (TT) is the best measure of the pharmacodynamic effect of dabigatran because of its linear and sensitive relationship with dabigatran exposure (WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests; ACTION AND CLINICAL PHARmacology, Pharmacodynamics, in the Product Monograph).

The aPTT test is widely available and provides an approximate indication of the anticoagulation intensity achieved with dabigatran. In patients who are bleeding, the aPTT test may be useful to assist in determining an excess of anticoagulant activity, despite its limited sensitivity. An aPTT greater than 80 sec at trough (when the next dose is due) is associated with a higher risk of bleeding.

Note that a PT (INR) test is not useful to assess the anticoagulant activity of PRADAX.

Drug-Lifestyle Interactions

No direct interaction between dabigatran etexilate and alcohol was demonstrated in animal models or has been hypothesized. The effect of PRADAX on the ability to drive and use machines has not been investigated. However, no such interaction is to be expected.

Administration

**DOSEAGE AND ADMINISTRATION**

PRADAX should be taken orally, with the entire capsule to be swallowed whole. The capsule should not be chewed, broken, or opened. PRADAX should be taken regularly, as prescribed, to ensure optimal effectiveness. All temporary discontinuations should be avoided, unless medically indicated.

**Recommended Dose and Dosage Adjustment**

- **Prevention of stroke and systemic embolism in patients with atrial fibrillation:** The recommended dose of PRADAX is 300 mg daily, taken orally as one 150 mg capsule twice a day (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Tables 24 and 25, in the Product Monograph).

If the usual recommended dose for most geriatric patients under the age of 80 years is 300 mg daily, taken orally as one 150 mg capsule twice a day, with capsule twice a day (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Tables 24 and 25, in the Product Monograph). However, in geriatric patients, especially those over the age of 75 with at least one other risk factor for bleeding (see WARNINGS AND PRECAUTIONS, Bleeding, Table 2), the administration of a dose of 220 mg of PRADAX daily, taken orally as one 110 mg capsule twice a day, may be considered. It should be noted, however, that the effectiveness of stroke prevention may be expected to be lessened with this dosage regimen, compared to that of the usual one of 300 mg of PRADAX daily. As with any anticoagulant, caution is required when prescribing PRADAX to the elderly (see CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS, Bleeding).

**Patients at risk of bleeding:** Prevention of stroke and systemic embolism in patients with atrial fibrillation: Patients with an increased risk of bleeding (see WARNINGS AND PRECAUTIONS, Bleeding, Table 1), should be closely monitored clinically (looking for signs of bleeding or anemia). In such patients, a dose of 220 mg, given as 110 mg twice daily may be considered. A coagulation test, such as aPTT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. As for any anticoagulant, PRADAX is NOT indicated in patients at excessive risk of bleeding (see CONTRAINDICATIONS).

**Renal impairment:** Following oral dosing with dabigatran etexilate, there is a direct correlation of systemic exposure to dabigatran with degree of renal impairment (see WARNINGS AND PRECAUTIONS, Renal). The kidneys account for 85% of dabigatran clearance. There are no data to support use in patients with severe renal impairment (CrCl <30 mL/min). Given the substantial increase in dabigatran exposure observed in this patient population, treatment with PRADAX is not recommended (see CONTRA-INDICATIONS, and ACTION AND CLINICAL PHARmacology, Renal Insufficiency).

**Patients with atrial fibrillation treated for prevention of stroke and systemic embolism having moderate renal impairment (CrCl 30-50 mL/min):** No dose adjustment is recommended (see CLINICAL TRIALS, Prevention of Stroke and Systemic Embolism in Patients with Atrial Fibrillation, Renal Impairment). Patients with moderate renal impairment (CrCl 30-50 mL/min) should be treated with a daily dose of PRADAX at 300 mg taken orally as one 150 mg capsule twice daily, with
caution. Regular assessment of renal status is required in these patients (see CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS, Renal). A coagulation test, such as aPTT (see WARNINGS AND PRECAUTIONS, Monitoring and Laboratory Tests), may help to identify patients with an increased bleeding risk caused by excessive dabigatran exposure. 

Creatinine clearance can be estimated using the Cockcroft-Gault formula as follows: 

Creatinine clearance (mL/min) = 

Males: \((140 - \text{age (years)}) \times \text{weight (kg)} \div 72 \times \text{serum creatinine (mg/100mL)}\) 

Females: \(0.85 \times (140 - \text{age (years)}) \times \text{weight (kg)} \div 72 \times \text{serum creatinine (mg/100mL)}\)

**P-glycoprotein inhibitors:** P-gp inhibitors like verapamil, quinidine, and amiodarone may be expected to increase systemic exposure to dabigatran. Combination use with oral ketoconazole is contraindicated (see CONTRAINDICATIONS). 

- **Patients with atrial fibrillation treated for prevention of stroke and systemic embolism:** No dose adjustment is recommended in patients concomitantly receiving amiodarone, quinidine or verapamil (see DRUG INTERACTIONS, Table 4, Summary of Drug-Drug Interactions; and ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic interactions in the Product Monograph). Patients should be treated with a daily dose of 300 mg PRADAX taken orally as one 150 mg capsule twice daily. To minimize potential for interaction, PRADAX should be given at least two hours before verapamil (see ACTION AND CLINICAL PHARMACOLOGY, Special Populations, Pharmacokinetic interactions in the Product Monograph). Caution should be exercised. Close clinical surveillance is recommended.

**Drugs that increase gastric pH, such as antacids, protein pump inhibitors (PPI):** Diminished clinical effect for antacids may occur (see DRUG INTERACTIONS, Table 4, Summary of Drug-Drug Interactions). Although no dosage adjustment is generally necessary, administer PRADAX at least two hours before antacids, if possible, to minimize interaction potential. No dose adjustment is required for pantoprazole or other PPIs.

**Concomitant antithrombotic use:** Concomitant use of ASA or clopidogrel with PRADAX in patients with atrial fibrillation approximately doubled the risk of major bleed, irrespective of dose of PRADAX used. A similar increase was noted with such concomitant use with the study comparator, warfarin. These observations contrasted with little apparent additional improvement in stroke and systemic embolic events with combined antithrombotic use and PRADAX (or warfarin). Concomitant use of PRADAX with an antithrombotic is not recommended for prevention of cardogenic thromboembolic stroke in patients with atrial fibrillation. Concomitant use of ASA or other antiplatelet agents based on medical need to prevent myocardial infarction should be undertaken with caution. Close clinical surveillance is recommended.

**Acute myocardial infarction (AMI):** Consideration should be given to discontinuing PRADAX in the setting of acute myocardial infarction should the treatment of myocardial infarction involve invasive procedures, such as percutaneous coronary revascularization, or coronary artery bypass surgery. Similar consideration should be given if thrombolytic therapy is to be initiated, because bleeding risk may increase. Patients with AMI should be treated according to current clinical guidelines for that disorder. In this setting, PRADAX may be resumed for the prevention of stroke and systemic embolism upon completion of these revascularization procedures.

**Children:** Since PRADAX has not been investigated in patients <18 years of age, treatment is not recommended.

**Patient Body Weight:** Population PK modelling shows that patients with a body weight of about 120 kg have about 20% lower drug exposure. Patients with a body weight of about 48 kg have about 25% higher drug exposure compared to patients with average weight. No dose adjustment deemed necessary.

**Switching from PRADAX treatment to parenteral anticoagulant:**

- In patients with atrial fibrillation treated for prevention of stroke and systemic embolism: wait 12 hours after the last dose of PRADAX before switching to a parenteral anticoagulant.

**Switching from parenteral anticoagulants treatment to PRADAX:** If deemed medically appropriate, treatment with PRADAX should be initiated 0–2 hours prior to the time that the next dose of the alternate therapy would be due, or at the time of discontinuation in case of continuous treatment (e.g., intravenous unfractionated heparin, (UFH)).

**Switching from Vitamin K antagonists to PRADAX:** If deemed medically appropriate, PRADAX should only be started after Vitamin K antagonists have been discontinued, and the patient’s INR is found to be below 2.0.

**Cardioversion:** Patients can be maintained on PRADAX while being cardioverted.

**Missed Dose:** Prevention of stroke and systemic embolism in patients with atrial fibrillation: If the prescribed dose of PRADAX is not taken at the scheduled time, the dose should be taken as soon as possible on the same day. A forgotten PRADAX dose may still be taken up to 6 hours prior to the next scheduled dose. From 6 hours prior to the next scheduled dose on, the missed dose should be omitted. Patients should not take a double dose to make up for missed individual doses. For optimal effect and safety, it is important to take PRADAX regularly twice a day, at approximately 12-hour intervals.

**Administration**

PRADAX may be taken with food, or on an empty stomach with water. The capsule should be swallowed intact. It should not be opened, broken, or chewed (see ACTION AND CLINICAL PHARMACOLOGY in the full Product Monograph, Pharmacokinetics).

**SUPPLEMENTAL PRODUCT INFORMATION**

**Adverse Reactions:**

**Liver Function Tests:** In the long-term RELY study, observed abnormalities of liver function tests (LFT) are presented below in Table 5.

**Table 5: Liver Function Tests in the RELY trial**

<table>
<thead>
<tr>
<th>Level of LFT</th>
<th>Dabigatran etexilate 110 mg twice daily (%)</th>
<th>Dabigatran etexilate 150 mg twice daily (%)</th>
<th>Warfarin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALT or AST &gt;5xULN</td>
<td>36 (7.2)</td>
<td>45 (7.7)</td>
<td>50 (8.9)</td>
</tr>
</tbody>
</table>

**OVERDOSE**

There is no antidote to dabigatran etexilate or dabigatan. Doses of PRADAX beyond those recommended expose the patient to increased risk of bleeding. Excessive anticoagulation may require discontinuation of PRADAX. In the event of hemorrhagic complications, treatment must be discontinued and the source of bleeding investigated. Since dabigatan is excreted predominantly by the renal route, adequate diuresis must be maintained. Appropriate standard treatment, e.g., surgical hemostasis as indicated and blood volume replacement, should be undertaken. In addition, consideration may be given to the use of fresh whole blood or the transfusion of fresh frozen plasma. As protein binding is low, dabigatran can be dialysed, although there is limited clinical experience in using dialysis in this setting. Activated prothrombin complex concentrates (e.g., FEIBA) or recombinant Factor VIIa or concentrates of coagulation factors II, IX or X, may be considered. There is some experimental evidence to support the role of these agents in reversing the anticoagulant effect of dabigatan but their usefulness in clinical settings has not yet been clearly demonstrated. Consideration should also be given to administration of platelet concentrates in cases where thrombocytopenia is present or long-acting antiplatelet drugs have been used. All symptomatic treatment should be given according to the physician’s judgement.

**For management of a suspected drug overdose, contact your regional Poison Control Centre.**

Product Monograph is available upon request or at www.boehringer-ingelheim.ca

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Road
Burlington, ON L7L 5H4

www.boehringer-ingelheim.ca

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November 8, 2010
**Situations where an increase in rosuvastatin plasma levels may occur**

- Alcohol abuse
- Disease (see CLINICAL TRIALS)

**INDICATIONS AND CLINICAL USE: Hypercholesterolemia**

- CRESTOR (rosuvastatin calcium) is indicated to:
  - Cardiovascular or cerebrovascular events, but with at least two conventional risk factors for cardiovascular disease (see CLINICAL TRIALS), CRESTOR is indicated to:
    - Reduce the risk of nonfatal myocardial infarction
    - Reduce the risk of nonfatal stroke
    - Reduce the risk of coronary artery revascularization

**CONTRAINDICATIONS:** CRESTOR (rosuvastatin calcium) is contraindicated:

- In patients who are hypersensitive to any component of this medication
- In patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 5 times the upper limit of normal (see WARNINGS AND PRECAUTIONS)
- In pregnant and nursing mothers (see SUPPLEMENTAL PRODUCT INFORMATION)
- In patients using concomitant cyclosporine (see DRUG INTERACTIONS)

**Contraindication for CRESTOR 40 mg:**

- Asian patients
- Patients with predisposing factors for myopathy/rhabdomyolysis such as:
  - Personal or family history of hereditary muscular disorders
  - Previous history of muscle toxicity with another HMG-CoA reductase inhibitor
  - Concomitant use of a fibrate or niacin
  - Severe hepatic impairment
  - Severe renal impairment (CrCl < 30 mL/min/1.73 m²) (see ADMINISTRATION, Patients with Renal Impairment)
  - Hyperthyroidism
  - Alcohol abuse
  - Situations where an increase in rosuvastatin plasma levels may occur

**Dose and Administration**

- **B e f o r e  i n s t i t u t i n g  t h e r a p y  w i t h  C R E S T O R  ( r o s u v a s t a t i n calcium), an attempt should be made to control hypercholesterolemia with appropriate diet, exercise, weight reduction in overweight patients, and to treat other underlying medical problems and associated cardiovascular risk factors. The patient should be advised to inform subsequent physicians of the prior use of CRESTOR or any other lipid-lowering agent.**

**Co-enzyme Q10 (ubiquinone):**

- Ubiquinone levels were not measured in CRESTOR clinical trials. Significant decreases in circulating ubiquinone levels in patients treated with other statins have been observed. The clinical significance of a potential long-term statin-induced deficiency of ubiquinone has not been established. It has been reported that a decrease in myocardial ubiquinone levels could lead to impaired cardiac function in patients with borderline congestive heart failure.

**Endocrine Function:**

- HMG-CoA reductase inhibitors interfere with cholesterol synthesis and lower cholesterol levels and, as such, might theoretically blunt adrenal or gonadal steroid hormone production. Rosuvastatin demonstrated no effect upon nonstimulated cortisol levels and no effect on thyroid metabolism as assessed by TSH plasma concentration. In CRESTOR-treated patients, there was no impairment of adrenocortical reserve and no reduction in plasma corticosteroid concentrations. Clinical studies with other HMG-CoA reductase inhibitors have suggested that these agents do not reduce plasma testosterone concentration. The effects of HMG-CoA reductase inhibitors on male fertility have not been studied. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown.

- Patients treated with rosuvastatin who develop clinical evidence of endocrine dysfunction should be evaluated appropriately. Caution should be exercised if an HMG-CoA reductase inhibitor or other agent used to lower cholesterol levels is administered to patients receiving other drugs (e.g., ketoconazole, spironolactone or cimetidine) that may decrease the levels of endogenous steroid hormones.

**Plasma Glucose:**

- In the JUPITER trial, rosuvastatin 20 mg was observed to increase plasma glucose levels, which were sufficient to shift some prediabetic subjects to the diabetes mellitus status (see ADVERSE REACTIONS).

**Lipoprotein(a):**

- In some patients, the beneficial effect of lowered total cholesterol and LDL-C levels may be partly blunted by a concomitant increase in the Lipoprotein(a) [LP(a)] concentrations. Present knowledge suggests the importance of high LP(a) levels as an emerging risk factor for coronary heart disease. It is thus desirable to maintain and reinforce lifestyle changes in high-risk patients placed on rosuvastatin therapy.

**Hepatic Effects:**

- CRESTOR is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases exceeding 3 times the upper limit of normal.

- As with other HMG-CoA reductase inhibitors, it is recommended that a liver function test be carried out prior to, and 3 months following, the initiation of CRESTOR or if the patient is limited to the dose of 40 mg. CRESTOR should be discontinued or the dose reduced if the level of transaminases is greater than 3 times the upper limit of normal.

**Contraindications:**

- CRESTOR, as well as other HMG-CoA reductase inhibitors, should be used with caution in patients who consume substantial quantities of alcohol and/or have a past history of liver disease.

- As with other HMG-CoA reductase inhibitors, a dose-related increase in transaminases has been observed in a small number of patients taking rosuvastatin (< 0.5%); the majority of cases were mild, asymptomatic and transient.

**Hepatic Impairment:**

- In subjects with varying degrees of hepatic impairment there was no evidence of increased exposure to rosuvastatin other than in 2 subjects with the most severe liver disease (Child-Pugh scores of 8 and 9). In these subjects, systemic exposure was increased by at least 2-fold compared to subjects with lower Child-Pugh scores (see ADMINISTRATION, Patients with Hepatic Impairment).

**Muscle Effects:**

- Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with CRESTOR and with other HMG-CoA reductase inhibitors.

- Effects on skeletal muscle such as myalgia, myopathy and, rarely, rhabdomyolysis have been reported in patients treated with CRESTOR at all doses and in particular with the 40 mg dose.

- Myopathy, defined as muscle pain or muscle weakness in conjunction with increases in creatine kinase (CK) values to greater than ten times the upper limit of normal, should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CK. Patients should be advised to report promptly any unexplained muscle pain, tenderness or weakness, particularly if associated with malaise or fever. Patients who develop any signs or symptoms suggestive of myopathy should have their CK levels measured. CRESTOR therapy should be discontinued if markedly elevated CK levels (> 10 x ULN) are measured or myopathy is diagnosed or suspected.

**Predisposing Factors for Myopathy/Rhabdomyolysis:**

- CRESTOR, as with other HMG-CoA reductase inhibitors, should be prescribed with caution in patients with predisposing factors for myopathy/rhabdomyolysis. Such factors include:
  - Personal or family history of hereditary muscular disorders
  - Age > 70 years
  - Previous history of muscular toxicity with another HMG-CoA reductase inhibitor
  - Hypothyroidism
  - Type 2 diabetes
  - Concomitant use of a fibrate or niacin
  - Alcohol abuse
  - Situations where an increase in plasma levels of rosuvastatin may occur

In CRESTOR trials there was no evidence of increased skeletal muscle effects when CRESTOR was dosed with concomitant therapy such as fibrinolytic derivatives (including fenoldopam and gemfibrozil), nicotinic acid, azole antifungals and macrolide antibiotics. However, an increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors together with these medicines.

**Renal Impairment:**

- Subjects with severe renal impairment (CrCl < 30 mL/min/1.73 m²) had a 3-fold increase in plasma concentration of rosuvastatin compared to healthy volunteers and, therefore, CRESTOR 40 mg is contraindicated in these patients (see CONTRAINDICATIONS and ADMINISTRATION, Patients with Renal Impairment).

- In subjects with varying degrees of renal impairment, mild to moderate renal disease had little influence on plasma concentrations of rosuvastatin.

- During the clinical development program, dipstick-positive proteinuria and microscopic hematuria were observed among rosuvastatin-treated patients, predominantly in patients dosed above the recommended dose range (i.e., > 80 mg). Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in patients taking CRESTOR and other HMG-CoA reductase inhibitors. This finding was more frequent in patients taking 40 mg when compared to lower doses of rosuvastatin or comparator statins. Shifts in urinal protein from none or trace to ++ (dipstick) or more were seen in < 1% of patients at some time during treatment with 10 and 20 mg, and in approximately 3% of patients treated with 40 mg. The protein detected was mostly tubular in origin. In most cases, proteinuria was
generally transient and it decreased or disappeared spontaneously on continued therapy. It has not been shown to be predictive of acute or progressive renal disease. Nevertheless, a dose reduction may be considered for patients with unexplained persistent proteinuria during routine testing.

**Hypersensitivity:** An apparent hypersensitivity syndrome has been reported rarely with other HMG-CoA reductase inhibitors. This has included one or more of the following features: anaphylaxis, angioedema, lupus erythematosus-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR) increase, eosinophilia, arthritis, arthralgia, urticaria, asthma, photosensitivity, fever, chills, flushing, malaise, dyspnea, toxic epidermal necrolysis, erythema multiforme including Stevens-Johnson syndrome. Treatment should be discontinued if hypersensitivity is suspected (see CONTRAINDICATIONS).

**Special Populations**

**Pregnant Women:** CRESTOP is contraindicated during pregnancy (see CONTRAINDICATIONS).

**Nursing Women:** It is not known whether rosuvastatin is excreted in human milk. Because of the potential for adverse reactions in nursing infants, women taking CRESTOP should not breastfeed (see CONTRAINDICATIONS).

**Pediatrics (≤ 18 years of age):** Treatment experience with CRESTOP in a pediatric population is limited to 8 patients with homozygous familial hypercholesterolemia. None of these patients was below 8 years of age (see ADMINISTRATION, Use in Children).

**Geriatrics (≥ 65 years of age):** There were no clinically significant pharmacokinetic differences between young and elderly patients (≥ 65 years) (see ADMINISTRATION, Use in Elderly). However, elderly patients may be more susceptible to myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects, Predisposing Factors for Myopathy/Rhabdomyolysis).

**Race:** Results of pharmacokinetic studies, including a large study conducted in North America, have demonstrated an approximate 2-fold elevation in median exposure in Asian subjects (having either Filipino, Chinese, Japanese, Korean, Vietnamese or Asian-Indian origin) when compared with a Caucasian control group. This increase should be considered when making rosuvastatin dosing decisions for Asian patients and the dose of 40 mg is contraindicated in these patients (see CONTRAINDICATIONS and ADMINISTRATION, Race).

**ADVERSE REACTION SERIOUSNESS AND INCIDENCE:** CRESTOP (rosuvastatin calcium) is generally well tolerated. The adverse events seen with CRESTOP are generally mild and transient. CRESTOP clinical trial experience is extensive, involving 9900 patients treated with CRESTOP in placebo-controlled trials and 9855 patients treated with CRESTOP in active-controlled clinical trials.

**Abnormal Hematologic and Clinical Chemistry Findings:** As with other HMG-CoA reductase inhibitors, a dose-related increase in liver transaminases and CK has been observed in a small number of patients taking rosuvastatin (see WARNINGS AND PRECAUTIONS, Muscle Effects, Predisposing Factors for Myopathy/Rhabdomyolysis). Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in a small number of patients taking CRESTOP and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on a continued therapy, and is not predictive of acute or progressive renal disease (see WARNINGS AND PRECAUTIONS, Renal Impairment).

In the JUPITER trial, occurrences of diabetes mellitus as a pre-specified secondary outcome were reported more frequently in the CRESTOP-treated patients (2.8%) than in placebo (2.3%) and a slight increase in the number of subjects whose fasting glucose levels increased to ≥ 5.6 mmol/L (126 mg/dL) was observed in subjects treated with CRESTOP. There was a 0.1% increase in mean HbA1c with CRESTOP compared to placebo. A causal relationship with statins and diabetes mellitus has not been definitely established.

**Postmarket Adverse Drug Reactions:** In addition to the events reported above, the following adverse events have been reported during postmarketing experience with CRESTOP, regardless of causality assessment.

- **Skeletal muscle effects:** Very rare: arthralgia
  - It has been observed that as with other HMG-CoA reductase inhibitors, the reporting rate for rhabdomyolysis in postmarketing use is higher at the highest marketed dose (see WARNINGS AND PRECAUTIONS, Muscle Effects).

- **Hepatobiliary disorders:** Very rare: jaundice, hepatitis

- **Nervous system disorders:** Very rare: memory loss

- **Other adverse reactions:** Very rare: gynecomastia

**DRUG INTERACTIONS:** In CRESTOP (rosuvastatin calcium) clinical trials, there was no evidence of increased skeletal muscle effects when rosuvastatin was dosed with any concomitant therapy. However, CRESTOP and other HMG-CoA reductase inhibitors may cause dose-related increases in serum transaminases and CK levels. An increase in the incidence of myositis and myopathy has been seen in patients receiving other HMG-CoA reductase inhibitors with cyclosporine, fibric acid derivatives (including gemfibrozil), niacinamide, azole antifungals and macrolide antibiotics.

**Cytochrome P450 Inhibitors:** In vitro and in vivo data indicate that rosuvastatin has no clinically significant cytochrome P450 interactions (as substrate, inhibitor or inducer). Consequently, there is little potential for drug-drug interactions upon coadministration with agents that are metabolized by cytochrome P450. Rosuvastatin clearance is not dependent on metabolism by cytochrome P450 3A4 to a clinically significant extent. This has been confirmed in studies with known cytochrome P450 3A4 inhibitors (ketonazole, erythromycin, itraconazole).

**Concomitant Therapy with Other Lipid Metabolism Regulators:** Coadministration of fenofibrate and CRESTOP 10 mg did not lead to a clinically significant change in the plasma concentrations of either drug. In addition, neither myopathy nor marked CK elevations (≥ 10 x ULN) were observed in a study of 128 patients who received CRESTOP 10, 20 and 40 mg plus extended-release niacin or in a second study of 103 patients who received CRESTOP 5 and 10 mg plus fenofibrate. Based on the above data, no pharmacokinetic or pharmacodynamic interaction was observed. No data is available with other fibrates.

Based on postmarketing surveillance, gemfibrozil, fenofibrate, other fibrates and lipid-lowering doses of niacin (nicotinic acid) may increase the risk of myopathy when given concomitantly with HMG-CoA reductase inhibitors, probably because they can produce myopathy when given alone (see WARNINGS AND PRECAUTIONS, Muscle Effects, Predisposing Factors for Myopathy/Rhabdomyolysis). Therefore, combined drug therapy should be approached with caution.

**Lopinavir/Ritonavir:** In a pharmacokinetic study, coadministration of CRESTOP and a combination product of two protease inhibitors (400 mg lopinavir/100 mg ritonavir) in healthy volunteers was associated with an approximately 2-fold and 5-fold increase in rosuvastatin steady-state AUC, and Cmax, respectively. Increased systemic exposure to rosuvastatin has been observed in subjects receiving CRESTOP with various protease inhibitors in combination with ritonavir. Consideration should be given to both the benefit of lipid lowering by the use of CRESTOP in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating CRESTOP doses in patients treated with protease inhibitors (see WARNINGS AND PRECAUTIONS, Muscle Effects, Predisposing Factors for Myopathy/Rhabdomyolysis).

**Concomitant Therapies Without Clinically Significant Interactions:** See SUPPLEMENTAL PRODUCT INFORMATION.

**Drug-Drug Interactions:** See SUPPLEMENTAL PRODUCT INFORMATION.

**Drug-Food Interactions:** CRESTOP can be taken with or without food (see ADMINISTRATION).

You can report any suspected adverse reactions associated with the use of health products to the Canada Vigilance Program by one of the following 3 ways:

**Report online** at www.healthcanada.gc.ca/medeffect

**Call toll-free** at 1-866-234-2345

**Complete a Canada Vigilance Reporting Form and:**

- Fax toll-free to 1-866-678-6789, or
- Mail to: Canada Vigilance Program
  - Health Canada
  - Postal Locator 0701C
  - Ottawa, ON K1A OK9

**Postage-paid labels, Canada Vigilance Reporting Form and the adverse reaction reporting guidelines are available on the MedEffect™ Canada website at www.healthcanada.gc.ca/medeffect.**

**NOTE:** Should you require information related to the management of side effects, contact your health professional. The Canada Vigilance Program does not provide medical advice.

**Administration**

Patients should be placed on a standard cholesterol-lowering diet (at least equivalent to the Adult Treatment Panel III (ATP III TLC diet)) before receiving CRESTOP (rosuvastatin calcium) and should continue on this diet during treatment with CRESTOP. If appropriate, a program of weight control and physical exercise should be implemented. Prior to initiating therapy with CRESTOP, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

CRESTOP may be taken in the morning or evening, with or without food.

**Recommended Dose and Dosage Adjustment**

**Hypercholesterolemia:** The dose range of CRESTOP is 5 to 40 mg orally once a day. The recommended starting dose of CRESTOP in most patients is 10 mg orally once daily. The majority of patients are controlled at the 10 mg dose. If necessary, dose adjustment can be made at 2- to 4-week intervals. The maximum response is usually achieved within 2-4 weeks and is maintained during chronic therapy.

Initiation of therapy with CRESTOP 5 mg once daily may be considered for patients requiring less aggressive LDL-C reductions or who have predisposing factors for myopathy (see WARNINGS AND PRECAUTIONS, Muscle Effects).

Patients who are switched to CRESTOP from treatment with another HMG-CoA reductase inhibitor should be started on 10 mg even if they were on a high dose of the previous HMG-CoA reductase inhibitor. A switch dose of 20 mg may be considered for patients with severe hypercholesterolemia.

For patients with severe hypercholesterolemia (including those with familial hypercholesterolemia), a 20 mg start dose may be considered. These patients should be carefully followed.

A dose of 40 mg once daily should only be used in patients with severe hypercholesterolemia who...
do not achieve their target treatment on 20 mg and have no predisposing factors for myopathy/ rhabdomyolysis (see CONTRAINDICATIONS). Consultation with a specialist is recommended when initiating the CRESCOR 40 mg dose. The dosage of CRESCOR should be individualized according to baseline LDL-C, Total-C/HDL-C ratio and/or TG levels to achieve the recommended desired lipid values at the lowest possible dose.

Prevention of Major Cardiovascular Events: A dose of 20 mg once daily has been found to reduce the major of all clinical trials (see CLINICAL TRIALS).

Dosing Considerations in Special Populations

Patients with Hepatic Impairment: The usual dose range applies in patients with mild to moderate hepatic impairment. Increased systemic exposure has been observed in patients with severe hepatic impairment and, therefore, in these patients the dose of CRESCOR should not exceed 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Hepatic Impairment).

Patients with Renal Impairment: The usual dose range applies in patients with mild to moderate renal impairment. Increased systemic exposure to rosuvastatin has been observed in patients with severe renal impairment. For patients with severe renal impairment (creatinine clearance < 30 mL/min/1.73 m²), the starting dose of CRESCOR should be 5 mg and not exceed 10 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Renal Impairment).

Race: The initial dose of CRESCOR, in Asian patients, should be 5 mg once daily. The potential for increased risk of systemic exposure must be considered when making treatment decisions. The maximum dose should not exceed CRESCOR 20 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Special Populations, Race).

Use in Children: Pediatric experience is limited to a very small number of children (aged 8 years and above) with homozygous familial hypercholesterolemia. Use in children should be supervised by specialists (see WARNINGS AND PRECAUTIONS, Special Populations, Pediatrics).

Use in Elderly: No dose adjustment is necessary in the elderly (see WARNINGS AND PRECAUTIONS, Special Populations, Geriatrics).

Concomitant Therapy: See WARNINGS AND PRECAUTIONS and DRUG INTERACTIONS.

SUPPLEMENTAL PRODUCT INFORMATION

CONTRAINDICATIONS:

Pregnant and nursing mothers: Cholesterol and other products of cholesterol biosynthesis are essential components for fetal development (including synthesis of steroids and cell membranes). CRESCOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible hazards. If the patient becomes pregnant while taking CRESCOR, the drug should be discontinued immediately and the patient apprised of the potential hazards to the fetus. Advise of the potential risk before pregnancy (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnancy, Nursing Women).

ADVERSE REACTIONS: Adverse events observed or reported in short- and long-term trials are as follows:

Clinical Trial Adverse Drug Reactions: Because clinical trials are conducted under very specific conditions, the adverse drug reaction rate observed in clinical trials may not reflect the rates observed in practice and should not be compared to rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.

Short-term Controlled Trials: Short-term controlled trials involved 1290 patients within placebo-controlled trials of 6 to 16 weeks' duration (576 of which were treated with rosuvastatin). In all controlled clinical trials, 3.2% of patients were withdrawn from CRESCOR therapy due to adverse events. This withdrawal rate was comparable to that reported in placebo-controlled studies.

Long-term Controlled trials: The frequency of adverse events in all clinical trials and considered possibly, probably or definitely drug-related are as follows:

<table>
<thead>
<tr>
<th>Body system/Adverse event</th>
<th>Placebo (%)</th>
<th>Total rosuvastatin 20 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole body</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>2.2</td>
<td>2.7</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>0.5</td>
<td>1.3</td>
</tr>
<tr>
<td>Arthrosis</td>
<td>2.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>1.4</td>
<td>1.0</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1.3</td>
<td>1.6</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>1.9</td>
<td>0.7</td>
</tr>
<tr>
<td>Flatulence</td>
<td>2.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Nausea</td>
<td>1.6</td>
<td>2.2</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.5</td>
<td>1.6</td>
</tr>
<tr>
<td>Nervous system</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sickness</td>
<td>1.6</td>
<td>0.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>1.9</td>
<td>0.4</td>
</tr>
</tbody>
</table>

Long-term Controlled Morbidity and Mortality Trials: In the Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) study involving 10,053 participants treated with CRESCOR 20 mg once daily (N=9801) or placebo (N=9491), CRESCOR was clinically well tolerated. Subjects were followed for a mean duration of 2.7 years. Discontinuation of therapy due to an adverse event occurred in 5.6% of subjects treated with CRESCOR and 5.5% of subjects treated with placebo. The most common adverse events that led to discontinuation from the study were: myalgia, arthralgia, abdominal pain and constipation. The associated adverse reactions reported in ≥ 1% of patients and at a rate greater or equal to placebo was myalgia (2.4% CRESTOR, 2.0% placebo).

Less Common Clinical Trial Adverse Drug Reactions (< 1%): The frequency of adverse events in all clinical trials and considered possibly, probably or definitely drug-related are as follows:

<table>
<thead>
<tr>
<th>Body system/Adverse event</th>
<th>Placebo (%)</th>
<th>Total rosuvastatin 20 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body system/Adverse event</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total rosuvastatin 20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total rosuvastin 20 mg</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>2.3</td>
<td>2.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Body system/Adverse event</th>
<th>Placebo (%)</th>
<th>Total rosuvastatin 20 mg (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Body system/Adverse event | Placebo (%) | Total rosuvastatin 20 mg (%) |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bleed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myalgia</td>
<td>2.1</td>
<td>2.2</td>
</tr>
<tr>
<td>Myalgia</td>
<td>0.9</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Less Common Clinical Trial Adverse Drug Reactions (< 1%): The frequency of adverse events in all clinical trials and considered possibly, probably or definitely drug-related are as follows:

<table>
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<td>2.3</td>
<td>2.4</td>
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<td>1.0</td>
</tr>
</tbody>
</table>
Prevention of Major Cardiovascular Events

In the JUPITER study (Information for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin), 18,644 people with no pre-existing cardiovascular disease were screened and 17,802 (95.8%) were double-blinded randomized to CRESTOR 20 mg once daily (n=8901) or placebo (n=8901). The primary endpoint was a composite consisting of the time-to-first occurrence of any of the following cardiovascular events: cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, unstable angina, or an arterial revascularization procedure.

The results of the primary composite endpoint and the individual components are presented in Table 5. CRESTOR significantly reduced the risk of nonfatal myocardial infarction (p=0.0001), nonfatal stroke (p=0.004) and arterial revascularization procedures (p=0.034). There were no statistically significant treatment differences between the CRESTOR and placebo groups for deaths due to cardiovascular causes or hospitalizations for unstable angina.

Table 5: Number of First Events by Treatment Group for the Composite Primary Endpoint (ITT Population)

<table>
<thead>
<tr>
<th>Country</th>
<th>Placebo</th>
<th>Rosuvastatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>United States</td>
<td>1901</td>
<td>901</td>
</tr>
<tr>
<td>Japan</td>
<td>612</td>
<td>252</td>
</tr>
<tr>
<td>Germany</td>
<td>292</td>
<td>135</td>
</tr>
<tr>
<td>France</td>
<td>242</td>
<td>115</td>
</tr>
<tr>
<td>Italy</td>
<td>182</td>
<td>89</td>
</tr>
<tr>
<td>Canada</td>
<td>81</td>
<td>41</td>
</tr>
</tbody>
</table>

*Cardiovascular death included fatal MI, fatal stroke, sudden death and other adjudicated causes of CV death.

The management of a suspected drug overdose, contact your local Poison Control Centre.

Product Monograph available on request.

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www.astrazeneca.ca

Figure 1: Time to First Occurrence of Major Cardiovascular Events

- **HR 0.56 (95% CI 0.46-0.69)**
- **p<0.001**

The clinical relevance of this interaction has not been studied. However, the effect was mitigated when the antacid was dosed 2 hours after CRESTOR. This interaction should not be clinically relevant in patients using this type of antacid infrequently. A frequent antacid user should be instructed to take CRESTOR at a time of day when they use less likely to need the antacid.

The concurrence of use of CRESTOR and cyclosporine is contraindicated (see CONTRAINDICATIONS).

Table 6: Dose Response in Patients with Mild to Moderate Hypercholesterolemia

<table>
<thead>
<tr>
<th>Propensity name</th>
<th>Effect</th>
<th>Clinical comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coumarin</td>
<td>Antacids</td>
<td>The clinical relevance of this interaction has not been studied. However, the effect was mitigated when the antacid was dosed 2 hours after CRESTOR. This interaction should not be clinically relevant in patients using this type of antacid infrequently. A frequent antacid user should be instructed to take CRESTOR at a time of day when they use less likely to need the antacid.</td>
</tr>
</tbody>
</table>
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welcome@healthmatchbc.org

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