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LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE

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Delirium in Older Adults
Eeles and Rockwood

Imaging Pulmonary Embolism in Pregnancy
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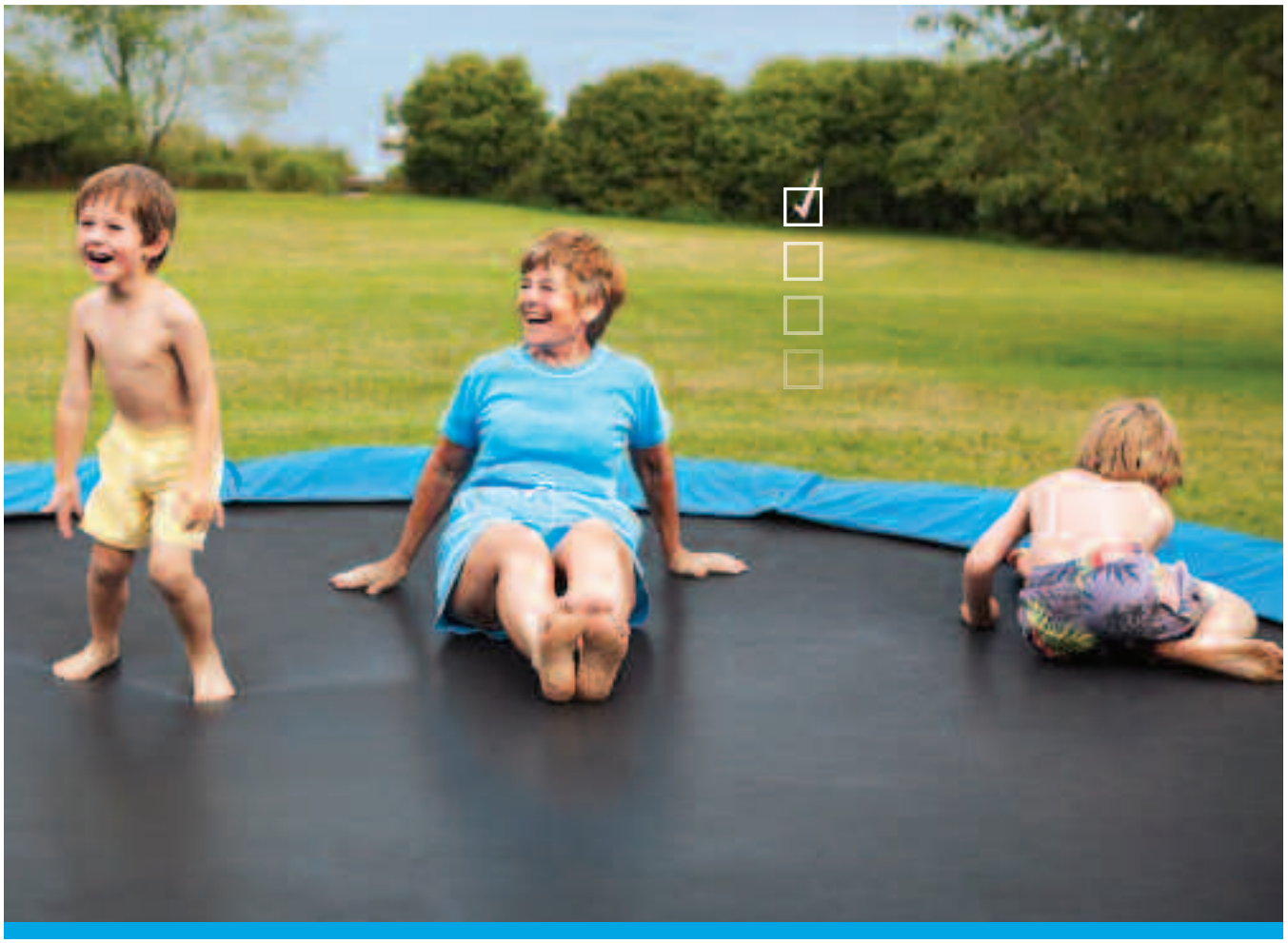

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Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with CRESTOR and with other HMG-CoA reductase inhibitors.

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Most commonly reported adverse events in prevention of major cardiovascular events vs. placebo were urinary tract infection (8.7% vs. 8.6%), nasopharyngitis (7.6% vs. 7.2%), back pain (7.6% vs. 6.9%) and myalgia (7.6% vs. 6.6%).

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

Reference: 1. CRESTOR® Product Monograph. AstraZeneca Canada Inc. April 28, 2010.

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See prescribing summary on page 128

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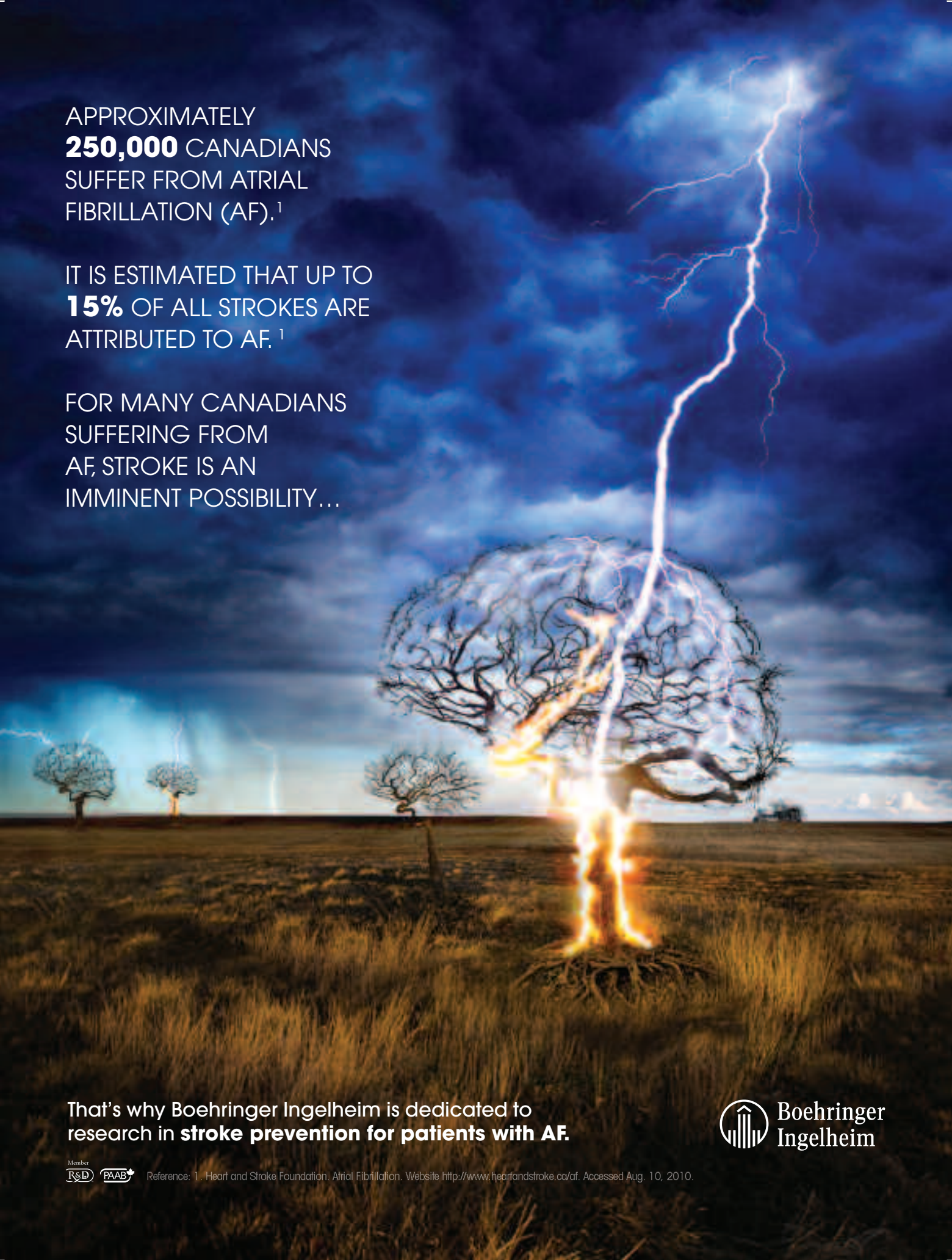
ABOUT THE COVER

This photo was taken by Randy Dyke, a photographer in the Vancouver area. He combines traditional techniques enhanced by HDR and Photoshop, allowing for heightened creativity.

The image shows a contemporary Haida totem, carved by Don Yeomans and commissioned by Vancouver International Airport Foundation. It sits at the centre of the Links building and is a part of "Celebrating Flight."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A Rose by Any Other Name ...

Finlay McAlister MD

About the Author
Finlay McAlister is a member of the Division of General Internal Medicine at the University of Alberta, in Edmonton, Alberta. Correspondence may be directed to Finlay.McAlister@ualberta.ca.

Although everyone reading this article likely has a firm sense of what a general internist is and does, it is unlikely that all of us agree on the job description. While I would wager that no two readers perform exactly the same job, I would also bet that most of us don't perform exactly the same job two days in a row. That is the beauty of being a general internist – every day and every patient encounter is unique. But that is also the challenge for those who try to advance the cause of general internal medicine (GIM) in the corridors of power at institutions such as the Royal College of Physicians and Surgeons of Canada (RCPSC) or provincial licensing bodies. Not infrequently the question is asked by others, "What is the difference between an internist and a general internist?"

In the Canadian context, internists are individuals who have passed the Royal College fellowship examination in internal medicine. Usually, they have completed 4 years of postgraduate training in internal medicine. In the 3 core years, they rotate through various subspecialties for lengths of time (from 1 to 4 months in duration), and spend another year in either an "undifferentiated" program or an RCPSC-recognized subspecialty. The current attempt by the Canadian Society of Internal Medicine (CSIM) to have GIM recognized as the 17th subspecialty of medicine was covered extensively in the last issue of *Canadian Journal of General Internal Medicine*. Residents who complete their 4th year of training in the undifferentiated stream are considered general internists. Others define GIM by what we don't do: we aren't cardiologists, nephrologists, or the like. However, if you ask our colleagues practising family medicine or emergency medicine who we are, they know: they ask us to see patients with disparate symptoms arising from diseases of several organ systems.

We're the general *specialists*. We are consultants, distinct from the more primary care role played by our American counterparts, "Doctors for Adults." With the occasional exception, our interactions are often limited to one or two visits, advising family physicians and colleagues on matters of diagnosis and comprehensive care.

The general specialist is an important position in the Canadian health care system. As one of our members wrote to me during the consultation process for the Royal College application: "It is rare for even large urban centres outside of the university settings to have a full complement of subspecialists. In such hospitals, the general internist *is* the subspecialist, especially when it comes to critical and cardiac care" (Dr. Ravi Agarwala, personal communication, August 24 2010). However, I believe that as general internists we are more than just subspecialists when no one else is around: even in tertiary care centres well stocked with subspecialists of all types, general internists play a *distinct role*. As David Sackett pointed out in his foreword to *Care-Fully: Defining a Plan for General Internal Medicine* in Canada (available at www.csimonline.com): "When encountering patients with undifferentiated or multi-system disease, general internists excel at 'sorting out' their illnesses and balancing the management of multi-system disease. They are particularly skilled in the evaluation and care of such patients when they are acutely ill. This is in contrast to subspecialists who, by focusing on deeper but narrower aspects of single-system disease, are more comfortable practising in a "rule-out" mode. We are also the medical specialist of first resort for patients with multisystem disease in the peri-operative and peri-partum periods. For those interested in further exploring the different roles general internists have assumed in Canada, I recommend reading the *Care-Fully* document.

Thus, we do bring unique skill sets and competencies to the table, and I believe we should continue to strive to be defined by what we do, rather than what we don't do. Although some have suggested that we change the name *general internal medicine* to *advanced internal medicine*, to me the term generalist captures the strength of our profession. In the words of William Osler (1892), "American Medicine is producing dangerously narrow minded practitioners … (we) need to treat the whole of the patient, not just a body part."

Qu'y a-t-il en un nom? Ce que nous nommons rose, sous un autre nom, ...

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.

Bien que tous les lecteurs aient probablement une très bonne idée de ce qu'est et de ce que fait l'interniste généraliste, il est fort peu probable qu'ils s'entendent sur la description du poste. Au même titre que je parierais qu'il n'y a pas deux lecteurs qui remplissent les mêmes fonctions, je gagerais également que les activités professionnelles de la plupart d'entre nous varient d'une journée à une autre. C'est ça la beauté de la médecine interne générale – chaque jour et chaque patient sont uniques. Mais là réside également le défi que doivent relever tous ceux qui se font les ardents défenseurs de la médecine interne générale dans les allées du pouvoir des institutions comme le Collège royal des médecins et chirurgiens du Canada (CRMCC) ou les ordres de médecins provinciaux. En effet, il n'est pas rare d'entendre la question : quelle est la différence entre un interniste et un interniste généraliste?

Au Canada, l'interniste est le médecin qui a réussi l'examen du Collège royal menant au certificat de médecin spécialiste en médecine interne. En règle générale, il a terminé au préalable une formation postdoctorale de quatre ans en médecine interne. Il a effectué des stages dans diverses surspécialités d'une durée allant d'un à quatre mois au cours des trois premières années de la résidence et il a consacré la dernière année à une formation « générale » ou à la formation dans une surspécialité reconnue par le CRMCC. Le dernier numéro de *La Revue canadienne de médecine interne générale* rend compte du projet que mène la Société canadienne de médecine interne (SCMI) en vue d'obtenir la reconnaissance de la médecine interne générale à titre de 17e surspécialité médicale. Le résident qui consacre la quatrième année de sa formation postdoctorale en médecine interne à un volet général est considéré comme un interniste généraliste. D'autres circonscrivent la médecine interne générale par ce que l'interniste ne fait pas : il n'est pas un cardiologue, ni un néphrologue, ni… En revanche, si vous posez la question à nos collègues médecins de famille ou urgentologues, vous constaterez qu'eux, ils savent : ils nous adressent les patients qui présentent des symptômes divers, manifestations de maladies multiorganiques.

Nous sommes les *spécialistes* généralistes. Nous sommes des médecins consultants et ce mode d'exercice de la profession nous distingue de nos homologues américains, les « docteurs des adultes », présents en première ligne. À quelques exceptions près, nos interactions se limitent à une ou deux visites, à conseiller le médecin de famille ou un autre collègue à propos du diagnostic et des soins médicaux complets.

Le spécialiste généraliste est un acteur important dans le système de santé canadien ainsi qu'en témoigne un membre durant la consultation au sujet de la demande de reconnaissance adressée au Collège royal : « Il est rare que même les grands centres urbains hormis les villes universitaires puissent compter sur la gamme complète de surspécialistes. Dans les hôpitaux de ces centres, l'interniste généraliste est le surspécialiste, surtout en ce qui concerne les soins intensifs et la cardiologie », de m'écrire le Dr Ravi Agarwala le 24 août 2010. J'estime, cependant, que l'interniste généraliste est bien plus que le surspécialiste de service par défaut : même dans l'établissement de soins tertiaires pourvu en *surspécialistes* de toutes les disciplines, l'interniste généraliste occupe une place particulière. Comme David Sackett le souligne dans son avant-propos à *Care-Fully: Defining a Plan for General Internal Medicine in Canada* (qui paraît à www.csimonline.com) : « Que dire de la capacité inégalée de l'interniste généraliste à départager les diverses affections du patient atteint d'une maladie complexe ou multisystémique et à déterminer la prise en charge globale de la maladie multisystémique. Il est particulièrement compétent dans l'évaluation et la prise en charge de la maladie grave en phase aiguë. Cette aptitude tranche nettement avec celle du surspécialiste qui, se concentrant sur des aspects plus complexes, mais plus restreints de la maladie unisystémique, établit généralement le diagnostic sur le mode de 'l'élimination' ». L'interniste généraliste est également le médecin spécialiste de premier recours pour la personne aux prises avec une maladie multisystémique dans les périodes périopératoire et périnatale. Je recommande la lecture de *Care-Fully* à tous ceux qui désirent en savoir plus sur les fonctions qu'exercent les internistes généralistes au Canada.

C'est donc un fait, nous possédons des aptitudes et des compétences particulières, et je suis d'avis que nous devrions faire en sorte d'être définis par ce que nous faisons, plutôt que par ce que nous ne faisons pas. Certains proposent de remplacer l'appellation *médecine interne générale* par *médecine interne de pointe*, mais j'estime que le terme *généraliste* illustre l'atout majeur de la profession. Je terminerai par ce mot de William Osler (1892) : « La médecine américaine accouche de praticiens à l'esprit dangereusement étroit… (nous) devons traiter le patient, pas simplement une partie du corps. »

Osler Awards 2010

The Canadian Society of Internal Medicine Osler Awards are conferred on nominees who exemplify the qualities of leadership, clinical skill, research, and teaching in the manner of Sir William Osler.

Don Echenberg

Dr. Echenberg is an associate professor in the Faculty of Medicine at the University of Sherbrooke. He completed undergraduate studies at McGill and his residency at the Royal Victoria Hospital in Montreal. He has an extensive history of community GIM practice (Sherbrooke Hospital), where he held several administrative positions including head of the Department of Medicine and president of the Council of Physicians, Dentists and Pharmacists.

He was GIM program director from 1998 to 2006 and was appointed vice-dean for the promotion of the academic mission of Hotel Dieu 2001–2004. He became director of medical education for Sherbrooke University Hospital. He is a past president of CSIM (2006–2008), with extensive input into many of the society's committees, and has been a national voice for internal medicine for two decades.

He is recognized as an exemplary role model and leader in medicine in Canada, with a passion for his profession and commitment to passing this art onto the next generation. As a healer, he is also an advocate for health and for the healthy lifestyles and public policies that empower populations to take control of their health and wellness. His academic interests include thromboembolic disease, cardiovascular disease, clinical examination, and medical education. He is married with three children, and enjoys cycling, cross-country skiing and "alternative transportation."

Howard Abrams

Dr. Abrams is division head at the University Health Network and Mount Sinai Hospital, Toronto. He graduated from McMaster University Medical School and completed postgraduate studies in internal medicine and clinical epidemiology at the University of Toronto.

During his career, he has made major contributions to the Division of GIM, particularly in the areas of education, medical consultation, and ambulatory care. He has consistently received outstanding evaluations for his performance as a clinical teacher. He is an innovator in the organization of patient care on the wards (ED-GIM Project, GIM CTU), improving both the efficiency of patient care and the learning environment for his students.

Dr. Abrams has published extensively on topics including pre-operative assessment, decision analysis, and medical informatics. His leadership of the Division of GIM has been central to its growth and success. He is a strong advocate of "doing the right thing for patients," and is an exemplar of the clinical, administrative, and educational virtues that qualify him for an Osler Award.

MARK YOUR CALENDARS!

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The CSIM is a society of volunteers and encourages members to become involved.

Volunteering on one of CSIM's many committees (Membership, Education, and Annual Meeting Committees) is a great opportunity to contribute to your specialty and to meet new colleagues and contacts from across the country.

If you are interested in becoming more involved in the CSIM, please speak to a member of CSIM Council. Or you may contact the CSIM Office at csim@royalcollege.ca / 613-730-6244.


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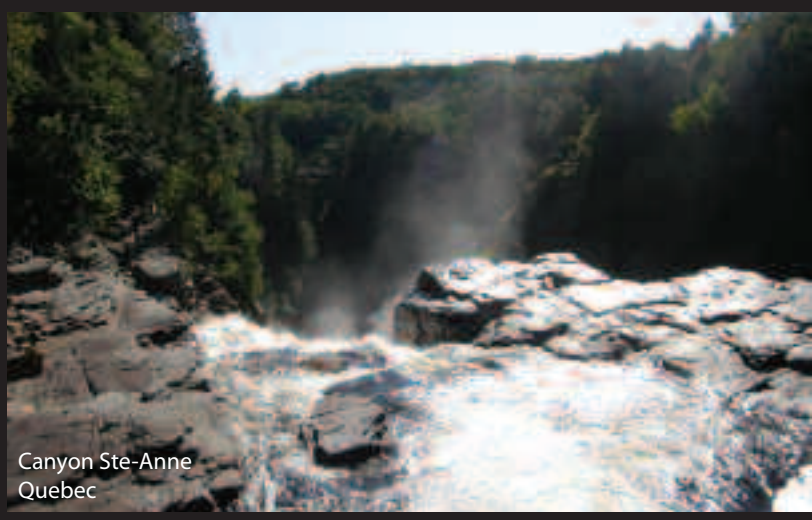
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Imaging Pulmonary Embolism in Pregnancy: Radiation Exposure and Proposed Imaging Algorithm

Amr M. Ajlan MD, Ana Maria Bilawich MD, John R. Mayo MD

About the Authors

Amr Ajlan, Ana Maria Bilawich, and John Mayo are members of the Department of Radiology, Vancouver General Hospital, University of British Columbia, Vancouver, British Columbia. Correspondence may be directed to amrajlan@yahoo.com.

Pregnancy carries an approximately fivefold increased risk of pulmonary embolism (PE)[1] due to several factors, including increased venous stasis, pregnancy-related hypercoagulability, prolonged bed rest, decreased fibrinolysis, and familial predisposition.[2,3] Among pregnant patients suspected clinically of having PE, approximately 2–20% prove to have a positive PE diagnosis.[2]

However, diagnosing PE in pregnancy is not an easy task. First, the presentation of PE is not specific, as some of the normal pregnancy-related physiological changes, including dyspnea, pain, tachypnea, tachycardia, and leg swelling, can be the same as symptoms and signs associated with PE.[1,2] Second, untreated PE in pregnancy carries a relatively high risk of morbidity and mortality.[1] In fact, PE is the most common cause of maternal mortality.[2,3] Third, this diagnosis has important treatment and prophylactic implications, which may affect the patient's future pregnancies as well.[1,2] Finally, the principal diagnostic modalities used to diagnose PE are imaging based, exposing the patient to radiation, intravenous (IV) contrast media, or nuclear medicine contrast media, all of which cause major concerns to both the physician and the patient. This review outlines the strengths and limitations of available imaging modalities currently used to diagnose PE in pregnancy. We provide a suggested imaging algorithm for the evaluation of suspected PE in the pregnant patient.

Fetal Radiation Concerns

Ionizing radiation, either in the x-ray or gamma ray energy, is a known carcinogen and teratogen. Therefore, the use of both x-ray and nuclear medicine imaging modalities in pregnant patients has always been a source of concern. However, it is important to recognize that everyone, including pregnant mothers and their fetus, are naturally exposed to both x-ray and gamma radiation. Natural background radiation from the ground, food, and cosmic radiation sources ranges from 2 to 8 mSv in Canada. In the normal 9-month gestation period, the fetus is exposed to 1.1–2.5 mGy from these sources.[2,3]

In the past 100 years of study, it has been established that fetal radiation doses <50 mGy have no detectable effect on the fetus.[2,4] None of the radiation-based imaging modalities used to diagnose PE deliver more than 1 mGy of radiation to the fetus. In fact, the combination of chest radiography, computed tomography pulmonary angiography (CTPA), lung scintigraphy, and conventional angiography in one patient would deliver only 1.5 mGy to the fetus.[3,4] These data underpin the policy statement published by the American College of Obstetricians and Gynecologists: "Women should be counseled that x-ray exposure from a single diagnostic procedure does not result in harmful fetal effects. Specifically, exposure to less than 5 rad [50 mGy] has not been associated with an increase in fetal anomalies or pregnancy loss."[5] It is noted that doses of 100 mGy carry a 1% chance of organ dysgenesis and cancer induction.[2,4] Therefore, in the appropriate clinical situation, all diagnostic imaging modalities can be safely used to diagnose PE in the pregnant patient. However, it is still mandatory to use appropriate clinical judgement in patient selection, follow a rational diagnostic imaging algorithm, and minimize the radiation dose for each imaging test in the pregnant patient.[6] This approach supports the radiation dose concept of ALARA (*a*s *l*ow *a*s *r*easonably *a*chievable)[2] that is universally employed by the diagnostic imaging community.

Lower-Extremity Ultrasonography

Ultrasonography (US) is a widely available, inexpensive, non-invasive, and radiation-free modality that can be performed in a timely fashion with no known harmful effect to the fetus.[2,6] Lower-extremity US should be performed as the first diagnostic examination in all pregnant patients suspected of having PE.[2,6] If US identifies a deep venous thrombosis, anticoagulation treatment can be started and no further imaging tests are required. However, a negative lower-extremity US does not exclude PE as the pulmonary embolus may have originated from the pelvic veins or the entire clot burden may have migrated to the lungs, with no thrombus remaining in the leg veins.[6] Therefore, a negative leg venous ultrasound examination must be followed by further imaging of the chest.

Chest Radiography

Chest radiographs can be normal or abnormal in the presence of PE.[7] Even if the chest radiograph is abnormal, the findings are not sufficiently specific to definitively diagnose PE, and further imaging is required. We recommend this modality as an initial step in evaluating the pregnant patient with suspected PE who has a negative lower-extremity US for two reasons: First, a normal chest radiograph assists in determining if the patient is a candidate for a ventilation-perfusion (V/Q) scan.[2,6] Second, it is useful to exclude other potential causes of the patient's presentation (such as a pneumonia or pneumothorax, for example).[2,7] The fetal dose from frontal and lateral chest radiographs is very low, about 0.01 mGy.[2]

Computed Tomography Pulmonary Angiography

CTPA can directly detect the presence of PE and estimate the overall embolic burden. The advantages of CTPA cannot be overemphasized. It is accessible, quick, cost-effective, and highly accurate (sensitivity >90%, specificity >95%) and can provide an alternative diagnosis.[2,6] Negatives to this procedure include an estimated fetal radiation exposure of about

0.01–0.66 mGy, as well as 10–70 mGy maternal breast radiation exposure.[2] This breast exposure is substantial when compared with a two-view mammogram (5–10 mGy). Thus, when performing CTPA, radiation dose reduction must be performed in keeping with the ALARA concept. Radiation dose reduction manoeuvres include fetal shielding, automatic radiation dose reduction techniques, elimination of lateral scout images, scanning the minimum volume to cover central and segmental pulmonary arteries, and avoidance of unnecessary sequences, to name a few.[2,6] CT venography should never be performed in pregnancy due to the fact that the fetus would be directly radiated.[2]

Another CTPA issue is the requirement for iodinated IV contrast material, which carries the risk of developing maternal allergic reactions and contrast-induced nephropathy. Thus, CTPA should be avoided in patients with a previous allergy to iodinated IV contrast and those with renal impairment.[2] Fetal exposure to iodinated contrast material can occur either via the trans-placenta route or by direct amniotic fluid aspiration.[2] A theoretical risk of contrast-induced fetal/neonatal hypothyroidism has been raised.[8] Thus, it is recommended that neonatal thyroid function should be tested in the first week of life in all neonates exposed to iodinated contrast in utero.

One of the potential problems encountered in performing CTPA in the pregnant patient is a non-diagnostic examination secondary to poor contrast opacification of the pulmonary arteries. The reasons for this include an interruption of contrast-enhanced blood from the superior vena cava by non-enhanced blood from the inferior vena cava during deep inspiration; the increased blood flow associated with the increased cardiac output of pregnancy; and the dilution of contrast media by the increased blood volume found in pregnancy.[9] Acquiring CTPA images with the patient in shallow inspiration or held expiration rather than deep inspiration has been proposed as a solution to the interruption of contrast material.[9] Bolus triggering with a shorter scan delay, a high concentration of contrast medium, a high flow rate of contrast material flow, and the use of low-kilovoltage techniques can be used to overcome the other two pregnancy-induced contrast dilution effects.[9]

Lung Scintigraphy

The use of radionuclide material is considered safe in pregnancy.[2] A V/Q lung scan should only be performed in patients with normal chest radiographs and no underlying severe asthma or chronic obstructive airway disease.[2,9] This test is diagnostic in 95% of the cases when performed in the correct clinical setting.[2,9] Scintigraphy is reliable when the test is normal or is of high probability but is not useful when the test shows intermediate probability or low probability with a high clinical suspicion.[2] A significant advantage of using V/Q scan is that it has an effective dose of 0.22–0.28 mGy per maternal breast, which is much lower than that of CTPA (about 10–70 mGy). The fetal radiation dose from V/Q scanning is about 0.01–0.8 mGy, which is comparable to that from CTPA.[2] However, further reduction of this dose can be achieved by applying V/Q dose-reduction techniques, including eliminating the ventilation component of the study if the perfusion component is normal and decreasing the dose of the perfusion component by 50%.[2] However, V/Q scanning is relatively time consuming and not available after working hours in many institutions. A significant limitation of V/Q scanning is its inability to provide any information regarding an alternative diagnosis.

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) is not widely used to diagnose PE due to expense, difficult accessibility, longer acquisition, and lack of trials

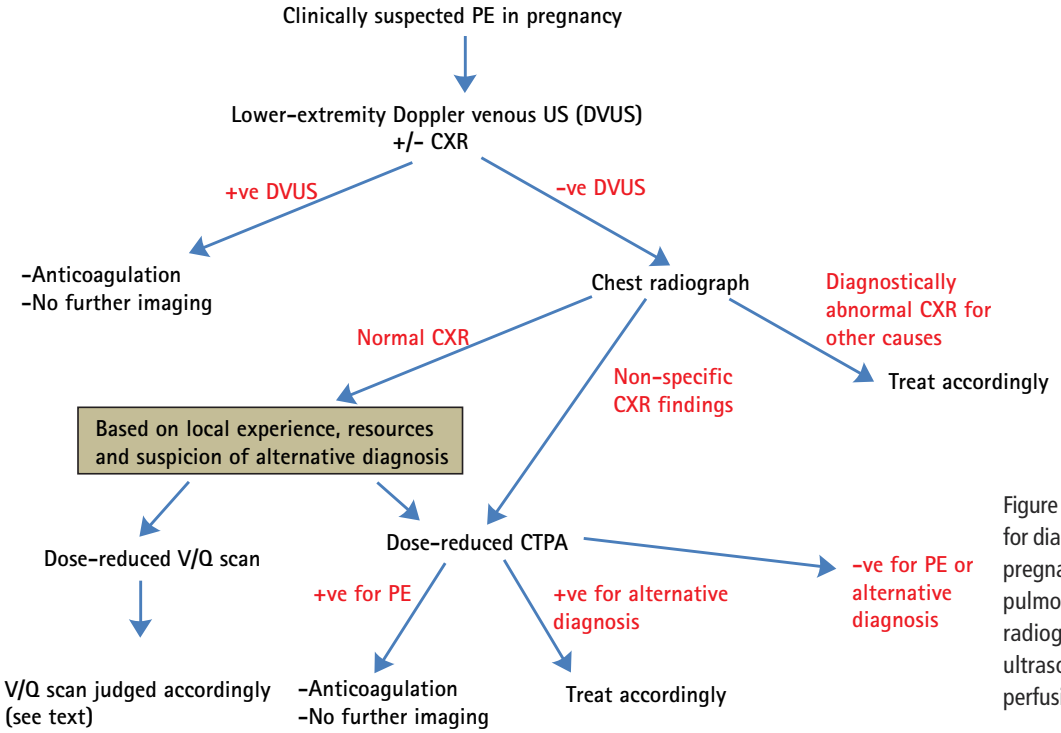

Figure 1. Proposed imaging-based algorithm for diagnosis of pulmonary embolism (PE) in pregnancy. CTPA = computed tomography pulmonary angiography; CXR = chest radiography; DVUS = Doppler venous ultrasonography; V/Q = ventilation-perfusion.

validating its use in pregnancy.[2] This modality carries no known harm to the mother or fetus and does not expose the patient to radiation. Due to superior contrast resolution, central PE can be diagnosed by MRI without the use of IV contrast. However, if peripheral PE is questioned, paramagnetic MRI contrast agents are required.[2] Unfortunately, MR contrast media has not been evaluated in pregnancy and is not approved for use in the pregnant patient.[6] In addition, MRI has limited ability to make an alternative diagnosis because of limited signal intensity in an air-filled lung.

Conclusion

The accurate diagnosis of PE during pregnancy is of utmost importance. In clinically suspected cases, confirming the diagnosis using imaging tests is necessary and acceptable. Advantages and disadvantages of each modality should be considered when deciding on the most appropriate test to use. When radiation is an issue, dose-reduction techniques should be used, adhering to the ALARA concept. Figure1 shows a simplified proposed imaging-based algorithm.

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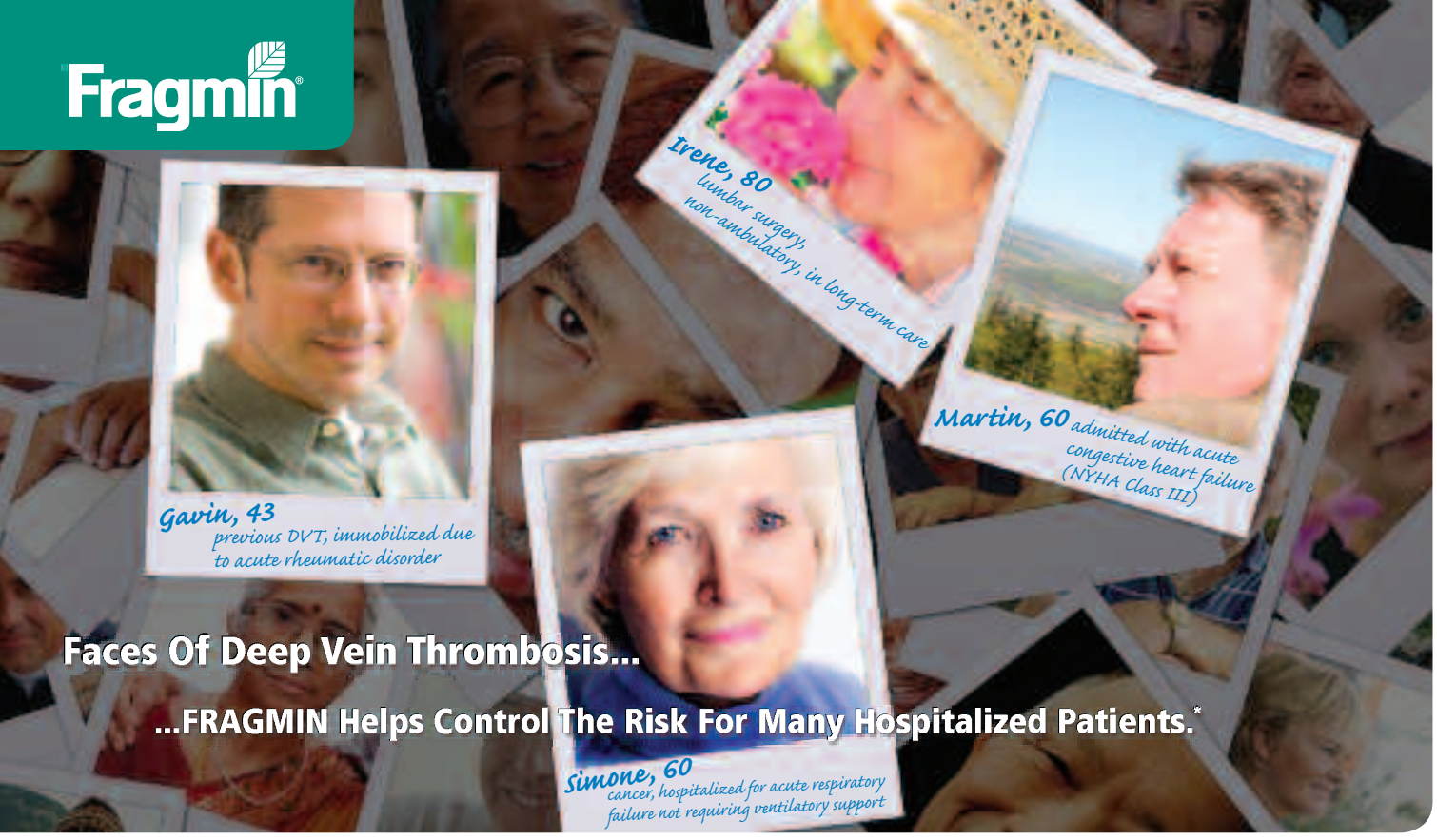


Faces Of Deep Vein Thrombosis...

...FRAGMIN Helps Control The Risk For Many Hospitalized Patients.*

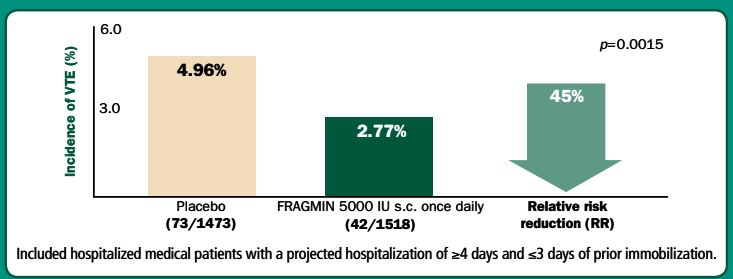
Based on composite patient data. May not be representative of all patients.

FRAGMIN demonstrated a 45% reduction in VTE, including verified DVT.

*FRAGMIN is indicated for the reduction of deep vein thrombosis (DVT) in hospitalized patients with severely restricted mobility during acute illness. Decreased mortality due to thromboembolic events and complications has not been demonstrated.

Hospital immobilization puts patients at increased risk of venous thromboembolism (VTE). In fact, 50% to 70% of symptomatic VTE occurs among patients who have not undergone surgery.

FRAGMIN significantly reduced VTE, including verified DVT compared to placebo (p=0.0015)†,‡



Included hospitalized medical patients with a projected hospitalization of ≥4 days and ≤3 days of prior immobilization.

FRAGMIN prophylactic effect was sustained through 90 days.

FRAGMIN demonstrated a low incidence of major bleeding events in PREVENT

	FRAGMIN	Placebo	*p* value
Major bleeding events	0.49% (9/1848)	0.16% (3/1833)	0.15

- Study investigators also reported a low incidence of thrombocytopenia with FRAGMIN
- Day 21: Thrombocytopenia 0.54% (10/1848) FRAGMIN vs. 0.44% (8/1833) Placebo

Bleeding was assessed at day 21 and classified as major if it was intraocular, spinal/epidural, intracranial or retroperitoneal; if hemoglobin decreased ≥2 g/dL; if it required transfusion of ≥2 units of blood; if it required significant medical or surgical intervention; or if it resulted in death. All other bleeding was classified as minor.

- FRAGMIN offers simple, once daily dosing – 5000 IU s.c. In clinical trials, the usual duration of administration was 12 to 14 days.
- FRAGMIN is eligible for reimbursement under many provincial formularies.

Adverse Events: Clinically significant adverse reactions with FRAGMIN and other LMWHs include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions. In clinical trials with hospitalized patients with severely restricted mobility, the incidence of thrombocytopenia was 0.54% at days 14 and 21. Injection site hematomas are a common side effect with FRAGMIN, occurring at a frequency of <5% with lower (prophylaxis) doses and <10% with higher (treatment) doses.
FRAGMIN should be used with care in patients with hepatic insufficiency, renal insufficiency or a history of gastrointestinal ulceration. Please consult the Prescribing Information for complete dosing instructions, warnings and precautions, and adverse events.

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

FRAGMIN should NOT be administered intra-muscularly.
FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Contraindications: FRAGMIN should not be used in patients who have: hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) or to other low molecular weight heparins and/or heparin or pork products; history of confirmed or suspected immunologically mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an *in vitro* platelet-aggregation test in the presence of FRAGMIN is positive; septic endocarditis (endocarditis lenta, subacute endocarditis); uncontrollable active bleeding; major blood-clotting disorders; acute gastroduodenal ulcer; cerebral hemorrhage; severe uncontrolled hypertension; diabetic or hemorrhagic retinopathy; other conditions or diseases involving an increased risk of hemorrhage; injuries to and operations on the central nervous system, eyes and ears; spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100–120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding.

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† 45% relative risk reduction in VTE and sudden death vs. placebo at day 21 (decreased mortality due to thromboembolic events and complications has not been demonstrated). [0.55; 95% CI, (0.38–0.80)] Incidence of VTE: placebo: 4.96% (73/1473); FRAGMIN 5000 IU s.c. once daily: 2.77% (42/1518); p=0.0015. Primary endpoint: Venous thromboembolism (VTE) defined as a combination of symptomatic deep vein thrombosis (DVT); symptomatic pulmonary embolism (PE); a symptomatic proximal DVT detected by compression ultrasound (CUS) at day 21; and sudden death by day 21.

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See prescribing summary on page 132

What a General Internist Should Know about Delirium in Older Adults

Eamonn Eeles MD, Kenneth Rockwood MD

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Delirium is a disorder of consciousness[1] and manifests as a problem of cognition or, more broadly, of being unable to communicate normally. On a busy clinical service, where communication disorders are common – due to impaired cognition, or deafness, or noise – and where much still can be achieved with comparatively little input from patients, it is easy not to recognize delirium. Not recognizing delirium, however, can result in adverse patient outcomes,[2] and even without overt harm, leads to less satisfying experiences for all concerned. For these reasons, it is useful to know what delirium is, how to recognize it, and what to do for a delirious patient. This article reviews what a general internist can do for patients with delirium.

What Delirious Patients Look Like

If a patient cannot answer a question appropriately, it is worth considering why. If the patient speaks the language in which he or she is being addressed and is not deaf or aphasic, then cognitive impairment is likely. The need to communicate is deeply embedded, so when people cannot effectively communicate, it is common to feel annoyed or frustrated with them. Delirium, as a disorder of consciousness, commonly further induces a characteristic feeling in the observer. In fact, it is characteristic enough that it is possible to diagnose delirium with high accuracy from how people make you feel in the first seconds of your interaction with them, even if they are unknown to you. It is easier to recognize delirium in a patient whom you know. Likewise, a cognitive disorder should be suspected if a patient is described (e.g., by house staff or nursing staff) as being "a poor historian," "difficult to manage," or "confused," especially if this is communicated to you with a certain exasperation. Unfortunately, while this seems specific, it is not sensitive; sometimes patients who are "no trouble at all" may in fact have hypoactive delirium and have simply disengaged from their environment. Special attention should therefore always be paid when relatives complain that their loved one is confused, not right, etc. Note that superficial pleasantries may however still be preserved – how many social encounters in everyday life almost depend on well intended yet meaningless content? Cognitive problems may only become apparent on diligent probing.

Typically, alertness and arousal are affected and can be decreased (the patient may look stuporous) or increased (the patient may look hyper-aroused). Most commonly, cognition fluctuates. Attention typically is impaired, as is temporal orientation (tested by asking the patient the time, day, and date). Delirium is commonly seen in both the emergency department and medical wards, where illness converges with vulnerability in the form of advanced age and frailty. Delirium is more common in patients with dementia.

Once delirium is suspected, the key questions are (1) why can't this patient communicate? (e.g., because of deafness, aphasia, cognitively impairment); (2) how long has this been going on? and (3) how long has it been getting worse? (for delirium complicating dementia). In establishing a rate of onset, review the condition's variability and the inference of acute illness. Collateral history provides the fulcrum for the clinical diagnosis of delirium and its imitators.

Delirium: How to Think about Its Causes

Less frail (and younger) patients with delirium are more likely to have a single and specific brain cause, such as a focal lesion (classically non-dominant parietal) or infection (classically herpetic encephalitis). In contrast, in frail elderly people or those with dementia, delirium is better thought of as a sensitive, but non-specific sign of illness (almost any illness) than as having a neurological or psychiatric cause. That is because older patients who are frail can be likened to complex systems on the edge of failure. When complex systems fail, higher-order functions, such as cognition, are the first to go. It may take a small precipitant to cause this dramatic response. Other higher-order functions, such as balance, functional status, and social interaction can be compromised in frail elderly patients with an acute illness.

Delirium and the Physical Examination

The clinical approach must be tailored to the patient's age, co-operativeness, and other mitigating factors. As with the assessment of a comatose patient, one should look for neurological signs above and below the tentorium and for signs of meningeal irritation. A computed tomography scan can help but is less likely to be revealing without focal signs. A lumbar puncture is usually only helpful when clinical findings suggest meningeal inflammation or hemorrhage. In the absence of a neurological cause, the etiology is usually "toxic-metabolic." Clouding of consciousness occurs, but conventional measures may be insensitive, including (e.g., Glasgow Coma Scale values of 14 or 15). Observation often yields clues; restless agitation and faltering but pressured speech are suggestive of a hyperactive delirium. Withdrawal, pressure ulcers, and poverty of movement in a patient surrounded by uneaten food trays are consistent with hypoactive delirium.

Delirium and Cognitive Assessment

Attention is the closest measurable output of consciousness, and its impairment is a strong indicator of delirium. Most cognitive tests rely on attention to a degree; therefore, using whatever tools are most familiar is reasonable – the Mini-Mental State Examination, a clock-drawing test, or

direct measures of attention (e.g., digit or spelling manipulation). We find particular merit in the attention and concentration axis of the Brief Cognitive Rating Scale.[3] It proposes this order, from highest function to lowest function: serial 7s from 100, serial 4s from 40, serial 2s from 20, counting backwards from 10 to 1, and counting from 1 to 10. This Guttmann-type scale is efficient to use as people who can perform the higher-order tasks can perform each of the tasks lower on the scale. With experience, it is easy to pick out the task that the patent is just able to complete; it can then be done quickly enough (no more than 2 minutes) to allow a daily assessment of performance. What cognitive instruments lack in incisive cut-offs is gained with qualitative information. An inability to focus (tangential communication), sustain (drifting off mid-task), or shift attention (perseveration) all provide clues, in conjunction with other core features, to the disordered thought processes of delirium. Whatever tool is used, we can re-evaluate repeatedly in order to estimate the potential for recovery or persistence. The presence of lingering impairment guides follow-up and discharge support. If the diagnosis remains in doubt, rating scales can be used (e.g., Delirium Rating Scale-revised-98[4]) that incorporate many of the non-cognitive and behavioural changes associated with delirium. Abnormalities on electro-encephalography have been well described as part of the delirium syndrome[2] but are of limited practical relevance except to exclude epileptiform activity or pure psychosis. An occupational therapy assessment can also quantify the extent of functional impairment; commonly, therapists take a history to know whether the functional impairment has worsened.

Differential Diagnosis

Most patients with dementia who present acutely to hospital will have, or go on to develop, a delirium.[2] Behavioural changes in this setting may be mistakenly perceived as an inevitable part of dementia. However, an abrupt deterioration in cognitive abilities, particularly a new onset of hallucinations and delusions, associated with fluctuation is strongly suggestive of a superimposed delirium. Collateral history is the greatest ally of the clinician to corroborate unfolding events. After all, clouding of consciousness represents lack of awareness of self and the environment. Care partners form both an intimate part of that world and are potentially astute observers of changes in this relationship.

Dementia with Lewy bodies may also masquerade as delirium. Fluctuation of cognition, visual hallucinations, illusions, and sleep disorder are features common to both disorders. By contrast, dementia with Lewy bodies is a neurodegenerative disorder and has a correspondingly insidious onset (weeks or months to years). Acute medical illness may be lacking in patients with features of Lewy body disease, but this may be less discriminatory in the acute hospital setting. Parkinsonian signs or a previous adverse reaction to neuroleptic medication should also alert the clinician to possible Lewy body dementia.

Depression and delirium may share "negative symptoms" and even a broad range of cognitive deficits.[5] Again, the rapidity of onset should raise the suspicion of a delirium. Certainly, de novo presentation with "depression" or its evolution during a hospital stay should be considered to be delirium until proven otherwise.

Acute cognitive disturbance, while a core feature, is not the preserve of delirium alone. Vascular dementia may present with a similar rate of onset. However, in the acute setting and in the absence of focal

Table 1. Common Causes of Delirium

Medications (prescribed)
Medications (over the counter)
Medications (alcohol and recreational drugs)
Heart disorders (especially heart failure)
Infection
Iatrogenic (urethral catheterization, restraint, etc.)
Metabolic causes
Combination of some of the above
Something else* (includes focal neurological disorders)

*The "something else" category is included to avoid the common pedagogical error in delirium teaching of presenting endless lists of causes. It is evident that if delirium is a non-specific sign of illness, any illness that comes on in older adults can cause delirium.

Table 2. Classes of Commonly Prescribed Medications with High Estimated Cholinergic Burden in Older Patients*

Compound Example	Drug Class	Comment in Relation to Delirium
Acepromazine	Neuroleptic (phenothiazine)	Special caution with suspected LBD
Alimemazine	Antihistamine, sedative (phenothiazine)	Consider non-sedating alternatives
Alprazolam	Anxiolytic (benzodiazepine)	Consider graded withdrawal
Alverine	Antispasmodic	Consider simple analgesia
Amitriptyline	Tricyclic antidepressant	Watch for serotonergic syndrome
Codeine	Analgesic, antipyretic	Constipation can contribute to delirium
Colchicine	Anti-hyperuricemic, anti-inflammatory	Diarrhea can contribute to delirium
Digoxin	Antiarrhythmic, cardiotonic	Toxicity possible even at therapeutic levels
Furosemide	Diuretic, antihypertensive	Doses frequently adjusted in hospital
Orphenadrine	Anti-parkinsonian	Avoid co-administration of neuroleptics
Oxybutynin	Antispasmodic	Watch for urinary retention in hospital
Theophylline	Bronchodilator, anti-asthmatic	Consider alternative bronchodilators

LBD = Lewy body dementia.

*As with the introduction of medications "start low and go slow," so too with withdrawal "reduce cautiously and slowly."

Source: Adapted from Ancelin et al.[13]

neurological signs, delirium is more common. Vascular dementia should nevertheless be considered when the typical risks for delirium are absent, particularly in a patient with an established vascular burden.

Causes of Delirium

"Old age does not come alone" and neither does delirium. Polypharmacy is common and affords fertile grounds for the precipitation of delirium.[6] A necessarily exhaustive list of the causes of delirium emphasizes the many types of medications available to older adults (Table 1). Cholinergic load (Table 2) is probably the biggest determinant of delirium facilitated through altered drug handling in the older patient.[7] Acute organ failure is usually superimposed on chronic organ disease (cardiac, liver, and renal). A patient's history helps to guide and focus the examination of these systems. Endocrine disturbance (hypothyroidism and Cushing's syndrome) are rare but reversible and easily screened. Mild electrolyte disturbances (especially hyponatremia) are common associations, but unless considered a primary cause of delirium may be treated expectantly. Delirium tremens may be readily apparent from the history. The emergence of psychomotor agitation after "drying out" or 48–72 hours after presentation to hospital is strongly suggestive. Bacteriuria is a frequent finding but not a common cause of delirium, all other things being the same. A delirium-like syndrome is common at the end of life. Whether it merits the same approach as delirium does otherwise is controversial.[2]

Management of Delirium

To manage delirium, you must first fix the precipitants. Mobilize. Have a family meeting. Remember that the precipitants may be multiple and often iatrogenic or nosocomial: half of delirium cases occur after initial presentation. Therapeutic interventions, such as urethral catheterization or a new medication, can trigger delirium. In patients with, or at risk of, delirium, revoke unnecessarily obtrusive interventions (restraints, catheterization, cannulation, excessive medications, sedation). Aggressive treatments are rarely justified in elderly patients, and should be used only after less invasive and restrictive actions have demonstrably failed. Delirium, though recoverable, carries a significant excess in-hospital mortality, and this should be factored in to family discussions. Family involvement is to be encouraged, although not at the expense of care partners' own health. When delirium is complicated by psychomotor agitation, family members commonly help keep the patient calm and not over-medicated. Hospitals often employ sitters, but their role is typically derided as they are meant simply to "watch" the patient and commonly are prohibited from interacting, helping, or providing systematic observations to care team. Consider early rehabilitation and maintain cognitive stimulation through recreational therapy. Persistent delirium warrants close attention, given its poor prognosis.[8]

Drug treatment of the psychiatric features of delirium is a challenging and controversial. When you are asked for sedation to treat a delirious patient, ask the question, "Who is being distressed by this condition?" If it is not the patient and this person's behaviour does not pose a risk to the self or others, then non-pharmacological intervention is the ideal first-line approach. If the risks of treatment are on balance favourable, given the hazard of falls and worsening of cognition, then haloperidol is a reasonable first approach.[9] Beware of neuroleptic sensitivity, characterized by sudden onset of confusion, rigidity, sedation, and immobility, which can be potentially fatal. One should avoid neuroleptic agents in suspected dementia with Lewy bodies. Atypical antipsychotics may be safer than conventional neurolpetics but are not entirely without risk

The dosing of neuroleptics needs not be heavy handed; even 0.5 mg of intramuscular haloperidol, when mixed with an equal dose of lorazepam, can be effective in frail older adults, especially those with an underlying dementia. Behavioural changes may pose a challenge to the provision of basic medical and nursing care. Consequently, fluid balance, oral hygiene, mobility and balance, dietary intake, and pressure areas should be monitored closely and addressed accordingly.[10]

Management consists of treating the precipitating causes and, otherwise, is largely supportive, including early mobilization and rehabilitation. Patients report that the experience of delirium is very frightening. They appreciate calm reassurance, for example, by saying, "I know things must seem very mixed up for you right now, but we are working on it and it will get better." For the hospitalized patient, added to the burden of confusion is an unfamiliar environment. Orientation strategies reinforce whereabouts in time and space and optimize sensory capability (ensuring visual and hearing aids are present) and emotional connections (the company of or even just pictures of family and friends). Sleep disturbance is common, and appropriate circadian lighting and quiet, may help restore a normal sleep pattern.

Delirium Prognosis

Delirium is a risk for dementia, especially if the delirium has not resolved by the time of discharge.[8] If so, a follow-up visit at a memory clinic is worthwhile. Frequently, delirium is associated with a loss of independence (increased institutionalization, functional decline, and length of stay[11]). Patients at high risk on discharge home (e.g., those who live alone) should receive a multidisciplinary review for consideration of additional support. Rethinking the delivery of care on a whole ward (or even whole hospital) to encourage a "frail friendly" environment is important.[12] The presence of delirium, and a sense that there is nothing that can be done for it, can erode morale among health care providers.

Future Challenges

Although delirium is a common problem, there is only a comparatively narrow evidence base for many of the treatment interventions recommended here. Preventive manoeuvres are better established, but only uncommonly implemented in routine hospital care. Delirium is a particularity fruitful area for clinical research.

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Personal Commentary

De-stigmatizing Medical Terminology

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"What did the physical examination show?"
"The patient had stigmata of liver disease."

Stigmata? They actually say that? As a third-year clerk on my internal medicine rotation, I first heard this term at morning report, when the clinical manifestations of cirrhosis were discussed. I knew the word *stigmata* to have the meaning many members of the general public would recognize: "marks resembling the wounds on the crucified body of Christ," as defined in *Webster's Dictionary*. *Stigma* (Greek, pleural stigmata) refers to a mark or cut burned into the skin of criminals, slaves, or traitors in order to visibly identify them as blemished or morally polluted persons. The word was later applied to other personal attributes that are considered shameful or discrediting. Despite the very uncommon use of this term in the vernacular, which probably peaked in, well, the Middle Ages, the word stigmata is ubiquitous in medical terminology, not only in established settings such as endocarditis and cirrhosis, but in newer ones too: "stigmata of a high-risk GI bleed," "stigmata of autoimmune disease," even "stigmata of apoptosis."

As physicians, we love to group together patients' physical signs, especially, but not exclusively, those on the skin, and collectively declare them stigmata. However, it seems arbitrary which ones we call stigmata. Taken to the extreme, the entire field of dermatology could be termed "stigmatology" by the definition that seems to apply. This is reminiscent of the normal abdominal examination, which is the only system often reported to be "benign," and the "grossly normal" neurological examination that probably never actually happened.

I will grant that the term does serve the useful educational function of alerting clinicians to look for a collection of findings that might be seen in a particular condition. However, there are collective signs of raised intracranial pressure that are called just that; similarly, there are findings to suggest congestive heart failure that are labelled that way. Why not just call them what they are: physical signs or findings?

Although some may take issue with the religious implication of the term, this is not where my argument against this practice lies. Language is important, and often influences our perceptions in ways that are not immediately obvious, and may be subconscious. The business world frequently uses this fact to its advantage. A quick look through car advertisements in the newspaper shows this readily: "previously loved vehicle," "reconditioning process," "leather appointed seating surfaces." Labels we apply to groups of people can be insidious and damaging, even, as is probably the case with *stigmata*, with the best of intentions.

Besides the antiquated nature of the term stigmata, and the fact that the public would probably find our use of it in medicine bizarre and maybe even offensive, it is the implication to patients that is more disturbing. In an age when we strive to provide patient-centred care, we are intentionally applying a stigma to our patients and labelling it as such. It is a practice that may encourage or perpetuate a power imbalance between physician and patient, in a way not dissimilar to starting consultation letters with an almost always positive, but irrelevant judgment of a patient's personality: "Thank-you for referring this most pleasant 73-year old lady…."

Our patients with cirrhosis or endocarditis have enough problems; let's move our medical parlance from the 13th to the 21st century and stop stigmatizing them.

Fatal Bilateral Adrenal Hemorrhage after Thrombolytic Therapy for Venous Thromboembolism

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Case Report

A 56-year-old male presented to the emergency department with a 1-week history of shortness of breath, palpitations, and pain and swelling in the left lower leg. The patient had long-standing essential hypertension that was treated with perindopril. On history, there were no apparent clinical risk factors for venous thromboembolism (VTE). On examination, his blood pressure was 147/66 mm Hg, pulse was 117 beats/minute and regular, respiratory rate was 18 breaths/minute, and oxygen saturation was 95% on room air. He was diaphoretic. There was no jugular venous distension, and heart sounds were unremarkable. The lungs were clear to auscultation bilaterally. The left calf was tender and erythematous, without edema.

Initial investigations showed that his hemoglobin level was 98 g/L (140–175 g/L), white blood cell count was 10.8×10^9 g/L ($4.0–11.0 \times 10^9$ g/L), and platelet count was 139×10^9 g/L ($150–400 \times 10^9$ g/L). Serum electrolytes, glucose, and creatine were normal. D-dimer was >4,000 μg fibrinogen equivalent units (<500 μg FEU). The prothrombin time (PT) was 14.6 s (11.5–14.5 s), the international normalized ratio (INR) was 1.2, and the partial thromboplastin time (PTT) was prolonged at 43.4 s (27.0–35.0 s). Creatinine kinase was 98 ng/mL (30–95 ng/mL) and troponin T was <0.010 U/L (0.000–0.070 U/L). His fecal occult blood test was negative. His chest radiograph was normal.

The electrocardiogram showed only sinus tachycardia at 107 beats per minute. Computed tomography angiography revealed multiple bilateral pulmonary emboli in the upper and lower lobes. There was also a large deep vein thrombosis (DVT) occupying the left external iliac and left common femoral veins. Echocardiography showed mild to moderate pulmonary hypertension with an estimated pulmonary artery pressure of 50 mm Hg (15–25 mm Hg), but normal right ventricular systolic function. An abdominal sonogram showed a fatty, non-cirrhotic liver and splenomegaly (15.3 cm).

After assessing the patient clinically and ensuring that there were no contraindications to thrombolysis, an intravenous dose of 100 mg of alteplase was given over 2 hours to treat the patient's extensive pulmonary embolism (PE) and DVT. This was followed by continuous administration of intravenous unfractionated heparin throughout his admission, with frequent blood test monitoring to maintain a PTT value between two and three times the upper limit of normal (with blood tests every 6 hours initially until therapeutic target was achieved, and daily thereafter). The patient remained on intravenous heparin over the course of his admission to allow for easy reversal of his PTT.

Upon investigating the patient's anemia, his serum haptoglobin of <0.10 g/L (0.3–2.0 g/L), lactate dehydrogenase of 426 U/L (110–220 U/L), and a positive direct Coombs' test were all consistent with a hemolytic anemia. A workup for thrombophilia was done to identify underlying risk factors for VTE. Factor V Leiden mutation was absent, his protein C level was 0.89 SI units (0.7–1.30 SI units), and his protein S level was decreased at 0.28 SI units (0.93–1.26 SI units). The lupus anticoagulant normalized ratio was elevated at 2.32 (0.10–1.20).

Six days after his admission, the patient reported new, episodic lower back pain radiating to the thoracic region. That morning, his blood tests revealed a hemoglobin of 92 g/L, a platelet count of 177×10^9 g/L, a sodium of 132 mmol/L (134–144 mmol/L), and a potassium level of 3.1 mmol/L (3.5–5.5 mmol/L). Approximately 12 hours later, the patient developed orthostatic hypotension, with a supine blood pressure of 140/70 mm Hg that decreased to 120/60 mm Hg while standing. He also developed nausea, vomiting, and a fever of 38.5°C. His clinical condition rapidly deteriorated, and he became unresponsive and pulseless. The patient died after unsuccessful attempts at resuscitation according to Advanced Cardiac Life Support guidelines.

An autopsy was performed. This showed bilateral pulmonary emboli and bilateral pulmonary congestion. Abdominal findings included acute bilateral adrenal hemorrhage, moderate hepatomegaly of 2,600 g (97th percentile of normal for the patient's age and sex), and congestive splenomegaly 720 g (70–225 g) There was generalized, reactive, moderately prominent lymphadenopathy, without histological evidence of lymphoma.

Discussion

Thrombolysis is the therapy of choice for patients who have hemodynamic instability as a consequence of PE.[1] Acutely, thrombolytic therapy has also been shown to prevent cardiogenic shock, hasten clot lysis, improve right ventricular function, and reduce the risk of early recurrent PE when compared with standard anticoagulant therapy.[2] Neither retrospective nor clinical studies have been able to demonstrate statistically significant differences in acute all-cause mortality rates between patients who are thrombolysed and those who are treated with anticoagulant therapy alone.[1,3] However, patients who receive standard therapy with heparin are more likely to receive rescue thrombolysis after their initial treatment phase because of clinical deterioration.[4] With respect to treatment for DVT, thrombolysis has been shown to increase the rate of complete or significant lysis when compared with anticoagulant therapy alone. Furthermore, some studies have shown that thrombolysis for acute DVT reduces the long-term risk of developing post-thrombotic syndrome and the occurrence of leg ulceration.[5] However, despite all the aforementioned benefits, thrombolytic therapy can cause serious, fatal

bleeding events.[6,7] As such, it is still unknown whether the benefits of thrombolysis outweigh the risks when compared with treatment with heparin alone.

Because of its potential risks and uncertain clinical benefits, the clinician's assessment of the severity of VTE should be used to decide whether a patient is likely to benefit from thrombolysis.[2] This assessment should include the consideration of clinical findings such as hypotension, tachycardia, respiratory rate and pulse oximetry, jugular venous distension or the presence of the systolic murmur associated with tricuspid regurgitation, and an accentuated P2 on physical examination to identify right ventricular dysfunction. Biochemical findings such as elevated troponin levels may indicate right ventricular microinfarction. The electrocardiogram should be examined for the presence of a new right bundle branch block, S1 Q3 T3, or T-wave inversion in leads V1–V4. Echocardiograms that show right ventricular hypokinesis in a patient with acute PE should alert the clinician to the severity of the PE.

After his admission, our patient had several abnormal laboratory values, including a low concentration of protein S, the presence of a hemolytic anemia, and a positive test for the presence of lupus anticoagulant. He died before these values could be repeated for confirmation, and before the underlying cause of the hemolytic anemia could be discovered. However, these laboratory values indicated that he had several risk factors for VTE.

Prior to administering thrombolysis, all patients must be carefully screened for contraindications to lysis therapy, including known intracranial disease such as neoplasm, acute infarct, recent surgery or trauma, or uncontrolled hypertension. Our patient was given thrombolysis based on his extensive VTE, his significant clot burden, and no apparent contraindications to thrombolytic therapy. In one large retrospective study of thrombolysis for pulmonary embolism, 3.0% of patients who received thrombolysis developed intracranial hemorrhage within 14 days of thrombolysis as compared with 0.3% of patients treated with heparin alone.[6] As well, other bleeding complications have been reported in association with thrombolysis, such as vaginal bleeding[7] and retro-orbital hematoma.[8] To our knowledge, no cases of fatal, autopsy-proven, bilateral adrenal hemorrhage occurring as a complication of acute thrombolytic therapy for VTE have been reported previously.

Conclusion

There remains uncertainty about the precise role of thrombolytic therapy for the treatment of venous thromboembolic disease. Before the decision to use thrombolysis to treat VTE is made, patients must undergo careful risk stratification for both potential risk as well as benefit of lytic therapy. If thrombolysis is administered, patients should be closely monitored for bleeding, and any change in clinical status should prompt investigation for bleeding, which may be occult. Because of the paucity of studies on the benefits and harms of administering thrombolysis, in addition to heparin, for the treatment of PE and extensive DVT, there is an urgent need for randomized controlled studies to precisely clarify the role of lysis in patients with acute VTE.

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Something Less from Something More

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An 80-year-old woman with a history of hypertension was complaining of rapid palpitations. Her 12-lead electrocardiogram (EKG) is shown in Figure 1. Why is her heart rate so slow? Does she need a pacemaker?

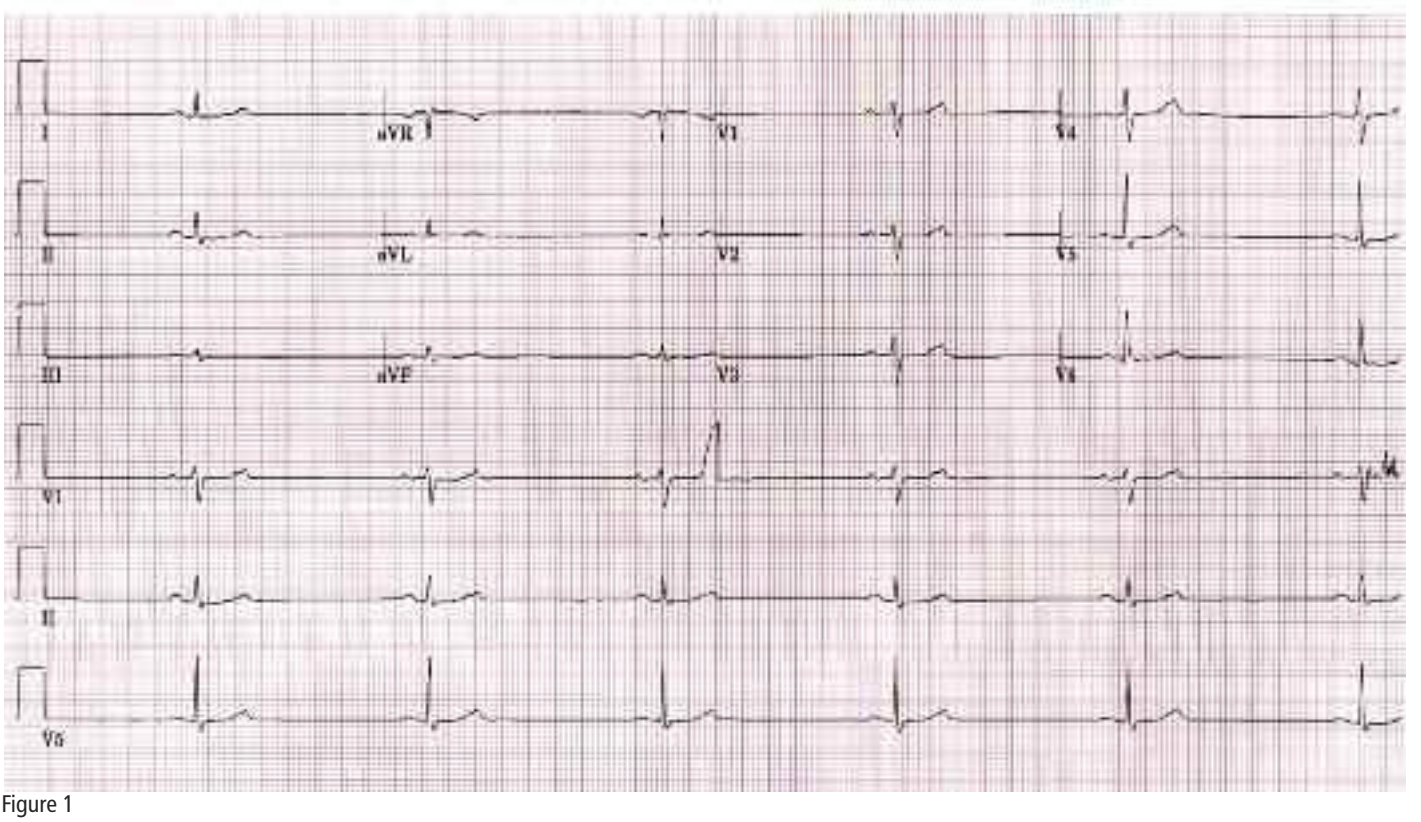

Figure 1

Discussion

The 12-lead EKG in Figure 1 seems to show sinus bradycardia at about 40 bpm. On close inspection, there are small high-frequency deflections in the T wave that are best seen in lead V1. These P waves are non-conducted premature atrial contractions (PACs), and because they occur after every sinus beat, this rhythm is called non-conducted atrial bigeminy. The sinus rate appears slow, but remember that there are two P waves for each QRS complex, so the atrial rate is actually averaging 80 bpm. The sinus node is probably reset by each PAC, so the actual sinus rate corresponds to about 50 bpm (just count from a PAC to the next sinus P wave), which isn't that slow after all.

When this EKG was performed, the patient was asymptomatic. Atrial bigeminy, whether non-conducted (as in the EKG shown in Figure 1), or conducted (as in the EKG shown in Figure 2, recorded a few minutes after the EKG shown in Figure 1) might cause someone to experience a palpitation described as slow and forceful heart rhythm because the effective diastolic interval in either case is long; but this patient described *rapid* palpitations. Hypertensive older adult patients with frequent premature atrial beats often have atrial fibrillation (AF), a paroxysm of which is shown in the EKG in Figure 3 (recorded a few minutes after the EKG shown in Figure 2).

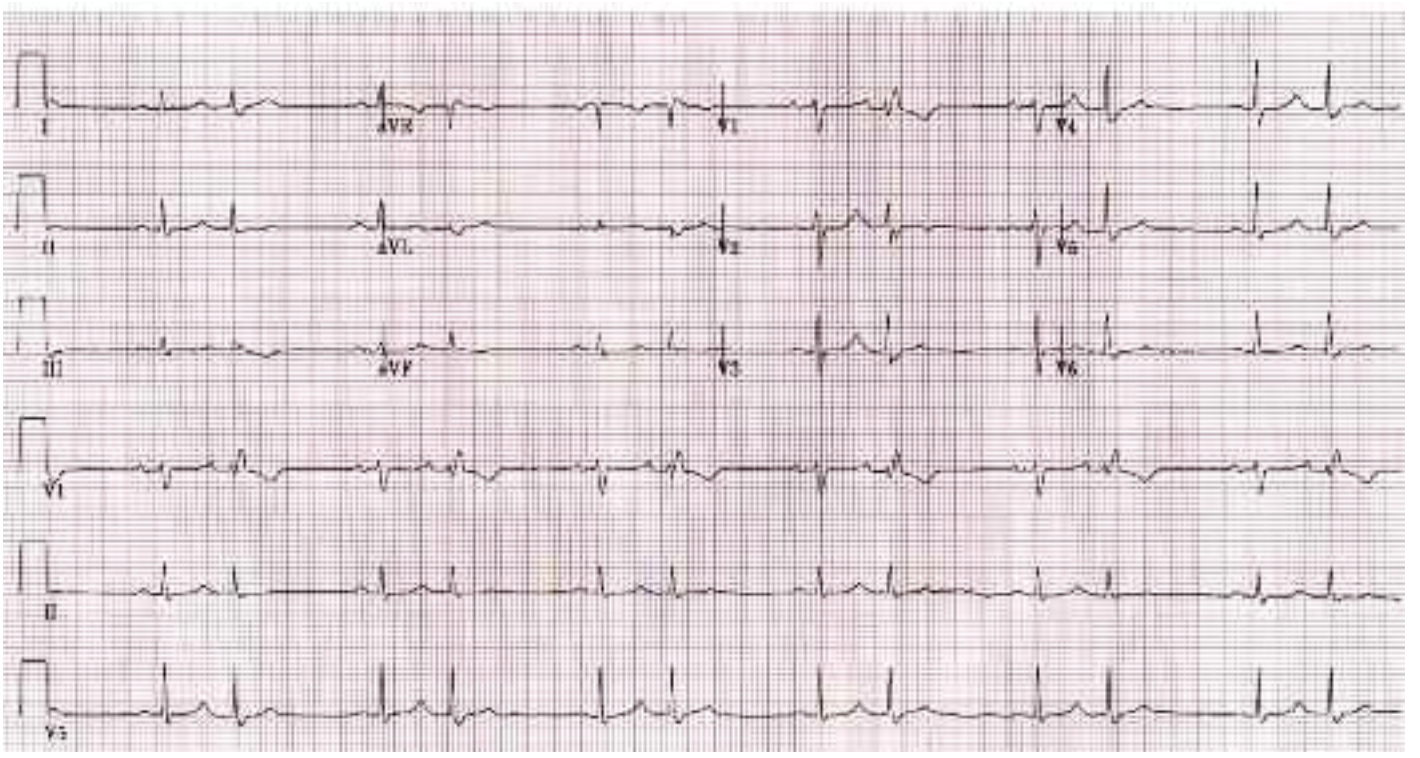

Figure 2

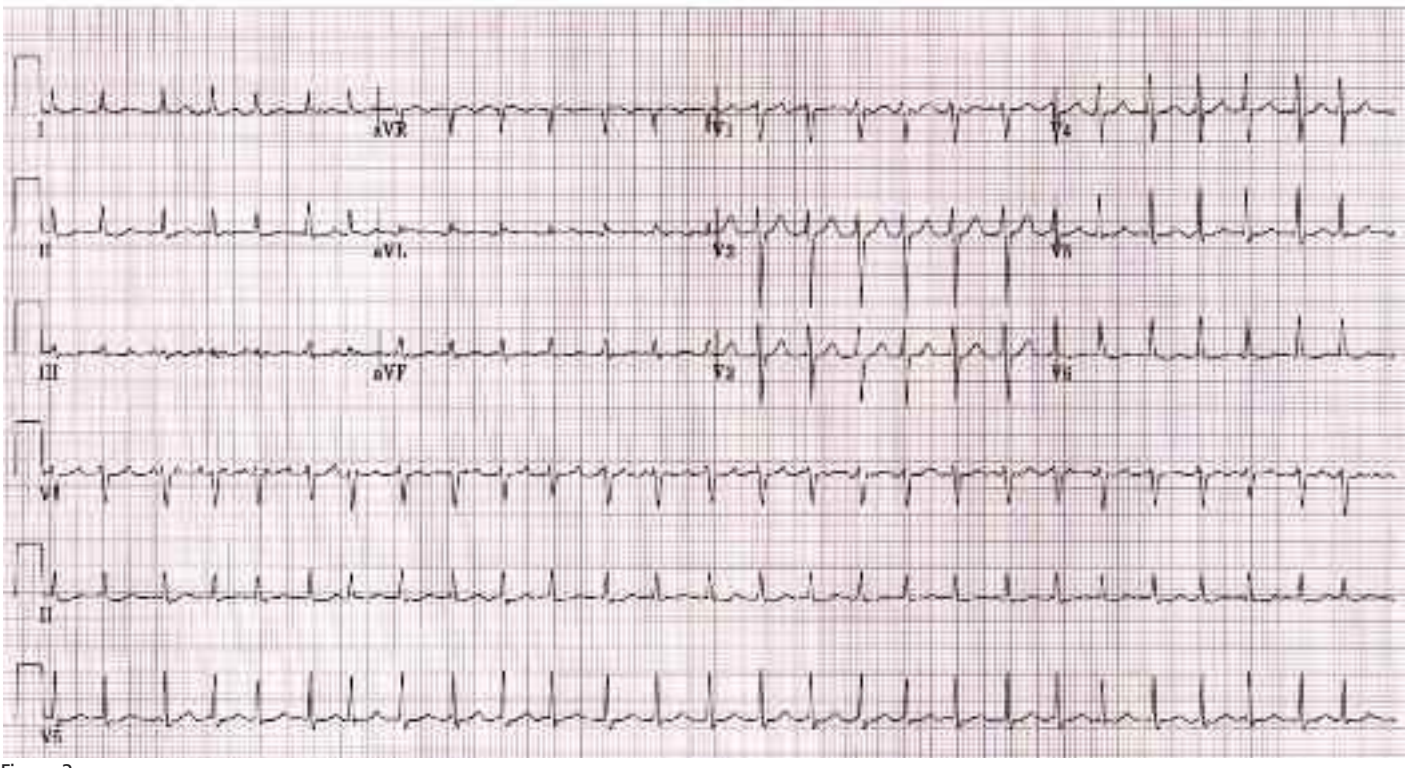

Figure 3

There really are only three major indications for a pacemaker: (1) symptomatic sinus node dysfunction without a reversible cause, (2) symptomatic AV block without a reversible cause, and (3) asymptomatic advanced His-Purkinje disease. This patient had no symptoms of bradycardia. It is noteworthy that sinus node dysfunction commonly accompanies paroxysmal AF in this age group (tachy-brady syndrome), and medications used to treat AF can further impair sinus node function.

The PACs in Figure 1 are not conducted, and the EKG in Figure 2 shows intermittent complete right bundle branch block when the PACs do conduct. Does this patient have asymptomatic advanced His-Purkinje disease that might require a pacemaker? This question will be answered in the next issue.

Massive Pyogenic Liver Abscesses

Natalie K. Kozij BSc, Paul E. Bunce MD

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A 67-year-old woman presented to hospital with a 6-day history of epigastric pain, anorexia, rigors, and malaise. She had a history of peripheral arterial disease and factor V Leiden deficiency, for which she was taking warfarin. On examination, she was afebrile and tachycardic but otherwise appeared well and was not jaundiced. Abdominal examination revealed mild tenderness in the right upper quadrant.

Laboratory investigations were notable for an elevated leukocyte count of 28.9×10^9 cells/L (range, 4.0–11.0×10^9 cells/L); increased liver enzymes with an aspartate aminotransferase of 134 U/L (normal, 5–34 U/L), an alanine aminotransferase of 131 U/L (normal, 7–40 U/L), and an alkaline phosphatase of 268 U/L (normal, 40–150 U/L); and an international normalized ratio (INR) >13.0. A computed tomography (CT) scan of the abdomen revealed multiple hepatic abscesses (the largest measuring 7 cm) dominating most of the liver parenchyma (Figure 1). Empiric antimicrobial therapy was initiated with piperacillin-tazobactam, and drainage of selected abscesses was undertaken via interventional radiology. Cultures of both the blood and abscess drainage were positive for *Streptococcus anginosus*.

The patient's antimicrobial therapy was changed to intravenous penicillin G for a 4-week course, followed by oral amoxicillin for an additional 5 months. Her liver enzymes gradually normalized. Repeat abdominal CT performed 8 months after her initial presentation demonstrated complete resolution of the abscesses.

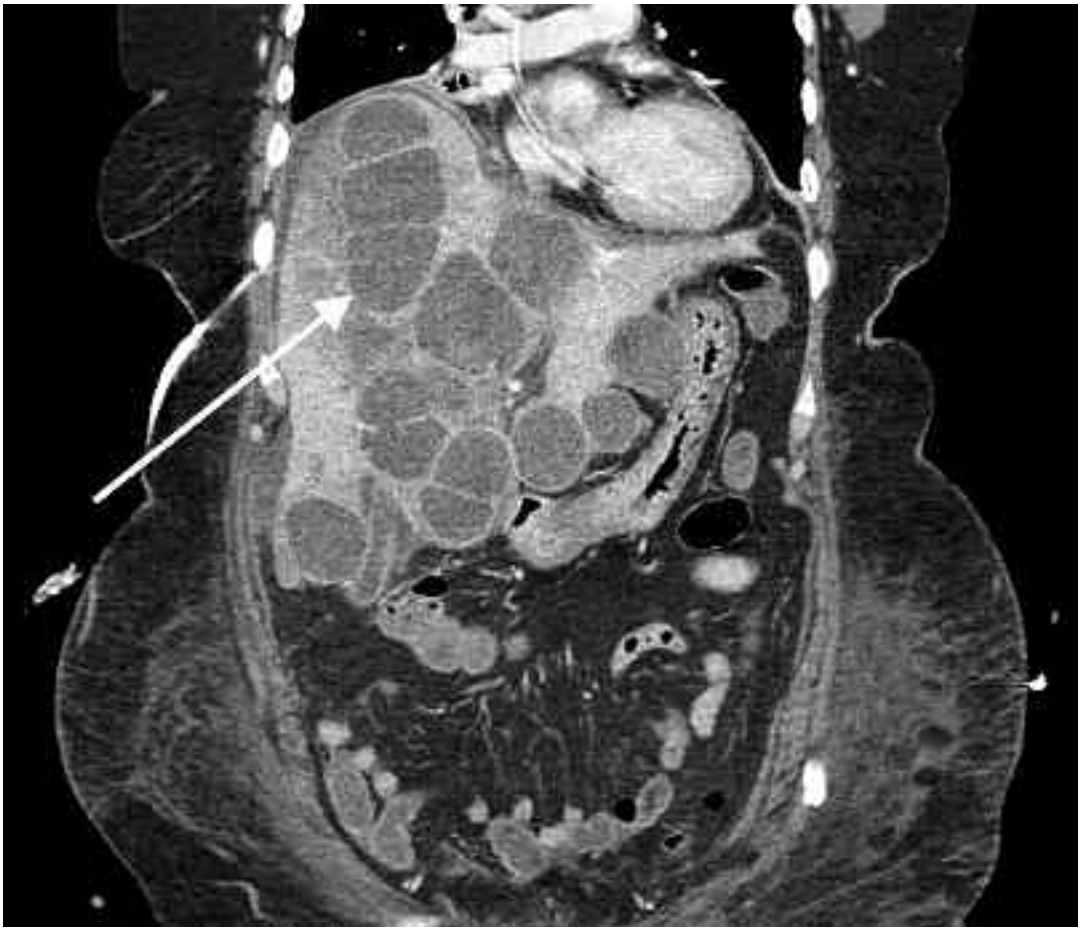

Figure 1. Abdominal computed tomography (coronal) image demonstrating multiple hepatic collections consistent with abscesses.

Even a Small Clot May Pose a Great Risk.

Xarelto®

For the prevention of VTE following elective THR or TKR surgery.[1]*

One 10 mg oral tablet, once-daily.[1]§

Xarelto® (rivaroxaban tablet) is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement (THR) or total knee replacement surgery (TKR).

Contraindications: Xarelto® is contraindicated in patients: with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk; with clinically significant active bleeding, including hemorrhagic manifestations, and bleeding diathesis; with lesions at increased risk of clinically significant bleeding, e.g., cerebral infarction (hemorrhagic or ischemic) within the last 6 months, and patients with spontaneous impairment of hemostasis; receiving concomitant **systemic** treatment with strong inhibitors of both CYP3A4 and P-gp; who are pregnant; who are nursing; or who are hypersensitive to Xarelto® or to any ingredient in the formulation.

Warnings and Precautions: The use of Xarelto® is contraindicated in patients receiving concomitant **systemic** treatment with strong inhibitors of both CYP3A4 and P-gp (such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir). These drugs may increase Xarelto® plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk.

Strong CYP3A4 inducers should be administered with caution in combination with Xarelto®.

Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs) and platelet aggregation inhibitors. Coadministration of Xarelto® with other anticoagulants or antithrombotic therapy has not been adequately studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk. Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.

Due to the pharmacological mode of action, Xarelto® may be associated with an increased risk of occult or overt bleeding which may result in posthemorrhagic anemia. The signs, symptoms, and severity will vary according to the location and degree, or extent, of the bleeding. The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. Hemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache, or unexplained swelling.

Xarelto® is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk. The limited data available for patients with mild hepatic impairment without coagulopathy indicate that there is no difference in pharmacodynamic response or pharmacokinetics as compared to healthy subjects.

The use of Xarelto® is not recommended in patients with severe renal impairment. Patients who develop acute renal failure while on Xarelto® should discontinue such treatment. Xarelto® should be used with caution in patients with moderate renal impairment (CrCl 30–49 mL/min) concomitantly receiving other drugs which increase Xarelto® plasma concentrations.

Physicians should consider the benefit/risk of anticoagulant therapy before administering Xarelto® to patients with moderate renal impairment with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy.

The safety profile of Xarelto® with regard to adverse events and serious adverse events was similar to that of enoxaparin 40 mg OD in the RECORD 1, 2, and 3 studies. Treatment-emergent drug-related adverse events (pooled data of RECORD 1, 2, and 3) occurring in >1% include: nausea (1.25%, Xarelto® vs. 1.52%, enoxaparin); anemia (1.07% vs. 1.11%); post procedural hemorrhage (1.55% vs. 1.39%); increase in transaminases (1.99% vs. 2.78%); and increase in Gamma-glutamyltransferase (1.12% vs. 1.56%).

Please see Xarelto® Product Monograph for complete prescribing information.

*VTE=Venous thromboembolic events; THR= Total hip replacement; TKR=Total knee replacement

§The initial dose should be taken within 6–10 hours after surgery, provided that hemostasis has been established. If hemostasis is not established, treatment should be delayed. Patients should be treated for 35 days after elective THR surgery and 14 days after elective TKR surgery.

Reference: 1. Xarelto® (rivaroxaban tablet) Product Monograph, 2008.

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See prescribing summary on page 136

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Inspiration for a Canadian School of Internal Medicine

Alexandre Lafleur MD

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Alexandre Lafleur is a 4th-year internal medicine resident at Université Laval in Quebec City, Quebec. He is the winner of the 2010 CSIM travel award. He has a special interest in the field of medical education. Correspondence may be directed to alexandre.lafleur.1@ulaval.ca.

The 13th European School of Internal Medicine (ESIM) was held in Brighton, England, in July 2010. The CSIM gave me the opportunity to attend this international event, the only trainee from North America. About 50–70 general internal medicine (GIM) residents from all over the world (mainly from European countries) met, and heard lectures topics of common interest. In my opinion, ESIM should be a source of inspiration for a Canadian School of Internal Medicine, to promote and strengthen a sense of pride and group spirit among the future leaders of our specialty. Dr. Chris Davidson, director of ESIM 2010, wrote: "Although the focus was on Internal medicine as a cornerstone of future healthcare systems, many other aspects of professional and personal life were discussed. We believe that the links formed this week among potential leaders of Internal medicine are vital for the future of the speciality. Indeed this is a key objective of the School and the Federation [European Federation of Internal Medicine]."

The first objective of ESIM was to share knowledge in internal medicine. Each country put on an interactive clinical case presentation. We realized that although there are many differences between the definitions of GIM in European countries, we all face acutely ill patients with complex or multiple diseases, and use a similar diagnostic and therapeutic approach in their management. "All GIM residents seem to have the same global perspective of the patient supported by a wide range of knowledge," stated my colleague from France.

ESIM is also a forum for discussions about the role of European GIM specialists, their training programs, and the future of the specialty in general terms. Canadian internists may seem less valued within the health care system; they may lack formal specialty recognition by the Royal College. However, I believe Canada is the best place in the world to train and practise GIM. My European colleagues were impressed by the popularity of GIM as a career option among our post-graduate trainees. Although all residents agreed that generalism is beneficial for a patient-centred cost effective health system, many reported that their system encourages sub-specialization, decreasing and even abolishing the role of the internist.

Workshops offer a great opportunity to highlight European initiatives in medical education, for example, funded research opportunities included within the residency training period; more outpatient clinic experience; flexibility to train in part in other European countries; and a work schedule influenced by the European Union's 48-hours time directive. Canada seemed to be a leader in internal medicine education and clinical skills evaluation; the CanMEDS competencies were known to, and used in, a growing number of countries. The future of GIM training would undoubtedly benefit from a similar meeting of Canadian residents coming from coast to coast.

ESIM was an occasion for all participants to create long-lasting relationships and a team spirit that will serve our specialty well. The recipe is quite simple: limit the number of participants to 60 trainees and select residents from different universities sharing the same interest for the future of GIM. Different from a formal conference, the school is designed as an interactive team learning experience. I believe that Canadian residents should continue to attend such international events, but we should also create a similar networking opportunity within our own country.

As former ESIM director Antonio Martins Baptista has said, "The school is about opening your mind and opening your heart." Judging by the way my European colleagues and I lived the experience, it is really about opening our minds to other ways of practice and training and heading back home with a renewed passion and pride for our future as GIM specialists.

Hyponatrémie sévère en centre tertiaire entre 2004 et 2007

Laurie Malenfant MD, Matthieu Touchette MD, Luc Lanthier MD

Au sujet des auteurs

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L'hyponatrémie est un problème électrolytique fréquent. On estime sa prévalence, chez les patients hospitalisés, entre 2,5 et 30 % selon la définition utilisée.[1–4] La sévérité, sa rapidité d'installation, et même son traitement peuvent mener à des conséquences sérieuses et irréversibles. Certaines études rapportent une association entre l'hyponatrémie et une augmentation de l'utilisation des ressources en santé ainsi qu'une association entre la survenue d'effets adverses et une augmentation du taux de mortalité.[5–7] Malgré la fréquence relativement élevée de cette anomalie électrolytique, l'information concernant les caractéristiques des patients avec hyponatrémie, de même que leur prise en charge, est restreinte. Quatre études principales portent sur ce sujet, dont trois datant de plus de 10 ans[4,8,9] et une autre de 2003.[7] Nous avons donc voulu évaluer les caractéristiques, les causes, les symptômes, les investigations et le traitement de sujets contemporains présentant cette condition dans notre milieu.

Méthode

Tous les patients se présentant au Centre Hospitalier Universitaire de Sherbrooke (CHUS) souffrant d'une hyponatrémie sévère (définie arbitrairement comme une natrémie ≤ 115 mEq/L) entre janvier 2004 et décembre 2007 ont été inclus dans notre étude. Cette valeur de sodium pouvait être notée dès l'arrivée du patient ou plus tard pendant l'hospitalisation. Afin d'identifier les sujets correspondant à nos critères, la banque de données CIRESSS (Centre Informatisé de Recherche Évaluative en Services et Soins de Santé) de notre centre hospitalier a été utilisée. Cette banque est un outil développé pour faciliter l'accès aux informations cliniques à des fins de recherche, de gestion, d'évaluation, d'analyse et de contrôle. Comme la recherche a été basée sur les valeurs de sodium ≤ 115 mEq/L, chaque hospitalisation a été retenue comme un épisode de soins, certains patients ayant présenté plus d'un épisode d'hyponatrémie. Nous avons utilisé les analyses statistiques du Khi-carré de Pearson, le test exact de Fisher ainsi que le T-test de Student pour évaluer les différences entre les groupes. Une valeur de $p < 0,05$ a été considéré comme étant statistiquement significative.

Résultats

Quatre-vingt quatre (84) patients totalisant 102 épisodes de soins ont présenté une hyponatrémie ≤ 115 mEq/L pendant les quatre années de l'étude. Nous avons exclus de notre analyse deux épisodes de soins en raison d'absence de données d'investigation et de traitement (décision de soins palliatifs seuls dès l'arrivée à l'hôpital chez une mort cérébrale et une anoxie cérébrale sévère). En tout, 10 patients ont eu plus d'un épisode d'hyponatrémie ≤ 115 mEq/L (entre 2 et 7 épisodes). L'âge moyen des sujets était de 68 ± 13,2 ans et 65 % de ceux-ci étaient des femmes. Pour ce qui est de la médication, il est à noter que plus de la moitié des sujets sont sous traitement diurétique (54 %); dans 68 % de ces cas, l'hydrochlorothiazide est le diurétique utilisé (Tableau 1).

Tableau 1. Caractéristiques des patients à l'étude (*n* = 82)

Âge moyen (ans)	67,6 > 13,2
Sexe (femmes)	53 (65 %)
Score de Charlson	
0–2	55 (67 %)
3–5	17 (21 %)
6–9	10 (12 %)
Diabétique type 1 ou 2	16 (20 %)
Médications	
Diurétiques	44 (54 %)
Tricycliques	1 (1 %)
ISRS	12 (15 %)
Opiacés	7 (9 %)
Carbamazépine	1 (1 %)

ISRS = inhibiteur sélectif de la recapture de la sérotonine.

Le nadir de sodium dans la population étudiée était de 111 mEq/L. Chez la grande majorité des sujets, le bilan complet recommandé[2] pour l'hyponatrémie a été réalisé.

Les causes les plus fréquemment rapportées pour l'hyponatrémie étaient

Tableau 2. Causes d'hyponatrémie rapportées (*n* = 100)

Diurétiques	35
Autres médicaments*	6
SIADH	34
Potomanie	36
Pertes digestives	10
Manque d'apport	9
Hypothyroïdie	0
Insuffisance surrénalienne	1
Période post-opératoire	0
Insuffisance cardiaque	3
Cirrhose	3
Insuffisance rénale aigüe ou chronique	3
Hyperglycémie	3
Plus d'une cause mentionnée	39

SIADH = syndrome de sécrétion inappropriée d'hormone antidiurétique.

*Comprend les antidépresseurs tricycliques et les inhibiteurs sélectifs de la recapture de la sérotonine.

Tableau 3. Symptômes associés avec l'hyponatrémie (*n* = 100)

Nausées et/ou vomissements	68
Céphalées	19
Crampes musculaires	4
Confusion	39
Ralentissement psychomoteur ou altération de l'état de conscience	50
Convulsions	5
Aucun symptôme	16

les diurétiques (35 %), une sécrétion inapproprié d'hormone antidiurétique (SIADH) (34 %) et la potomanie (36 %, dont 50 % reliés à la consommation d'alcool); 39 % des sujets se sont vus attribuer plus d'une cause à leur hyponatrémie (Tableau 2).

Du point de vue des symptômes, 16 % n'en rapportaient aucun. Parmi les autres, 68 % ont présenté des nausées ou des vomissements, 50 % un ralentissement psychomoteur ou une altération de l'état de conscience, 39 % de la confusion et 5 % des convulsions (Tableau 3).

Pour ce qui est du traitement, 3 % ont bénéficié d'une restriction hydrique seule, 14 % de NaCl PO, 16 % de furosémide et 2 % d'antiépileptiques. Parmi les 95 % des sujets ayant reçu un soluté, 6 % ont reçu du D5 %, 2 % du D10 %, 11 % du NaCl 0,45%, 73 % du NaCl 0,9 % et 65 % du NaCl 3% (740 mL en moyenne). Si on compare le choix des solutés et la vitesse de correction du sodium entre les patients sans symptômes neurologiques (37 %) et ceux avec symptômes neurologiques (63 %), il n'y a pas de différence significative entre les deux groupes.

La moyenne de correction du sodium à 24 heures dans notre étude est de 11 mEq/L ± 6 mEq/L, et à 48 heures, de 15 mEq/L ± 7 mEq/L. Aucun patient n'a présenté de myélinolyse centropontique.

Discussion

L'hyponatrémie est un problème médical fréquent qu'il convient de reconnaître et de savoir traiter afin d'éviter les complications s'y rattachant. Dans notre population de patients avec hyponatrémie sévère (≤ 115 mEq/L), les étiologies peuvent se résumer ainsi : 1/3 des cas sont causés par les diurétiques, 1/3 causés par un SIADH et 1/3 causés par une potomanie. Alors que plusieurs références rapportent la période post-opératoire,[4,10] l'insuffisance cardiaque[4,7] et l'hyperglycémie[4,7] comme des causes fréquentes d'hyponatrémie, la faible incidence de ces étiologies dans notre étude pourrait s'expliquer par le niveau très bas de sodium que nous avons utilisé comme critère d'inclusion, ce qui a exclu ces étiologies qui sont probablement rattachées à des épisodes d'hyponatrémie moins sévères. De plus, l'incidence de la potomanie comme cause de l'hyponatrémie, donnée très mal décrite dans la littérature, est probablement élevée en raison du niveau bas de sodium décrivant notre hyponatrémie sévère. Dans une étude comportant des patients avec un sodium > 110 mEq/L, 43 % des hyponatrémies chroniques étaient secondaires aux diurétiques et 33 % secondaires à un SIADH; ceci étant assez semblable à nos résultats.[9]

La fréquence des symptômes des patients de notre étude diffère des études précédemment publiées. En effet, dans l'étude de Nzerue et coll.[7] (étude rétrospective réalisée entre 1997 et 2001 comportant 92,[8] % d'Afro-Américains avec hyponatrémie < 115 mEq/L), 47% des patients étaient asymptomatiques par rapport à 16 % dans notre cohorte. Par ailleurs, aucun patient n'a été asymptomatique dans les deux études de Sterns, une où le sodium était ≤ 105 mEq/L[8] et ≤ 110 mEq/L.[9] Par ailleurs, pour ce qui est des autres symptômes, notre étude a démontré une prévalence de nausées et/ou vomissements de 68 % (vs 4,8% dans Nzerue[7]), d'altération de l'état de conscience de 50 % (32 %9 à 51,7 %[7] dans Sterns) et de convulsions de 5 % (14 %[8]–22,5 %[7]). Ces différences peuvent être le fruit de biais causés par la nature rétrospective de ces études ou par les différences de définition ou de population étudiée. Entre autres, les vomissements pourraient être vus comme la cause plutôt que la conséquence de l'hyponatrémie. Des caractéristiques de base ou une prise en charge différentes des patients peuvent également expliquer cette discordance au niveau des symptômes, notamment au niveau des convulsions.

Dans notre étude, la prise en charge des patients n'a pas semblé être différente selon la présence ou non de symptômes, mais la sévérité de l'hyponatrémie de nos patients a pu justifier une approche plus agressive, même chez les sujets asymptomatiques. La correction moyenne s'est avéré un peu plus rapide que les recommandations actuelles. En effet, la limite supérieure recommandée de correction du sodium en 24 et 48 heures est en diminution lorsqu'on révise la littérature sur ce sujet. En 1994, on suggérait un maximum de correction 12 mEq/L en 24 heures et de 18 mEq/L en 48 heures.[8] Puis, en 1997, cette limite est passée à 10 mEq/L en 24 heures.[11] Depuis les années 2000, on reconnaît que les risques associés au traitement sont probablement évités avec une correction inférieure à 10 mEq/L en 24 heures et 18 mEq/L en 48 heures, mais on suggère de viser un maximum de 8 mEq/L en 24 heures pour éviter une surcorrection.[8,12] Récemment, Sterns a publié un article diminuant encore une fois les limites suggérées pour la correction du sodium, celles-ci devenant : 6–8 mEq/L en 24 heures, 12–14 mEq/L en 48 heures et 14–16 mEq/L en 72 heures.[13] Il convient d'admettre que plusieurs facteurs ont une influence sur les complications de l'hyponatrémie et de son traitement, rendant difficile d'établir un seuil de correction sécuritaire applicable pour tous. Il demeure cependant important de traiter rapidement une hyponatrémie sévère ou symptomatique, tout en s'assurant un contrôle sur la correction à moyen-long terme (dans les premières 24 à 72 heures) avec un suivi paraclinique serré. Par contre, il est à noter que malgré une moyenne de correction excédant quelque peu les recommandations, aucune myélinolyse centropontique n'a été rapportée dans notre cohorte de 100 épisodes de soins.

Notre étude est rétrospective et comporte donc certaines limites. Les causes d'hyponatrémie rapportées sont celles notées dans les dossiers et les vitesses de correction de sodium de même que les solutés utilisés sont une estimation des données relevées aux dossiers. De plus, notre étude comporte un nombre assez restreint de patient; ceci reste malgré tout comparable aux études similaires antérieures.[4,7–9]

En conclusion, notre étude des patients présentant une hyponatrémie sévère (Na+ ≤ 115 mEq/L) dans notre centre a démontré que celle-ci est le plus fréquemment causée par 3 étiologies courantes (diurétique, SIADH, potomanie), est multifactorielle chez près de 40 % et est la plupart du temps symptomatique (chez 84 %) à ce niveau. Un traitement en fonction de l'étiologie corrige rapidement et efficacement l'hyponatrémie sévère, sans complications importantes rapportées.

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Physician Health

Well Doc? What Are the Most Satisfying Aspects of Work for Physicians?

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Background

This is the fourth in a series of articles based on data from interviews with 54 internal medicine physicians who spoke with us about factors related to their wellness. In the first three articles, we reported on how these physicians view their quality of life, what they perceive as sources of work stress, and how they cope with work stress.[1–3] In this article, we identify the aspects of work that physicians feel positively affect their job satisfaction. Job satisfaction can be defined as the extent to which an individual likes his or her job. Understanding this facet of wellness is important given that physician job satisfaction has been linked to critical outcomes such as recruitment and retention and quality of patient care.[4,5] Moreover, it is an important goal in and of itself to ensure that physicians enjoy the work that they do. The objective of this qualitative research was to identify and explore what factors contribute to job satisfaction for internal medicine physicians.

Methods

Refer to the first article in this series, "Well Doc? What Constitutes Quality of Life for Physicians?"[1] for a detailed description of the research methodology.

The study received ethics approval from the Conjoint Health Ethics Review Board of the University of Calgary.

Results

We asked the internal medicine physicians the question, "What parts of your job do you like or enjoy the most, which give you the greatest sense of satisfaction?" In describing what gives them the greatest sense of job satisfaction, two major themes emerged: (1) activities specifically involving patient care and (2) problem solving and the diversity in work activities.

Activities Involving Patient Care

In describing the various activities involving patient care, almost half of the participants (44%) identified caring for patients, having contact with patients, or interacting with patients as the most satisfying aspect of their job. Another 39% of physicians indicated that having a positive impact

on patients and successful patient outcomes was the most satisfying part of their work. Others (15%) mentioned that dealing with challenging, interesting, or rare patient cases was the most enjoyable for them. Less frequently mentioned aspects included being efficient in treating patients, having appreciative patients, receiving positive feedback from patients, getting to know patients, and developing a relationship with patients. The following quotations illustrate some examples:

> "What really gives me the most satisfaction is really challenging clinical problems and really sick patients and being able to improve things that way … It can be the most frustrating, the most heartbreaking, but you also get the most satisfaction. You get somebody who says, even years after, they feel they have their life back."

> "The happiest time for me [is seeing] Mr. So-and-so again, to see how he is, having a really good relationship … They start telling me about the things that are not really pertinent to my job, like, 'My wife died.' They confide in me. It's a real relationship, and that is really rewarding for me."

> "I like working with people one on one, even though we're seeing more grumpy patients these days. They wait in 'emerg' for a long time and get grumpy. Usually by the time I've finished my interaction, they've settled down. We have a good rapport going. It's nice to be able to diffuse somebody who's not had a great experience and make their health care experience nicer."

> "Seeing a patient do well, that is the single most important thing. When they come back, they tell me, 'You know what? My disease is well controlled. I'm doing well at work. I'm having no side effects.' That's the most gratifying thing I get out of this. Getting positive feedback is icing on the cake."

> "I love the patients. I love the diversity of people we deal with, different ages, socioeconomic classes of people, just the different backgrounds, both cultural and life backgrounds. I deal with people I would never normally get to meet."

> "I think when I meet sick patients, they are on the verge of life and death, at the end; from the work I do, I can discharge them home, and they are happy and healthy. That's the happiest time in the job, in my professional life."

Problem Solving and Diversity of Activities

One quarter of participants (26%) explained that the problem solving aspect of their job was most enjoyable in terms of figuring out things, resolving issues, or successfully completing a task. Others (22%) indicated that they enjoyed the diversity and different combinations of work tasks, including caring for patients, teaching, and engaging in research, that is, they enjoyed the whole package or "all of it." Another 22% mentioned that teaching and mentoring others was a very satisfying part of their work. Seventeen percent identified working with other health care professionals, being part of a team, and relationships with other staff as most satisfying. Less frequently mentioned aspects included research accomplishments (e.g., getting a project funded or an article published), having an impact on the system, being involved in strategic planning, having things run smoothly, and personal learning. The following quotations illustrate some examples:

> "The problem is, I like it all! *[laughs]* I enjoy patient care. I enjoy research. I enjoy teaching. I enjoy lecturing … There's very little I don't enjoy."

> "The variety and also the intellectual stimulation and contact with people and being on the cutting edge of things, to me, are a lot of fun."

> "I guess solving problems, and that's clinical, research, education, or administration. I really enjoy that. It's probably what gives me the most satisfaction, that 'eureka' moment!"

> "We've set up the clinic in such a way that is it easier for them to do well. So it's satisfying to know we've created an environment that makes it easier for this difficult-to-work-with group to get health care. We contribute to the health of individual patients but also to the public health in general, and that is very satisfying."

> "So I guess the accomplishments, the productivity … in research and in administration, teaching accomplishments, clinical accomplishments. All of those things – whether that means productivity in the literature or success with patients or administrative success with the division."

> "Working in a team, I think, a job well done. Taking a patient and the family and nursing, and OT/PT, medical clerks – taking them all together – we take sick people, make them feel better, and send them on their way. That's the process that's great. We work with a lot of fantastic people here. I think the quality of the people is fantastic."

> "I think it's the people interaction, with other levels, so residents, senior and junior residents, staff, students, patients, nurses, physical and occupational therapists, pharmacists. These are the people you interact with on a daily basis personally and professionally and make friends with as well. That's probably the thing I love the most."

Discussion

The internal medicine physicians interviewed in our study describe in their own words the most satisfying aspects of their work. Two major themes emerged: that of activities involving patient care; and the problem solving, diversity, and different combinations of activities afforded by their work. Previous research has also identified patient care and relationships with patients and colleagues as among the greatest predictors of physician job satisfaction,[6] with other important factors including professional autonomy, creativity, income satisfaction and security, control over personal time, and characteristics of individual practices, such as the ability to provide continuity of care.[6–9]

It is not surprising that physicians describe activities involving patient

care as a dominant factor contributing to their job satisfaction, given that those choosing the medical profession expect to spend much of their time caring for patients. In the first article in this series, job satisfaction was identified by our study participants as a major constituent of their quality of life in terms of engagement in satisfying, enjoyable, and meaningful work.[1] As illustrated in this article, patient care is a central feature of their work that contributes to their job satisfaction, which, in turn, improves their quality of life. Paradoxically, in the second article of this series, physicians also described how difficulties associated with patient care are one of the major sources of work stress.[2] It appears that patient care is associated with both rewards and challenges for physicians.

Another aspect of satisfying work described by physicians is the challenge of problem solving. One of the foundations skills of internal medicine is the expertise required to solve medical diagnostic dilemmas. Physicians in general are often expected to help resolve systems issues related to the delivery of health care, research, and medical education. A recently published article on physician coping strategies describes how physicians often use problem solving or active coping strategies (e.g., making a plan of action), especially if they perceive they have some degree of control over the situation.[9] Such coping strategies may be frustrating for physicians when many of the issues in health care systems are more difficult or impossible for individual physicians to resolve. Ironically, although problem solving is considered an aspect of physicians' work that makes work more satisfying, problem solving can also contribute to feelings of stress if the challenges are unsurmountable.[9]

The study participants also expressed fulfillment and contentment when they are able to perform a variety of different work tasks. As specialists, internal medicine physicians are frequently employed in academic centres where they are expected to contribute to an assortment of duties. Similarly, in the community or rural setting, they may assume leadership roles in health care administration, clinical research, and education. It is interesting to note, however, that when the challenges and complexities are combined with an excessive workload, they can be overwhelming and exhausting for physicians, thereby resulting in stress. In our earlier *CJGIM* article on job stress, we reported on how the internal medicine physicians who were involved in activities in addition to patient care, such as scholarly or administrative endeavours, seemed particularly burdened by the stress of having to multi-task, juggle activities, and find time beyond the usual work day to complete these supplementary duties.[2]

The factors affecting internal medicine physicians' job satisfaction are important as they relate to individual physician wellness as well as the wellness of the health care systems where physicians work.[4] Several narrative reviews discuss the many potential negative impacts of dissatisfied physicians, including evidence that these care providers have poorer prescribing habits and that their patients are less compliant with treatment plans.[4,5] In addition, dissatisfied physicians are more likely to show evidence of burnout, anxiety, and depression, measures that are being increasingly linked to poor quality of patient care. Poor retention of the physician workforce due to job dissatisfaction and the subsequent need for recruitment carry a huge financial cost as well as a cost to the quality of health care due to a loss of continuity of care and reduced efficiency for the health care organization.

Improving our understanding of the factors related to internal medicine physicians' job satisfaction can help guide their work arrangements. Optimizing the balance between the positive and negative aspects of physicians' duties and responsibilities can provide the opportunities for them to stay interested and challenged, deliver quality health care, and sustain the enjoyment of their work.

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PrCRESTOR®
rosuvastatin calcium

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Lipid Metabolism Regulator

INDICATIONS AND CLINICAL USE: Hypercholesterolemia: CRESTOR (rosuvastatin calcium) is 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)
- Homozygous familial hypercholesterolemia where CRESTOR is used either alone or as an adjunct to diet and other lipid-lowering treatment such as apheresis

Prevention of Major Cardiovascular Events: In adult patients without documented history of 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 3 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)

CRESTOR **40 mg** is contraindicated in:

- 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 m^2) (see ADMINISTRATION, Patients with Renal Impairment)
  - Hypothyroidism
  - Alcohol abuse
  - Situations where an increase in rosuvastatin plasma levels may occur

Safety Information

WARNINGS AND PRECAUTIONS: Before instituting therapy with CRESTOR (rosuvastatin 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 cortisol 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 titrated 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.

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
- Previous history of muscular toxicity with another HMG-CoA reductase inhibitor
- Concomitant use of a fibrate or niacin
- Hypothyroidism
- Alcohol abuse
- Excessive physical exercise
- Age > 70 years
- Renal impairment
- Hepatic impairment
- Diabetes with hepatic fatty change
- Surgery and trauma
- Frailty
- 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 fibric acid derivatives (including fenofibrate 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.

CRESTOR therapy should be temporarily withheld or discontinued in any patient with an acute serious condition suggestive of myopathy or predisposing to the development of rhabdomyolysis (e.g., sepsis, hypotension, major surgery, trauma, severe metabolic endocrine and electrolyte disorders, or uncontrolled seizures).

Renal Impairment: Subjects with severe renal impairment (CrCl < 30 mL/min/1.73 m^2) 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 urine 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 erythematous-like syndrome, polymyalgia rheumatica, vasculitis, purpura, thrombocytopenia, leukopenia, hemolytic anemia, positive antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR) increase, eosinophilia, arthritis, arthralgia, urticaria, asthenia, 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: CRESTOR 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 CRESTOR should not breastfeed (see CONTRAINDICATIONS).

Pediatrics (≤ 18 years of age): Treatment experience with CRESTOR 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: CRESTOR (rosuvastatin calcium) is generally well tolerated. The adverse events seen with CRESTOR are generally mild and transient. CRESTOR clinical trial experience is extensive, involving 9800 patients treated with CRESTOR in placebo-controlled trials and 9855 patients treated with CRESTOR in active-controlled clinical trials. Discontinuation of therapy due to adverse events occurred in 2.6% of patients receiving CRESTOR and 1.8% of patients receiving placebo. The most frequently reported adverse events at an incidence of ≥ 1% and at a rate greater than placebo were arthralgia, upper abdominal pain and ALT increase. See SUPPLEMENTAL PRODUCT INFORMATION.

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, Hepatic Effects, Muscle Effects).

Abnormal urinalysis testing (dipstick-positive proteinuria) has been seen in a small number of patients taking CRESTOR and other HMG-CoA reductase inhibitors. The protein detected was mostly tubular in origin. In most cases, proteinuria decreases or disappears spontaneously on 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 CRESTOR-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 CRESTOR. There was a 0.1% increase in mean HbA1c with CRESTOR 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 CRESTOR, 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: Rare: pancreatitis; Very rare: gynecomastia

DRUG INTERACTIONS: In CRESTOR (rosuvastatin calcium) clinical trials, there was no evidence of increased skeletal muscle effects when rosuvastatin was dosed with any concomitant therapy. However, CRESTOR 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), nicotinic acid, 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 (ketoconazole, erythromycin, itraconazole).

Concomitant Therapy with Other Lipid Metabolism Regulators: Coadministration of fenofibrate and CRESTOR 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 CRESTOR 10, 20 and 40 mg plus extended-release niacin or in a second study of 103 patients who received CRESTOR 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 CRESTOR 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 $AUC_{(0\text{-}24)}$ and C_{max}, respectively.

Increased systemic exposure to rosuvastatin has been observed in subjects receiving CRESTOR with various protease inhibitors in combination with ritonavir. Consideration should be given to both the benefit of lipid lowering by the use of CRESTOR in HIV patients receiving protease inhibitors and the potential for increased rosuvastatin plasma concentrations when initiating and up-titrating CRESTOR 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: CRESTOR 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 0K9

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 CRESTOR (rosuvastatin calcium) and should continue on this diet during treatment with CRESTOR. If appropriate, a program of weight control and physical exercise should be implemented.

Prior to initiating therapy with CRESTOR, secondary causes for elevations in plasma lipid levels should be excluded. A lipid profile should also be performed.

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

Recommended Dose and Dosage Adjustment

Hypercholesterolemia: The dose range of CRESTOR is 5 to 40 mg orally once a day. The recommended starting dose of CRESTOR 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 CRESTOR 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 CRESTOR 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 CRESTOR 40 mg dose.

The dosage of CRESTOR 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 risk of major cardiovascular events (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 CRESTOR 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 m^2), the starting dose of CRESTOR should be 5 mg and not exceed 10 mg once daily (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS, Renal Impairment).

Race: The initial dose of CRESTOR, in Asian patients, should be 5 mg once daily. The potential for increases in systemic exposure must be considered when making treatment decisions. The maximum dose should not exceed CRESTOR 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). CRESTOR should be administered to women of childbearing age only when such patients are highly unlikely to conceive and have been informed of the possible harm. If the patient becomes pregnant while taking CRESTOR, the drug should be discontinued immediately and the patient apprised of the potential harm to the fetus. Atherosclerosis being a chronic process, discontinuation of lipid metabolism-regulating drugs during pregnancy should have little impact on the outcome of long-term therapy of primary hypercholesterolemia (see WARNINGS AND PRECAUTIONS, Special Populations, Pregnant Women, 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 rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the 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 (768 of which were treated with rosuvastatin) and 11,641 patients within placebo- and active-controlled clinical trials of 6 to 52 weeks' duration (5319 of which were treated with rosuvastatin). In all controlled clinical trials, 3.2% of patients were withdrawn from CRESTOR therapy due to adverse events. This withdrawal rate was comparable to that reported in placebo-controlled studies.

Associated adverse events occurring at an incidence ≥ 1% in patients participating in placebo-controlled clinical studies of rosuvastatin, are shown in Table 1.

Table 1: Number (%) of Subjects with Associated Adverse Events Occurring with ≥ 1% Incidence in any Treatment Group: Placebo-Controlled Pool

Body system/Adverse event	Placebo (%) (N=367)	Total rosuvastatin (%) (N=768)
Whole body		
Abdominal pain	2.2	1.7
Asthenia	0.5	1.3
Headache	2.2	1.4
Digestive		
Constipation	1.4	1.0
Diarrhea	1.6	1.3
Dyspepsia	1.9	0.7
Flatulence	2.7	1.8
Nausea	1.6	2.2
Musculoskeletal		
Myalgia	0.5	1.6
Nervous system		
Dizziness	1.6	0.5
Insomnia	1.9	0.4

Long-term Controlled Morbidity and Mortality Trials: In the **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuation **R**osuvastatin (JUPITER) study involving 17,802 participants treated with CRESTOR 20 mg once daily (n=8901) or placebo (n=8901), CRESTOR 20 mg was generally well tolerated. Subjects were followed for a mean duration of 2 years.

Discontinuation of therapy due to an adverse event occurred in 5.6% of subjects treated with CRESTOR 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 reaction reported in ≥ 1% of patients and at a rate greater than or equal to placebo was myalgia (2.4% CRESTOR, 2.0% placebo).

Treatment emergent adverse events regardless of causality occurring at an incidence ≥ 1% and at a rate greater than placebo in patients participating in the JUPITER trial are shown in Table 2.

Table 2: Number (%) of Subjects with Treatment Emergent Adverse Events Regardless of Causality Occurring with ≥ 1% Incidence and > than Placebo: JUPITER

Body system/Adverse event	Placebo (%) (N=8901)	Total rosuvastatin 20 mg (%) (N=8901)
Blood		
Anemia	2.1	2.2
Cardiac		
Palpitations	0.9	1.0
Gastrointestinal		
Diarrhea	4.6	4.7
Constipation	3.0	3.3
Nausea	2.3	2.4
General disorders		
Edema peripheral	3.0	3.7
Fatigue	3.5	3.7
Hepatobiliary		
Cholelithiasis	0.9	1.0
Infections		
Urinary tract	8.6	8.7
Nasopharyngitis	7.2	7.6
Bronchitis	7.1	7.2
Sinusitis	3.7	4.0
Influenza	3.6	4.0
Lower respiratory tract	2.7	2.9
Gastroenteritis	1.7	1.9
Herpes zoster	1.4	1.6
Injury		
Contusion	1.4	1.7
Investigation		
ALT increased	1.0	1.4
Blood glucose increased	0.7	1.0
Metabolism		
Diabetes mellitus	2.5	3.0
Musculoskeletal		
Back pain	6.9	7.6
Myalgia	6.6	7.6
Arthritis	5.6	5.8
Arthralgia	3.2	3.8
Muscle spasms	3.2	3.6
Osteoarthritis	1.4	1.8
Bursitis	1.3	1.5
Neck pain	1.0	1.1
Osteoporosis	0.8	1.0
Neoplasms		
Basal cell carcinoma	0.9	1.0
Psychiatric		
Insomnia	2.3	2.5
Renal		
Hematuria	2.0	2.4
Proteinuria	1.3	1.4
Respiratory		
Epistaxis	0.8	1.0

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:

- Uncommon (≥ 0.1% and < 1%): Pruritus, rash, urticaria, arthralgia, muscle weakness, arthritis, constipation, nausea, dyspepsia, gastroesophageal reflux disease, ALT increase, creatine phosphokinase increase, hepatic enzyme increase, creatinine increase, paraesthesia, tremor, general pain, proteinuria, sinusitis, insomnia, abnormal hepatic function, vertigo, diabetes mellitus
- Rare (≥ 0.01% and < 0.1%): Myopathy (including myositis), rhabdomyolysis and hypersensitivity reactions including angioedema

The following additional adverse events were reported in controlled clinical trials, regardless of causality: Accidental injury, back and chest pain, flu syndrome, infection, urinary tract infection, diarrhea, flatulence, gastroenteritis, hypertonia, bronchitis, increased cough, rhinitis and pharyngitis.

In long-term controlled clinical trials, CRESTOR was shown to have no harmful effect on the ocular lens.

DRUG INTERACTIONS:

Concomitant Therapies Without Clinically Significant Interactions

Bile Acid Sequestrants: CRESTOR can be used in combination with bile acid sequestrants (e.g., cholestyramine).

Ketoconazole: Coadministration of ketoconazole with CRESTOR resulted in no change in plasma concentrations of rosuvastatin.

Erythromycin: Coadministration of erythromycin with CRESTOR resulted in small decreases in plasma concentrations of rosuvastatin. These reductions were not considered clinically significant.

Itraconazole: Coadministration of itraconazole with CRESTOR resulted in a 28% increase in the AUC of rosuvastatin. This small increase was not considered clinically significant.

Fluconazole: Coadministration of fluconazole with CRESTOR resulted in a 14% increase in the AUC of rosuvastatin. This small increase was not considered clinically significant.

Digoxin: Coadministration of digoxin and CRESTOR did not lead to any clinically significant interactions.

Other Drugs: Although specific interaction studies were not performed, CRESTOR has been studied in over 5300 patients in clinical trials. Many patients were receiving a variety of medications including antihypertensive agents (beta-adrenergic blocking agents, calcium channel blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers and diuretics), antidiabetic agents (biguanides, sulfonylureas, alpha glucosidase inhibitors, and thiazolidinediones), and hormone replacement therapy without evidence of clinically significant adverse interactions.

Drug-Drug Interactions: The drugs listed in Table 3 are based on either drug interaction case reports or studies or potential interactions due to the expected magnitude and seriousness of the interaction (i.e., those identified as contraindicated).

Table 3: Established or Potential Drug-Drug Interactions

Proper name	Effect	Clinical comment
Gemfibrozil	Coadministration of a single rosuvastatin dose (10 mg) to healthy volunteers on gemfibrozil (600 mg BID) resulted in a 2.2- and 1.9-fold increase in mean C_{max} and mean AUC of rosuvastatin, respectively.	Patients taking this combination should not exceed a dose of CRESTOR 20 mg once daily and the concomitant use of CRESTOR 40 mg once daily is contraindicated.

Proper name	Effect	Clinical comment
Coumarin anticoagulants	As with other HMG-CoA reductase inhibitors, coadministration of CRESTOR and coumarin (e.g., warfarin) may result in a rise in International Normalized Ratio (INR) compared to coumarin alone. In healthy subjects, the coadministration of rosuvastatin 40 mg (10 days) and warfarin 25 mg (single dose) produced a higher mean $_{max}$INR and AUC-INR than achieved with warfarin alone. Coadministration of CRESTOR 10 and 80 mg to patients on stable warfarin therapy resulted in clinically significant rises in INR (> 4, baseline 2-3). The mechanism for this effect is unknown, but is likely due to a pharmacodynamic interaction with warfarin rather than a pharmacokinetic interaction as no relevant differences in the pharmacokinetics of either drug was observed.	In patients taking coumarin, monitoring of INR is recommended at initiation or cessation of therapy with rosuvastatin or following dose adjustment. Rosuvastatin therapy has not been associated with bleeding or changes in INR in patients not taking anticoagulants.
Antacids	Simultaneous dosing of CRESTOR with an antacid suspension containing aluminum and magnesium hydroxide resulted in a decrease of rosuvastatin plasma concentration by approximately 50%.	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 are less likely to need the antacid.
Oral contraceptives	When CRESTOR 40 mg was coadministered with a representative oral contraceptive (ethinyl estradiol [35 µg] and norgestrel [180 µg on days 1 to 7, 215 µg on days 8 to 15, and 250 µg on days 16 to 21]), no reduction in contraceptive efficacy was observed. An increase in plasma concentrations (AUC) of ethinyl estradiol (26%) and norgestrel (34%) occurred.	These increased plasma levels should be considered when selecting oral contraceptive doses.
Immunosuppressants (including cyclosporine)	CRESTOR 10 and 20 mg were administered to cardiac transplant patients (at least 6 months post-transplant) whose concomitant medication included cyclosporine, prednisone and azathioprine. Results showed that cyclosporine pharmacokinetics were not affected by rosuvastatin. However, cyclosporine did increase the systemic exposure of rosuvastatin by 11-fold (C_{max}) and 7-fold (AUC_{0-24}) compared with historical data in healthy individuals.	The concomitant use of CRESTOR and cyclosporine is contraindicated (see CONTRAINDICATIONS).

CLINICAL TRIALS:

Hypercholesterolemia

The following reductions in total cholesterol, LDL-C, TG, Total-C/HDL-C ratio and increases in HDL-C have been observed in a dose-response study, and may serve as a guide to treatment of patients with mild to moderate hypercholesterolemia:

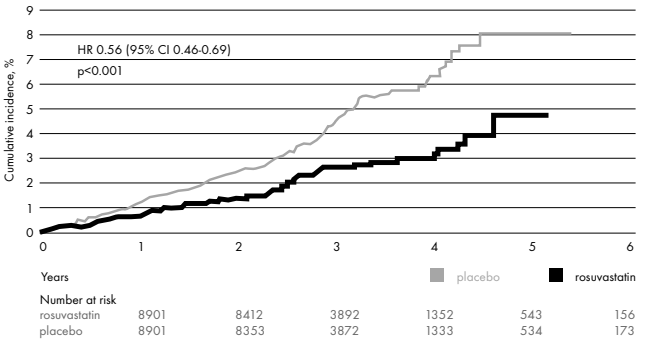
Table 4: Dose Response in Patients with Mild to Moderate Hypercholesterolemia (Mean Percent Change from Baseline)

CRESTOR dose (mg/day)	N	Total-C	LDL-C	TG	HDL-C	Total-C/ HDL-C ratio	ApoB
Placebo	13	-5	-7	-3	3	-8	-3
5	17	-33	-45	-35	13	-41	-38
10	17	-36	-52	-10	14	-43	-42
20	17	-40	-55	-23	8	-44	-46
40	18	-46	-63	-28	10	-51	-54

Prevention of Major Cardiovascular Events

In the JUPITER study (**J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin), 89,846 people with no pre-existing cardiovascular disease were screened and 17,802 (19.8%) were double-blindly 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.

Figure 1: Time to First Occurrence of Major Cardiovascular Events



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 death 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)

	CRESTOR (N=8901) n (%)	Placebo (N=8901) n (%)	Relative risk reduction† (95% CI)	Absolute risk reduction (%)	1.9-year NNT
PRIMARY (composite) ENDPOINT	142 (1.6)	252 (2.83)	44% (31, 54)	1.23	81
COMPONENTS OF PRIMARY ENDPOINT					
Cardiovascular death*	29 (0.33)	37 (0.42)	22% (-27, 52)	0.09	1112
Nonfatal stroke	30 (0.34)	57 (0.64)	48% (18, 66)	0.30	329
Nonfatal MI	21 (0.24)	61 (0.69)	66% (44, 79)	0.45	222
Unstable angina	15 (0.17)	27 (0.30)	45% (-4, 71)	0.13	741
Arterial revascularization	47 (0.53)	70 (0.79)	33% (3, 54)	0.26	387

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

†Negative numbers imply a risk increase.

CI: confidence interval, ITT: intent-to-treat, MI: myocardial infarction, NNT: number needed to treat

SYMPTOMS AND TREATMENT OF OVERDOSE: There is no specific treatment in the event of overdosage. Should an overdose occur, the patient should be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance clearance of rosuvastatin.

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

Product Monograph available on request.

AstraZeneca

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Mississauga, Ontario L4Y 1M4
www.astrazeneca.ca

Fragmin®

dalteparin sodium

Anticoagulant/Antithrombotic agent

Prescribing Summary

Patient Selection Criteria

INDICATIONS AND CLINICAL USE

PrFRAGMIN® (dalteparin sodium injection) is indicated for:

- Thromboprophylaxis in conjunction with surgery.
- Treatment of acute deep venous thrombosis.
- Unstable coronary artery disease (UCAD), i.e., unstable angina and non-Q-wave myocardial infarction.
- Prevention of clotting in the extracorporeal system during hemodialysis and hemofiltration in connection with acute renal failure or chronic renal insufficiency.
- Extended treatment of symptomatic venous thromboembolism to prevent recurrence of venous thromboembolism in patients with cancer.
- Reduction of deep vein thrombosis (DVT) in hospitalized patients with severely restricted mobility during acute illness. Decreased mortality due to thromboembolic events and complications has not been demonstrated.

CONTRAINDICATIONS

FRAGMIN should not be used in patients who have the following:

- Hypersensitivity to FRAGMIN or any of its constituents, including benzyl alcohol (when using the 25,000 IU multi-dose vial) (see **WARNINGS AND PRECAUTIONS, SPECIAL POPULATIONS, Pregnant Women**), or to other low molecular weight heparins and/or heparin or pork products
- History of confirmed or suspected immunologically-mediated heparin-induced thrombocytopenia (delayed-onset severe thrombocytopenia), and/or in patients in whom an *in vitro* platelet-aggregation test in the presence of FRAGMIN is positive
- Septic endocarditis (endocarditis lenta, subacute endocarditis)
- Uncontrollable active bleeding
- Major blood-clotting disorders
- Acute gastroduodenal ulcer
- Cerebral hemorrhage
- Severe uncontrolled hypertension
- Diabetic or hemorrhagic retinopathy
- Other conditions or diseases involving an increased risk of hemorrhage
- Injuries to and operations on the central nervous system, eyes and ears
- Spinal/epidural anesthesia is contraindicated where repeated high doses of FRAGMIN (100-120 IU/kg given twice daily or 200 IU/kg once daily) are required, due to an increased risk of bleeding

SPECIAL POPULATIONS

Pregnant Women:

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Cases of Gasping Syndrome have been reported in neonates when benzyl alcohol has been administered in amounts of 99-404 mg/kg/day. Manifestations of the disease include: metabolic acidosis, respiratory distress, gasping respirations, central nervous system dysfunction, convulsions, intracranial hemorrhages, hypoactivity, hypotonia, cardiovascular collapse and death. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women.

There are also postmarketing reports of prosthetic valve thrombosis in pregnant women with prosthetic heart valves while receiving low molecular weight heparins for thromboprophylaxis. These events led to maternal death or surgical interventions.

Pregnant women with prosthetic heart valves appear to be at exceedingly high risk of thromboembolism. An incidence of thromboembolism approaching 30% has been reported in these patients, in some cases even with apparent adequate anticoagulation at treatment doses of low molecular weight heparins or unfractionated heparin. Any attempt to anticoagulate such patients should normally only be undertaken by medical practitioners with documented expertise and experience in this clinical area.

Teratogenic Effects: As with other low molecular weight heparins (LMWH), FRAGMIN should not be used in pregnant women unless the therapeutic benefits to the patients outweigh the possible risks. There have been reports of congenital anomalies in infants born to women who received LMWHs during pregnancy, including cerebral anomalies, limb anomalies, hypospadias, peripheral vascular malformation, fibrotic dysplasia and cardiac defects. A causal relationship has not been established nor has the incidence been shown to be higher than in the general population.

Non-teratogenic Effects: There have been postmarketing reports of fetal death when pregnant women received low molecular weight heparins. Causality for these cases has not been established. Pregnant women receiving anticoagulants, including FRAGMIN, are at increased risk for bleeding. Hemorrhage can occur at any site and may lead to death of mother and/or fetus. Pregnant women receiving FRAGMIN should be carefully monitored. Pregnant women and women of child-bearing potential should be informed of the potential hazard to the fetus and the mother if FRAGMIN is administered during pregnancy.

Nursing Women:

It is not known whether FRAGMIN is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FRAGMIN is administered to nursing women.

Pediatrics:

The safety and effectiveness of FRAGMIN in children have not been established.

Geriatrics:

Elderly patients receiving low molecular weight heparins are at increased risk of bleeding. Careful attention to dosing intervals and concomitant medications, especially anti-platelet preparations, is advised. Close monitoring of elderly patients with low body weight (e.g., <45 kg) and those predisposed to decreased renal function is recommended.

Patients with Extreme Body Weight:

Safety and efficacy of low molecular weight heparins in high weight (e.g., >120 kg) and low weight (e.g., <46 kg) patients have not been fully determined. Individualized clinical and laboratory monitoring are recommended in these patients.

Safety Information

WARNINGS AND PRECAUTIONS

Special Warnings and Precautions

The multi-dose vial of FRAGMIN (25,000 IU/mL) contains benzyl alcohol (14 mg/mL) as a preservative. Benzyl alcohol has been associated with a potentially fatal "Gasping Syndrome" in neonates. Because benzyl alcohol may cross the placenta, FRAGMIN preserved with benzyl alcohol should not be used in pregnant women (see **Special Populations, Pregnant Women**).

General

FRAGMIN should NOT be administered intra-muscularly.

FRAGMIN CANNOT BE USED INTERCHANGEABLY (UNIT FOR UNIT) WITH UNFRACTIONATED HEPARIN (UFH) OR OTHER LOW MOLECULAR WEIGHT HEPARINS (LMWHs) AS THEY DIFFER IN THEIR MANUFACTURING PROCESS, MOLECULAR WEIGHT DISTRIBUTION, ANTI-Xa AND ANTI-IIa ACTIVITIES, UNITS AND DOSAGES. SPECIAL ATTENTION AND COMPLIANCE WITH INSTRUCTIONS FOR USE OF EACH SPECIFIC PRODUCT ARE REQUIRED DURING ANY CHANGE IN TREATMENT.

Cardiovascular

Use in Patients with Prosthetic Heart Valves: Cases of prosthetic valve thrombosis have been reported in these patients who have received low molecular weight heparins for thromboprophylaxis. Some of these patients were pregnant women in whom thrombosis led to maternal and/or fetal deaths. Pregnant women are at higher risk of thromboembolism (see **WARNINGS AND PRECAUTIONS**, **Patient Selection Critera, SPECIAL POPULATION**, **Pregnant Women**).

Use in Unstable Coronary Artery Disease: When thrombolytic treatment is considered appropriate in patients with unstable angina and non-Q-wave myocardial infarction, concomitant use of an anticoagulant such as FRAGMIN may increase the risk of bleeding.

Gastrointestinal

FRAGMIN should be used with caution in patients with a history of gastrointestinal ulceration.

Hematologic

Hemorrhage: Bleeding may occur in conjunction with unfractionated heparin or low molecular weight heparin use. As with other anticoagulants, FRAGMIN should be used with extreme caution in patients at increased risk of hemorrhage. Bleeding can occur at any site during therapy with FRAGMIN. An unexpected drop in hematocrit or blood pressure should lead to a search for a bleeding site.

Platelets/Thrombocytopenia: Platelet counts should be determined prior to the start of treatment with FRAGMIN and, subsequently, twice weekly for the duration of treatment. Thrombocytopenia of any degree should be monitored closely. Heparin-induced thrombocytopenia can occur with the administration of FRAGMIN. Its incidence is unknown at present.

Caution is recommended when administering FRAGMIN to patients with congenital or drug-induced thrombocytopenia or platelet defects.

During FRAGMIN administration, special caution is necessary in rapidly-developing thrombocytopenia and severe thrombocytopenia (<100 000/μL). A positive or unknown result obtained from *in vitro* tests for antiplatelet antibody in the presence of FRAGMIN or other low molecular weight heparins and/or heparins would contraindicate FRAGMIN.

Hepatic

FRAGMIN should be used with caution in patients with hepatic insufficiency, as these patients may have potentially higher risk of hemorrhage.

Peri-Operative Considerations

Spinal/Epidural Hematomas:

When neuraxial anesthesia (epidural/spinal anesthesia) or spinal puncture is employed, patients anticoagulated or scheduled to be anticoagulated with low molecular weight heparins or heparinoids for prevention of thromboembolic complications are at risk of developing an epidural or spinal hematoma which can result in long-term or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters for administration of analgesia or by the concomitant use of drugs affecting hemostasis such as non steroidal anti-inflammatory drugs (NSAIDs), platelet inhibitors or other anticoagulants. The risk also appears to be increased by traumatic or repeated epidural or spinal puncture.

Patients should be frequently monitored for signs and symptoms of neurological impairment. If neurological compromise is noted, urgent treatment is necessary.

The physician should consider the potential benefit versus risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis (see **CONTRAINDICATIONS** and **ADVERSE REACTIONS**).

When a higher dose (5000 IU s.c.) of FRAGMIN is administered for thromboprophylaxis in conjunction with surgery, no spinal/epidural invasion should be performed for at least 12 hours following the last dose of FRAGMIN and the next dose should be held until at least 12 hours after the anaesthetic procedure. Alternatively, when a lower dose (2500 IU s.c.) of FRAGMIN is administered, the dose can be initiated 1 - 2 hours prior to surgery. FRAGMIN injection should be given after spinal/epidural anaesthesia and only if the anaesthesiologist considers the spinal/epidural puncture as uncomplicated. Indwelling catheters should not be removed or manipulated for at least 10 - 12 hours following the last dose of FRAGMIN.

Use in Knee Surgery: The risk of bleeding in knee surgery patients receiving low molecular weight heparins may be greater than in other orthopedic surgical procedures. It should be noted that hemarthrosis is a serious complication of knee surgery. The frequency of bleeding events observed with FRAGMIN in orthopedic surgery patients is derived from clinical trials in hip replacement surgery patients. The physician should weigh the potential risks with the potential benefits to the patient in determining whether to administer a low molecular weight heparin in this patient population.

Selection of General Surgery Patients: Risk factors associated with postoperative venous thromboembolism following general surgery include history of venous thromboembolism, varicose veins, obesity, heart failure, malignancy, previous long bone fracture of a lower limb, bed rest for more than 5 days prior to surgery, predicted duration of surgery of more than 30 minutes, and age 60 years or above.

Renal

FRAGMIN should be used with caution in patients with renal insufficiency.

Patients with impaired renal function should be carefully monitored because the half-life for anti-Xa activity after administration of low molecular weight heparin may be prolonged in this patient population. Dose reduction should be considered in patients with severe renal impairment.

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinically significant adverse reactions observed with use of FRAGMIN and other low molecular weight heparins include bleeding events and local reactions, with a low incidence of thrombocytopenia and allergic reactions.

Post-Marketing Adverse Reactions

In post-marketing experience, the following undesirable effects have been reported:

Bleeding: Intracranial hemorrhage, gastrointestinal hemorrhage, retroperitoneal hemorrhage have been reported occasionally leading to fatality

Blood and Lymphatic System: thrombocytopenia, thrombocythemia

Skin and Subcutaneous Tissue Disorders: skin necrosis, alopecia, rash

Immune System Disorders: immunologically-mediated heparin-induced thrombocytopenia (type II, with or without associated thrombotic complications), anaphylactic reactions

Injury, Poisoning and Procedural Complications: spinal or epidural hematoma

DRUG INTERACTIONS

Drug-Drug Interactions

FRAGMIN should be used with caution in patients receiving oral anticoagulants, platelet inhibitors, non-steroidal anti-inflammatories and thrombolytic agents because of increased risk of bleeding. Acetylsalicylic acid (ASA), unless contraindicated, is recommended in patients treated for unstable angina or non-Q-wave myocardial infarctions.

Drug-Food Interactions

Interactions with food have not been established.

Drug-herb Interactions
Interactions with herbs have not been established.

Drug-lab tests Interactions
Interactions with lab tests have not been established.

Drug-lifestyle Interactions
Interactions with lifestyle have not been established.

To report an adverse event, please contact: **your physician, pharmacist or Pfizer Medical Information: 1-800-463-6001.**

Administration

DOSAGE AND ADMINISTRATION

FRAGMIN may be given by subcutaneous (s.c.) injection or by intermittent or continuous intravenous (i.v.) infusion, depending upon the circumstances. **FRAGMIN must NOT be administered intramuscularly**. Clinical trials conducted in support of clinical uses outlined below generally used subcutaneous dosing.

Dosing

Thromboprophylaxis in Conjunction with Surgery

The dose of FRAGMIN required for adequate prophylaxis without substantially increasing bleeding risk varies depending on patient risk factors.

General surgery with associated risk of thromboembolic complications: 2500 IU s.c. administered 1 - 2 hours before the operation, and thereafter 2500 IU s.c. each morning until the patient is mobilized, in general 5-7 days or longer.

General surgery associated with other risk factors: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative, 2500 IU s.c. is given 1-2 hours before the operation, with 2500 IU s.c. given again no sooner than 4 hours after surgery, but at least 8 hours after the previous dose, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

Elective hip surgery: 5000 IU s.c. is given the evening before the operation and then 5000 IU s.c. the following evenings. Treatment is continued until the patient is mobilized, in general for 5-7 days or longer.

As an alternative 2500 IU s.c. is given 1-2 hours before the operation and 2500 IU s.c. 4-8 hours after surgery, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer.

The pre-operative dose may be omitted and an initial dose of 2500 IU s.c. administered 4-8 hours after the operation, provided primary hemostasis is obtained. Starting on the day after surgery, 5000 IU s.c. is given each morning, in general for 5-7 days or longer. Omission of the pre-operative dose may reduce risk of peri-operative bleeding, however increased risk of venous thromboembolic events is possible. This option is based on the results of the North American Fragmin Trial (NAFT), which excluded patients at high risk of bleeding, i.e., documented cerebral or gastrointestinal bleeding within 3 months prior to surgery, defective hemostasis, e.g., thrombocytopenia (<100 x 10^9/L), ongoing anticoagulant treatment.

Treatment of Acute Deep Vein Thrombosis

The following dosage is recommended: 200 IU/kg body weight given s.c. once daily. The expected plasma anti-Xa levels during subcutaneous treatment would be <0.3 IU anti-Xa/mL before injection and <1.7 IU anti-Xa/mL 3 - 4 hours after injection. In order to individualize the dose, a functional anti-Xa assay should be performed 3 - 4 hours post-injection. The single daily dose should not exceed 18 000 IU.

The following weight intervals are recommended to be adapted to the single-dose prefilled syringes as in the table below.

Weight (kg)	Dosage (IU)
46-56	10 000
57-68	12 500
69-82	15 000
83 and above	18 000

For patients with increased risk of bleeding, a dose of 100 IU/kg body weight given s.c. twice daily or 100 IU/kg body weight administered over a period of 12 hours as continuous i.v. infusion, can be used . The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.0 IU anti-Xa/mL 3 - 4 hours after injection.

Normally concomitant treatment with vitamin-K antagonists is started immediately. Treatment with FRAGMIN should be continued until the levels of the prothrombin complex factors (FII, FVII, FIX, FX) have decreased to a therapeutic level, in general for approximately 5 days.

Extended Treatment of Symptomatic Venous Thromboembolism (VTE) to Prevent Recurrence of VTE in Patients with Cancer

Month 1: 200 IU/kg body weight given s.c. once daily for the first 30 days of treatment. The total daily dose should not exceed 18,000 IU daily.

Months 2-6: Approximately 150 IU/kg given s.c. once daily using the table shown below.

Weight (kg)	Dosage (IU)
≤56	7 500
57-68	10 000
69-82	12 500
83-98	15 000
≥99	18 000

Dose reductions for chemotherapy-induced thrombocytopenia: In the case of chemotherapy-induced thrombocytopenia with platelet counts <50,000/mm^3, FRAGMIN should be interrupted until the platelet count recovers above 50,000/mm^3. For platelet counts between 50,000 and 100,000/mm^3, FRAGMIN should be reduced by 17% to 33% of the initial dose (allowing for dosage adjustment using the pre-filled syringes), depending on the patient's weight (table below). Once the platelet count recovers to ≥100,000/mm^3, FRAGMIN should be re-instituted at full dose.

Weight (kg)	Scheduled Dose (IU)	Reduced Dose (IU)	Mean Dose Reduction (%)
≤56	7 500	5 000	33
57-68	10 000	7 500	25
69-82	12 500	10 000	20
83-98	15 000	12 500	17
≥99	18 000	15 000	17

Unstable Coronary Artery Disease (Unstable Angina and Non-Q-Wave Myocardial Infarction)

120 IU/kg body weight given s.c. twice daily with a maximum dose of 10 000 IU/12 hours.The expected plasma anti-Xa levels during subcutaneous treatment would be >0.1 IU anti-Xa/mL before injection and <1.6 IU anti-Xa/mL 3 - 4 hours after injection. These levels were obtained from another patient population. Treatment should be continued for up to 6 days. Concomitant therapy with ASA is recommended.

Deep Vein Thrombosis in Hospitalized Patients with Severely-Restricted Mobility

In hospitalized patients with severely-restricted mobility during acute illness, the recommended dose of FRAGMIN is 5000 IU administered by s.c. injection once daily. In clinical trials, the usual duration of administration was 12 to 14 days.

Use in Patients with Renal Impairment

All patients with renal impairment treated with low molecular weight heparins should be monitored carefully.

Administration of low molecular weight heparins to patients with renal impairment has been shown to result in prolongation of anti-Xa activity, especially in those with severe renal impairment (creatinine clearance <30 mL/min), which may lead to an increased risk of bleeding. This effect has not yet been determined for FRAGMIN. Consideration of dosage adjustment in patients with severe renal impairment should be undertaken.

Anticoagulation for Hemodialysis and Hemofiltration

Chronic renal failure, patients with no other known bleeding risk: Hemodialysis and hemofiltration for a maximum of 4 hours: dose as below, or only i.v. bolus injection of 5000 IU. Hemodialysis and hemofiltration for more than 4 hours: i.v. bolus injection of 30 - 40 IU/kg body weight followed by i.v infusion of 10 - 15 IU/kg body weight per hour. This dose normally produces plasma levels lying within the range of 0.5 - 1.0 IU anti-Xa/mL.

Acute renal failure, patients with high bleeding risk: i.v. bolus injection of 5 - 10 IU/kg body weight, followed by i.v. infusion of 4 - 5 IU/kg body weight per hour. Plasma level should lie within the range of 0.2 - 0.4 IU anti-Xa/mL.

Dilution

FRAGMIN solution for injection may be mixed with isotonic sodium chloride or isotonic glucose infusion solutions in glass infusion bottles and plastic containers. *Post-dilution concentration:* 20 IU/mL.

As with all parenteral drug products, intravenous admixtures should be inspected visually for clarity, particulate matter, precipitation, discolouration and leakage prior to administration, whenever solution and container permit.

	1 mL 10 000 IU
Isotonic NaCl Infusion (9 mg/mL)	500 mL
or	
Isotonic Glucose Infusion (50 mg/mL)	500 mL

The infusion rate is 10 mL/hour. The solution should be used within 24 hours.

Study References

Hospitalized patients

1. Leizorovicz A, Cohen A, Turpie A *et al*. for the PREVENT Medical Thromboprophylaxis Study Group. Randomized, placebo-controlled trial of dalteparin for the prevention ofvenous thromboembolism in acutely ill medical patients. *Circulation* 2004;110:874–879.

‡ Multi-centre, randomized, double blind, placebo-controlled trial. N=3681 general, non-surgical medical patients at risk for DVT/PE, including hospitalized medical patients with a projected hospitalization of ≥4 days and ≤3 days of prior immobilization. Patients were randomized to receive either FRAGMIN 5000 IU s.c. or placebo once daily for 14 days and followed for up to 90 days. Primary endpoint was incidence of VTE on day 21; secondary endpoints were all-cause mortality by days 14, 21, and 90; objectively verified symptomatic deep vein thrombosis or asymptomatic proximal deep vein thrombosis at day 21; major and minor bleeding, drug-related allergic reactions, and thrombocytopenia by day 21; and symptomatic venous thromboembolism at day 90.

2. FRAGMIN Product Monograph, Pfizer Canada Inc., July 2009.

3. Geerts W, Bergqvist D, Pineo GF *et al*. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines (8th edition). *Chest* 2008;133:381–453.

4. Drug Coverage.ca: A guide to reimbursement. www.drugcoverage.ca/. Accessed February 23, 2008.

SUPPLEMENTAL PRODUCT INFORMATION

Overdosage

Accidental overdosage following administration of FRAGMIN may lead to hemorrhagic complications. FRAGMIN should be immediately discontinued, at least temporarily, in cases of significant excess dosage. In more serious cases, protamine should be administered.

The anticoagulant effect of FRAGMIN is inhibited by protamine. This effect may be largely neutralized by slow intravenous injection of protamine sulphate. The dose of protamine to be given should be 1 mg protamine per 100 anti-Xa IU of FRAGMIN administered. A second infusion of 0.5 mg protamine per 100 anti-Xa IU of FRAGMIN may be administered if the APTT measured 2 to 4 hours after the first infusion remains prolonged. However, even with higher doses of protamine, the APTT may remain prolonged to a greater extent than usually seen with unfractionated heparin. Anti-Xa activity is never completely neutralized (maximum about 60%).

Particular care should be taken to avoid overdosage with protamine sulphate. Administration of protamine sulphate can cause severe hypotensive and anaphylactoid reactions. Because fatal reactions, often resembling anaphylaxis, have been reported with protamine sulphate, it should be given only when resuscitation equipment and treatment of anaphylactic shock are readily available. Refer to the protamine sulphate Product Monograph for further directions for use.

Product Monograph available on request.

Prescribing Summary

Patient Selection Criteria

INDICATIONS AND CLINICAL USE

Xarelto® (rivaroxaban tablet) is indicated for the prevention of venous thromboembolic events (VTE) in patients who have undergone elective total hip replacement or total knee replacement surgery.

Geriatrics (>65 years of age)

In phase III clinical studies, 53% (n=2,486) of the patients treated with Xarelto® were aged ≥65 years, and 15% (n=694) were aged >75 years (see WARNINGS AND PRECAUTIONS – Geriatrics (>65 Years of Age) and Renal, and DOSAGE AND ADMINISTRATION – Renal Impairment and Geriatrics (>65 years of age)).

Pediatrics (<18 years of age)

The safety and efficacy of Xarelto® have not been established in children less than 18 years of age; therefore, Xarelto® is not recommended in this patient population.

CONTRAINDICATIONS

- Hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk (see WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic)
- Clinically significant active bleeding, including hemorrhagic manifestations and bleeding diathesis
- Lesions at increased risk of clinically significant bleeding, e.g., cerebral infarction (hemorrhagic or ischemic) within the last 6 months, and patients with spontaneous impairment of hemostasis
- Concomitant **systemic** treatment with strong inhibitors of both CYP3A4 and P-gp (see WARNINGS AND PRECAUTIONS – General)
- Pregnancy
- Nursing women
- Hypersensitivity to Xarelto® or to any ingredient in the formulation. (For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING.)

Safety Information

WARNINGS AND PRECAUTIONS

General

The use of Xarelto® is contraindicated in patients receiving concomitant **systemic** treatment with strong inhibitors of both CYP3A4 and P-gp (such as ketoconazole, itraconazole, voriconazole, posaconazole and ritonavir). These drugs may increase Xarelto® plasma concentrations to a clinically relevant degree, which may lead to an increased bleeding risk (see DRUG INTERACTIONS).

Strong CYP3A4 inducers should be administered with caution in combination with Xarelto® (see DRUG INTERACTIONS – Drug-Drug Interactions).

Care should be taken if patients are treated concomitantly with drugs affecting hemostasis such as nonsteroidal anti-inflammatory drugs (NSAIDs) and platelet aggregation inhibitors (see DRUG INTERACTIONS). Coadministration of Xarelto® with other anticoagulants or antithrombotic therapy has not been adequately studied in clinical trials and is not recommended, as it may lead to an increased bleeding risk.

Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.

Cardiovascular

No QTc prolonging effects were observed with Xarelto®.

Hematologic

Hemorrhage

Xarelto®, like other anticoagulants, should be used with caution in patients with an increased bleeding risk such as congenital or acquired bleeding disorders, uncontrolled severe arterial hypertension, vascular retinopathy, or concomitant use of drugs affecting hemostasis.

Due to the pharmacological mode of action, Xarelto® may be associated with an increased risk of occult or overt bleeding which may result in posthemorrhagic anemia. The signs, symptoms, and severity will vary according to the location and degree, or extent, of the bleeding. The possibility of a hemorrhage should be considered in evaluating the condition of any anticoagulated patient. Hemorrhagic complications may present as weakness, asthenia, paleness, dizziness, headache, or unexplained swelling.

Hepatic/Biliary/Pancreatic

Patients with significant hepatic disease (e.g., acute clinical hepatitis, chronic active hepatitis, liver cirrhosis) were excluded from clinical trials. Therefore, Xarelto® is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk.

The limited data available for patients with mild hepatic impairment without coagulopathy indicate that there is no difference in pharmacodynamic response or pharmacokinetics as compared to healthy subjects.

Peri-operative Considerations

Neuraxial (Epidural/Spinal) Anesthesia

When neuraxial (epidural/spinal) anesthesia or spinal puncture is performed, patients treated with antithrombotics for prevention of thromboembolic complications are at risk for developing an epidural or spinal hematoma that may result in long-term neurological injury or permanent paralysis.

The risk of these events is increased by the use of indwelling epidural catheters or the concomitant use of drugs affecting hemostasis. The risk may also be increased by traumatic or repeated epidural or spinal puncture. If traumatic puncture occurs, the administration of Xarelto® should be delayed for 24 hours.

Patients who have undergone epidural puncture and who are receiving Xarelto® should be frequently monitored for signs and symptoms of neurological impairment (e.g., numbness or weakness of the legs, bowel or bladder dysfunction). If neurological deficits are noted, urgent diagnosis and treatment is necessary.

The physician should consider the potential benefit versus the risk before neuraxial intervention in patients anticoagulated or to be anticoagulated for thromboprophylaxis and use Xarelto® only when the benefits clearly outweigh the possible risks. An epidural catheter should not be withdrawn earlier than 18 hours after the last administration of Xarelto®. Xarelto® should be administered not earlier than 6 hours after the removal of the catheter.

Renal

Following oral dosing with Xarelto®, there is a direct relationship between the pharmacodynamic effects and the degree of renal impairment.

There are insufficient safety data in patients with severe renal impairment (CrCl<30 mL/min) as these patients were excluded from pivotal phase III trials. **Therefore, the use of Xarelto® is not recommended in patients with severe renal impairment.** Patients who develop acute renal failure while on Xarelto® should discontinue such treatment. Xarelto® should be used with caution in patients with moderate renal impairment (CrCl 30–49 mL/min) concomitantly receiving other drugs which increase Xarelto® plasma concentrations (see DOSAGE AND ADMINISTRATION – Renal Impairment and DRUG INTERACTIONS – Drug-Drug Interactions).

Physicians should consider the benefit/risk of anticoagulant therapy before administering Xarelto® to patients with moderate renal impairment with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy.

Sensitivity/Resistance

Xarelto® contains lactose. Patients with rare hereditary problems of lactose or galactose intolerance (e.g., the Lapp lactase deficiency or glucose-galactose malabsorption) should not take Xarelto®.

Special Populations

Pregnant Women

No data are available on the use of Xarelto® in pregnant women. Based on animal data, use of Xarelto® is contraindicated throughout pregnancy (see CONTRAINDICATIONS). If Xarelto® is to be used in women of childbearing potential, pregnancy should be avoided.

Nursing Women

No data are available on the use of Xarelto® in nursing mothers. In rats, Xarelto® is secreted into breast milk. Therefore, Xarelto® may only be administered after breastfeeding is discontinued (see CONTRAINDICATIONS).

Pediatrics (<18 Years of Age)

The safety and efficacy of Xarelto® have not been established in children less than 18 years of age; therefore, Xarelto® is not recommended in this patient population.

Geriatrics (>65 Years of Age)

No dose adjustment is required for the elderly (>65 years of age). Increasing age may be associated with declining renal and hepatic function (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS – Renal and Hepatic/Biliary/Pancreatic; and DOSAGE AND ADMINISTRATION – Renal Impairment and Hepatic Impairment). Physicians should take into consideration that elderly patients exhibited higher plasma concentrations than younger patients with mean AUC values being approximately 1.5-fold higher, mainly due to reduced (apparent) total and renal clearance.

Monitoring and Laboratory Tests

Prothrombin and Activated Partial Thromboplastin Time

Xarelto®, at recommended doses, prolongs several global (prothrombin time, activated partial thromboplastin time, HepTest®) and specific (inhibition of factor Xa activity) clotting tests. Prothrombin time (PT) is influenced by Xarelto® in a dose-dependent way if Neoplastin® is used for the assay. In patients undergoing elective total hip replacement or total knee replacement surgery, the 5/95 percentiles for PT (Neoplastin®) 2 to 4 hours after tablet intake (ie., at the time of maximum effect) ranged from 13 to 25 sec. In case of excessive doses, the PT is expected to be outside of this range. Although the activated partial thromboplastin time (aPTT) and HepTest® are also both prolonged dose-dependently, neither test is recommended for the assessment of the pharmacodynamic effects of Xarelto®. Similarly, antifactor Xa activity, as well as inhibition of factor Xa activity, are influenced by Xarelto® but, as for aPTT and HepTest®, neither test is recommended to follow the effects of Xarelto®.

Hemoglobin

Any unexplained fall in hemoglobin or blood pressure should lead to a search for a bleeding site.

Reporting Suspected Side Effects

To monitor drug safety, Health Canada through the Canada Vigilance Program collects information on serious and unexpected effects of drugs. If you suspect you have had a serious or unexpected reaction to this drug you may notify Canada Vigilance by:
Toll-free telephone: 866-234-2345
Toll-free fax: 866-678-6789
Online: www.healthcanada.gc.ca/medeffect
By email: CanadaVigilance@hc-sc.gc.ca

Administration

DOSAGE AND ADMINISTRATION

Recommended Dose and Dosage Adjustment

The recommended dose of Xarelto® for VTE prevention in patients following elective total hip replacement or elective total knee replacement surgery is one tablet (10 mg) once daily (see also Special Populations below). Xarelto® may be taken with or without food. The initial dose should be taken within 6 to 10 hours after surgery provided that hemostasis has been established. If hemostasis is not established, treatment should be delayed.

The duration of treatment depends on the type of surgery:

- After elective total hip replacement surgery, patients should be treated for 35 days.
- After elective total knee replacement surgery, patients should be treated for 14 days.

Special Populations

Hepatic Impairment

Xarelto® is contraindicated in patients with hepatic disease (including Child-Pugh Class B and C) associated with coagulopathy and a clinically relevant bleeding risk.

The limited clinical data for patients with moderate hepatic impairment indicate a significant increase in the pharmacological activity. No clinical data are available for patients with severe hepatic impairment (see CONTRAINDICATIONS; and WARNINGS AND PRECAUTIONS – Hepatic/Biliary/Pancreatic).

The limited data available for patients with mild hepatic impairment without coagulopathy indicate that there is no difference in pharmacodynamic response or pharmacokinetics as compared to healthy subjects.

Renal Impairment

The use of Xarelto® is not recommended in patients with severe renal impairment. Patients who develop acute renal failure while on Xarelto® should discontinue such treatment.

Xarelto® should be used with caution in patients with **moderate** renal impairment (CrCl 30–49 mL/min) concomitantly receiving other medicinal products which increase Xarelto® plasma concentrations (see WARNINGS AND PRECAUTIONS – Renal and DRUG INTERACTIONS – Drug-Drug Interactions).

Physicians should consider the benefit/risk of anticoagulant therapy before administering Xarelto® to patients with moderate renal impairment with a creatinine clearance close to the severe renal impairment category (CrCl <30 mL/min) or with a potential to have deterioration of renal function during therapy. Consideration should be given to follow the renal function in these patients.

Sex, Ethnicity, or Body Weight

Body Weight: The exposure of 10 mg Xarelto® in the extreme underweight group (<50 kg) resulted in a larger C_{max} by 24%, as compared to the normal subjects. The maximal effect of PT prolongation was approximately 20% higher at lower body weight. In overweight subjects with body weight higher than 120 kg, the PT maximal prolongation was less pronounced.

Sex: Sex effect was not observed.

Ethnicity: Ethnicity effect was not observed.

Pediatrics (<18 years of age)

The safety and efficacy of Xarelto® have not been established in children less than 18 years of age; therefore, Xarelto® is not recommended in this patient population.

Geriatrics (>65 years of age)

No dose adjustment is required for the elderly (>65 years of age). Increasing age may be associated with declining renal and/or liver function (see CONTRAINDICATIONS; WARNINGS AND PRECAUTIONS – Renal and Hepatic/Biliary/Pancreatic; and DOSAGE AND ADMINISTRATION – Renal Impairment and Hepatic Impairment).

Missed Dose

If a dose is missed, the patient should take Xarelto® immediately and continue on the following day with the once daily intake as before. A double dose should not be taken to make up for a forgotten tablet.

OVERDOSAGE

Overdose following administration of Xarelto® may lead to hemorrhagic complications due to its pharmacodynamic properties.

The use of activated charcoal to reduce absorption in case of Xarelto® overdose may be considered. Administration of activated charcoal up to 8 hours after overdose may reduce the absorption of Xarelto®.

Due to the high plasma protein binding, Xarelto® is not expected to be removed by dialysis.

Should bleeding occur, management of the hemorrhage may include the following steps:

Delay of next Xarelto® administration or discontinuation of treatment as appropriate. Xarelto® has a half-life of approximately 5 to 13 hours.

Appropriate symptomatic treatment, e.g., mechanical compression (e.g., for severe epistaxis), surgical interventions, fluid replacement and hemodynamic support, blood product or component transfusion should be considered.

If bleeding cannot be controlled by the above measures, consider administration of one of the following procoagulants:

- activated prothrombin complex concentrate (APCC)

- prothrombin complex concentrate (PCC)
- recombinant factor VIIa (rFVIIa)

However, there is currently no experience with the use of these products in individuals receiving Xarelto®.

Protamine sulfate and vitamin K are not expected to affect the anticoagulant activity of Xarelto®. There is no scientific rationale for benefit or experience with systemic hemostatics (e.g., desmopressin, aprotinin, tranexamic acid, aminocaproic acid) in individuals receiving Xarelto®.

DOSAGE FORMS, COMPOSITION AND PACKAGING

Excipients: Cellulose microcrystalline, croscarmellose sodium, hypromellose 5 cP, lactose monohydrate, magnesium stearate, sodium lauryl sulfate.

Film-coating: Ferric oxide red, hypromellose 15 cP, polyethylene glycol, titanium dioxide. Film-coated, round, biconvex, light red immediate release tablets of 6 mm diameter for oral use. Each tablet has the Bayer Cross on one side and 10 and a triangle on the other side. Xarelto® tablets are supplied in HDPE bottles of 50.

Study References

Xarelto® Product Monograph, Bayer Inc., 2008.

Supplemental Product Information

ADVERSE REACTIONS

Adverse Drug Reaction Overview

The safety of Xarelto® 10 mg has been evaluated in three randomized, double-blind, active-control phase III studies (RECORD 1, RECORD 2, and RECORD 3). In the phase III studies, 4,657 patients undergoing total hip replacement or total knee replacement surgery were randomized to Xarelto®, with 4,571 patients actually receiving Xarelto®.

In RECORD 1 and 2, a total of 2,209 and 1,228 THR patients, respectively, were randomized to Xarelto® 10 mg OD. In RECORD 1, the treatment period for both groups was 35±4 days postoperatively. In RECORD 2, patients randomized to Xarelto® were treated for 35±4 days postoperatively, and patients randomized to enoxaparin received placebo after day 12±2 until day 35±4 postoperatively. In RECORD 3, a total of 1,220 TKR patients were randomized to Xarelto® 10 mg OD, and both groups received study drug until day 12±2 postoperatively.

The safety profile of Xarelto® with regard to adverse events (AE) and serious adverse events (SAE) is similar to that of the active comparator in the RECORD 1, 2, and 3 studies.

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions, the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the 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.

The database of RECORD 1, 2, and 3 comprised 4,657 patients randomized to treatment with Xarelto® 10 mg OD and 4,692 patients randomized to enoxaparin 40 mg OD. Analysis of this pooled database showed that there was no statistically significant difference in bleeding (P>0.05) between Xarelto® and the active comparator (see Table 1).

Table 1 – RECORD 1, 2, and 3 – Treatment-Emergent Bleeding Events[a] (Safety Population with Central Adjudication) in Patients Randomized to Xarelto® (First Dose 6 to 8 Hours Postoperatively) or Enoxaparin (First Dose 12 Hours Preoperatively)

		Major Bleeding[b] n (%)	Major Bleeding Including Surgical Site Bleeding Events Associated With Hemoglobin Drops or Transfusions[c] n (%)	Any Bleeding (Major or Nonmajor)[d] n (%)
RECORD 1 (THR)	Xarelto® (N=2,209) 10 mg OD PO for 35±4 days	6 (0.3)	40 (1.8)	133 (6.0)
	Enoxaparin (N=2,224) 40 mg OD SC for 36±4 days	2 (0.1)	33 (1.5)	131 (5.9)
	P-value[e]	0.18	0.41	0.90
RECORD 2 (THR)	Xarelto® (N=1,228) 10 mg OD PO for 35±4 days	1(0.1)	23 (1.9)	81 (6.6)
	Enoxaparin (N=1,229) 40 mg OD SC for 12±2 days	1 (0.1)	19 (1.6)	68 (5.5)
	P-value[e]	1.00	0.54	0.27
RECORD 3 (TKR)	Xarelto® (N=1,220) 10 mg OD PO for 12±2 days	7 (0.6)	21 (1.7)	60 (4.9)
	Enoxaparin (N=1,239) 40 mg OD SC for 13±2 days	6 (0.5)	17 (1.4)	60 (4.8)
	P-value[e]	0.79	0.52	1.00
Pooled Analysis[f] (RECORD 1, 2, 3)	Xarelto® (N=4,657)	14 (0.3)	84 (1.8)	274 (5.9)
	Enoxaparin (N=4,692)	9 (0.2)	69 (1.5)	259 (5.5)
	P-value[e]	0.31	0.22	0.48

a Starts with administration of the first (placebo) tablet or (placebo) injection. Active Xarelto® treatment started after surgery. Active enoxaparin treatment started on the day before surgery.

b Major bleeding events included: (1) fatal, (2) bleeding into a critical organ (e.g., retroperitoneal, intracranial, intraocular or intraspinal bleeding/hemorrhagic puncture), (3) bleeding requiring reoperation, (4) clinically overt extra-surgical site bleeding associated with ≥2g/dL fall in hemoglobin or leading to infusion of ≥2 units of whole blood or packed cells.

c Surgical-site bleeding events associated with a decrease in hemoglobin were based on a determination by the investigator. Surgical-site bleeding events requiring transfusion were based on an algorithmic assessment of blood transfusions given within 48 hours of the bleeding event. In addition, both types of surgical-site bleeding events must have been based on bleeding events confirmed by the adjudication committee and reported as overt surgical-site bleeding events by the investigator.

d Nonmajor bleeding events were bleeding events that did not fulfill the criteria of major bleeding.

e P value calculated as Fishers two-sided exact test

f Note that the pooling was done despite the shorter duration of therapy with enoxaparin in RECORD 2

OD = once daily
PO = oral
SC = subcutaneous

Due to the pharmacological mode of action, Xarelto® may be associated with an increased risk of occult or overt bleeding which may result in posthemorrhagic anemia (see WARNINGS AND PRECAUTIONS – Hematologic).

The most common treatment-emergent adverse events reported by patients valid for safety analysis in the 3 phase III studies are presented in Table 2.

Table 2 – Treatment-Emergent Drug-Related Adverse Events Occurring in >1% of Any Treatment Group – Pooled Data of RECORD 1, 2, 3 (Patients Valid for Safety Analysis[a])

Medical Entity	Xarelto® (N=4,571)		Enoxaparin (N=4,601)	
	n	(%)	n	(%)
Gastrointestinal disorders				
Nausea	57	(1.25)	70	(1.52)
Injury, poisoning, and procedural complications				
Anemia (including laboratory parameter)	49	(1.07)	51	(1.11)
Post procedural hemorrhage	71	(1.55)	64	(1.39)
Investigations				
Increase in transaminases	91	(1.99)	128	(2.78)
Increase in Gamma-glutamyltransferase	51	(1.12)	72	(1.56)

Note: Incidence = number of events/number at risk, where: number of events = number of patients reporting the event; number at risk = number of patients in reference population. Only treatment emergent adverse events which occurred up to 2 days after the last dose of study medication are included. [a]Started after administration of oral study medication (Xarelto® or matching placebo tablet).

Less Common Clinical Trial Adverse Drug Reactions

Incidence is ≥0.1% to <1% unless specified.

Blood and the Lymphatic System Disorders: thrombocythemia (including platelet count increased)
Cardiac Disorders: tachycardia

Gastrointestinal Disorders: abdominal and gastrointestinal pain (including upper abdominal pain, stomach discomfort), constipation, diarrhea, dry mouth, dyspepsia (including epigastric discomfort), vomiting

General Disorders and Administration Site Conditions: edema peripheral, feeling unwell (including fatigue, asthenia), fever, localized edema

Hepatobiliary Disorders: abnormal hepatic function (≥0.01% to <0.1%)

Immune System Disorders: allergic dermatitis (≥0.01% to <0.1%)

Injury, Poisoning, and Procedural Complications: wound secretion

Investigations: bilirubin conjugated increased (with or without concomitant increase of ALT) (≥0.01% to <0.1%), blood bilirubin increased, increased alkaline phosphatase, increased amylase, increased LDH, increased lipase

Musculoskeletal, Connective Tissue, and Bone Disorders: pain in extremity

Nervous System Disorders: dizziness, headache, syncope (including loss of consciousness)

Renal and Urinary Disorders: renal impairment (including serum creatinine increased, blood urea increased)

Skin and Subcutaneous Tissue Disorders: contusion, pruritus (including rare cases of generalized pruritus), rash, urticaria (including rare cases of generalized urticaria)

Vascular Disorders: gastrointestinal tract hemorrhage (including gingival bleeding, rectal hemorrhage, hematemesis), genital tract hemorrhage (including menorrhagia), hematuria (including blood urine present), hemorrhage (including hematoma and rare cases of muscle hemorrhage), hypotension (including blood pressure decreased, procedural hypotension), nose bleed

In other clinical studies with Xarelto®, single cases of adrenal hemorrhage and conjunctival hemorrhage, and fatal gastrointestinal ulcer hemorrhage were reported; jaundice and hypersensitivity were rare and hemoptysis was uncommon. Intracranial bleeding (especially in patients with arterial hypertension and/or on concomitant antihemostatic agents) which in single cases may be potentially life-threatening has been reported.

Abnormal Hematologic and Clinical Chemistry Findings

The incidence rates of laboratory abnormalities in the Xarelto® and enoxaparin treatment groups were generally similar. In the RECORD 1, 2, and 3 studies, drug-related increases in transaminases were reported in 2.0% of Xarelto®- and 2.8% of enoxaparin-treated patients and drug-related increases in gamma-glutamyltransferase occurred in 1.1% of Xarelto®- and 1.6% of enoxaparin-treated patients.

DRUG INTERACTIONS

Overview

CYP Inhibition: Xarelto® does not inhibit CYP3A4 or any other major CYP isoenzymes.

CYP Induction: Xarelto® does not induce CYP3A4 or any other major CYP isoenzymes.

Drug-Drug Interactions

The use of Xarelto® is contraindicated in patients receiving concomitant systemic treatment with strong inhibitors of both CYP3A4 and P-gp (such as ketoconazole, itraconazole, voriconazole, posaconazole, or ritonavir). These drugs

may increase Xarelto® plasma concentrations to a clinically relevant degree which may lead to an increased bleeding risk (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General). Drugs strongly inhibiting only one of the Xarelto® elimination pathways, either CYP3A4 or P-gp, potentially increase Xarelto® plasma concentrations. The expected increase is considered not clinically relevant.

Table 3 – Established or Potential Drug-Drug Interactions

Concomitant Drug Class: Drug Name	Reference	Effect on Concentration of Xarelto®	Clinical Comment
Azole antimycotic: ketoconazole	CT	↑Xarelto®	Coadministration of Xarelto® with the azole-antimycotic ketoconazole (400 mg OD) a strong CYP3A4 and P-gp inhibitor, led to a 2.6-fold increase in mean Xarelto® steady state AUC and a 1.7-fold increase in mean Xarelto® C_{max}, with significant increases in its pharmacodynamic effects. The use of Xarelto® is contraindicated in patients receiving systemic treatment with ketoconazole (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General and Renal).
Protease inhibitor: ritonavir	CT	↑Xarelto®	Coadministration of Xarelto® with the HIV protease inhibitor ritonavir (600 mg BID), a strong CYP3A4 and P-gp inhibitor, led to a 2.5-fold increase in mean Xarelto® AUC and a 1.6-fold increase in mean Xarelto® C_{max}, with significant increases in its pharmacodynamic effects. The use of Xarelto® is contraindicated in patients receiving systemic treatment with ritonavir (see CONTRAINDICATIONS and WARNINGS AND PRECAUTIONS – General and Renal).
Anti-infectives: erythromycin	CT	↑Xarelto®	Erythromycin (500 mg TID), which inhibits CYP3A4 and P-gp moderately, led to a 1.3-fold increase in mean Xarelto® AUC and C_{max}. This increase is within the magnitude of the normal variability of AUC and C_{max} and is considered not clinically relevant.
rifampicin	CT	↓Xarelto®	Coadministration of Xarelto® with the strong CYP3A4 and P-gp inducer rifampicin led to an approximate 50% decrease in mean Xarelto® AUC, with parallel decreases in its pharmacodynamic effects. Strong CYP3A4 inducers should be administered with caution in combination with Xarelto®.
Antithrombotic: enoxaparin	CT	No effect on Xarelto®	After combined administration of enoxaparin (40 mg single dose) with Xarelto® (10 mg single dose), an additive effect on antifactor Xa activity was observed, without any additional effects on clotting tests (PT, aPTT). Enoxaparin did not affect the bioavailability and pharmacokinetics of Xarelto® (see WARNINGS AND PRECAUTIONS - General).
Nonsteroidal Anti-inflammatory Drugs (NSAIDS): naproxen	CT	No effect on Xarelto®	Coadministration with naproxen did not affect Xarelto® bioavailability and pharmacokinetics. No clinically relevant prolongation of bleeding time was observed after concomitant administration of Xarelto® and 500 mg naproxen. Nevertheless there may be individuals with more pronounced pharmacodynamic response (see WARNINGS AND PRECAUTIONS – General).
acetylsalicylic acid (ASA)	CT	No effect on Xarelto®	No clinically significant pharmacokinetic or pharmacodynamic interactions were observed when Xarelto® was coadministered with 500 mg acetylsalicylic acid (see WARNINGS AND PRECAUTIONS - General).
Anticonvulsants: phenytoin carbamazepine phenobarbitone	T	↓Xarelto®	The concomitant use of Xarelto® with strong CYP3A4 inducers (e.g., phenytoin, carbamazepine, or phenobarbitone) may also lead to a decreased Xarelto® plasma concentration. Strong CYP3A4 inducers should be administered with caution in combination with Xarelto®.
Antiplatelet drugs: clopidogrel	CT	No effect on Xarelto®	Clopidogrel (300 mg loading dose followed by 75 mg maintenance dose) did not affect Xarelto® bioavailability and pharmacokinetics, but a relevant increase in bleeding times was observed in a subset of patients which was not correlated to platelet aggregation, P-selectin, or GPIIb/IIIa receptor levels (see WARNINGS AND PRECAUTIONS - General).

Legend: CT=Clinical Trial; T=Theoretical

Interactions Shown Not to Exist: There were no mutual pharmacokinetic interactions between Xarelto® and midazolam (substrate of CYP3A4), digoxin (substrate of P-gp), or atorvastatin (substrate of CYP3A4 and P-gp).

Coadministration of the H_2-receptor antagonist ranitidine, the antacid aluminum hydroxide/magnesium hydroxide, naproxen, clopidogrel or enoxaparin did not affect Xarelto® bioavailability and pharmacokinetics.

Drug-Food Interactions

Xarelto® can be taken with or without food. Grapefruit juice is a moderate CYP3A4 inhibitor. Therefore, increase in Xarelto® exposure upon grapefruit juice consumption is not expected to be clinically relevant.

Drug-Herb Interactions

The concomitant use of Xarelto® with other strong CYP3A4 inducers (e.g., St. John's Wort) may lead to a decreased Xarelto® plasma concentration. Strong CYP3A4 inducers should be administered with caution in combination with Xarelto®.

Drug-Laboratory Interactions

Clotting parameter tests (PT, aPTT, HepTest®) are affected as expected by the mode of action of Xarelto®.

Complete Product Monograph is available upon request.

Pr Januvia®
(sitagliptin phosphate monohydrate)

Pr Janumet™
(sitagliptin phosphate monohydrate and metformin hydrochloride)

This document being a summary, please refer to the respective Product Monographs for complete information regarding JANUVIA®/JANUMET™

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION: Oral Antihyperglycemic Agent. DPP-4 inhibitor. Incretin Enhancer.

INDICATIONS AND CLINICAL USE

Monotherapy

JANUVIA® (sitagliptin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus and for whom metformin is inappropriate due to contraindications or intolerance.

Combination with Metformin

JANUVIA® is indicated in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, plus metformin do not provide adequate glycemic control.

JANUMET™(sitagliptin/metformin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.

Geriatrics (≥65 years of age): JANUVIA®: No dosage adjustment is required based on age however, greater sensitivity of some older individuals cannot be ruled out.

JANUMET™: Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUMET™ should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Pediatrics (<18 years of age): Safety and effectiveness in pediatric patients have not been established; therefore JANUVIA® or JANUMET™ should not be used in this population.

CONTRAINDICATIONS

JANUVIA®: Patients who are hypersensitive to this drug or to any ingredient in the formulation.

JANUMET™: Unstable and/or insulin-dependent (Type I) diabetes mellitus. Acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin. In patients with a history of lactic acidosis, irrespective of precipitating factors. In the presence of renal impairment or when renal function is not known, and also in patients with serum creatine levels above the upper limit of normal range. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥136 µmol/L [males], ≥124 µmol/L [females], or abnormal creatinine clearance (< 60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS AND PRECAUTIONS). In excessive alcohol intake, acute or chronic. In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, JANUMET™ should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia. During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter. In patients suffering from severe dehydration. During pregnancy and breastfeeding. Known hypersensitivity to sitagliptin, metformin or to any ingredient in the formulation

JANUMET™ should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function.

Safety Information

JANUMET™ Serious Warnings and Precautions

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET™ (see Endocrine and Metabolism, Lactic Acidosis section below).
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JANUMET™, since alcohol intake potentiates the effect of metformin on lactate metabolism (see Endocrine and Metabolism, Lactic Acidosis section below).

WARNINGS AND PRECAUTIONS

General

JANUVIA® or JANUMET™ should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis.

Hypersensitivity Reactions

There have been post-marketing reports of serious hypersensitivity reactions in patients treated with sitagliptin (JANUVIA®), one of the components of JANUMET™). These reactions include anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome. Onset of these reactions occurred within the first 3 months after initiation of treatment with sitagliptin, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue sitagliptin, assess for other potential causes for the event, and institute alternative treatment for diabetes (see CONTRAINDICATIONS and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions in the Supplemental Product Information section).

Endocrine and Metabolism

Metformin

Lactic Acidosis: Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET™; when it occurs, it is fatal in approximately 50% of cases. Lactic acidosis may also occur in association with a number of pathophysiologic conditions, including diabetes mellitus, and whenever there is significant tissue hypoperfusion and hypoxemia. Lactic acidosis is characterized by elevated blood lactate levels (>5 mmol/L), decreased blood pH, electrolyte disturbances with an increased anion gap, and an increased lactate/pyruvate ratio. When metformin is implicated as the cause of lactic acidosis, metformin plasma levels >5 µg/mL are generally found.

The reported incidence of lactic acidosis in patients receiving metformin hydrochloride is very low (approximately 0.03 cases/1000 patient-years, with approximately 0.015 fatal cases/1000 patient-years). Reported cases have occurred primarily in diabetic patients with significant renal insufficiency, including both intrinsic renal disease and renal hypoperfusion, often in the setting of multiple concomitant medical/surgical problems and multiple concomitant medications. Patients with congestive heart failure requiring pharmacologic management, in particular those with unstable or acute congestive heart failure who are at risk of hypoperfusion and hypoxemia, are at increased risk of lactic acidosis. In particular, treatment of the elderly should be accompanied by careful monitoring of renal function. Metformin treatment should not be initiated in patients ≥80 years of age unless measurement of creatinine clearance demonstrates that renal function is not reduced, as these patients are more susceptible to developing lactic acidosis. The risk of lactic acidosis increases with the degree of renal dysfunction and the patient's age. The risk of lactic acidosis may, therefore, be significantly decreased by regular monitoring of renal function in patients taking metformin and by use of the minimum effective dose of metformin.

In addition, metformin should be promptly withheld in the presence of any condition associated with hypoxemia, dehydration, or sepsis. Because impaired hepatic function may significantly limit the ability to clear lactate, metformin should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking metformin, since alcohol potentiates the effects of metformin hydrochloride on lactate metabolism. In addition, metformin should be temporarily discontinued prior to any intravascular radiocontrast study and for any surgical procedure.

The onset of lactic acidosis often is subtle, and accompanied only by nonspecific symptoms such as malaise, myalgias, respiratory distress, increasing somnolence, and nonspecific abdominal distress. There may be associated hypothermia, hypotension, and resistant bradyarrhythmias with more marked acidosis. The patient and the patient's physician must be aware of the possible importance of such symptoms and the patient should be instructed to notify the physician immediately if they occur. Metformin should be withdrawn until the situation is clarified. Serum electrolytes, ketones, blood glucose, and if indicated, blood pH, lactate levels, and even blood metformin levels may be useful. Once a patient is stabilized on any dose level of metformin, gastrointestinal symptoms, which are common during initiation of therapy, are unlikely to be drug related. Later occurrence of gastrointestinal symptoms could be due to lactic acidosis or other serious disease.

Levels of fasting venous plasma lactate above the upper limit of normal but less than 5 mmol/L in patients taking metformin do not necessarily indicate impending lactic acidosis and may be explainable by other mechanisms, such as poorly controlled diabetes or obesity, vigorous physical activity, or technical problems in sample handling.

Lactic acidosis should be suspected in any diabetic patient with metabolic acidosis lacking evidence of ketoacidosis (ketonuria and ketonemia).

Lactic acidosis is a medical emergency that must be treated in a hospital setting. In a patient with lactic acidosis who is taking metformin, the drug should be discontinued immediately and general supportive measures promptly instituted. Because metformin hydrochloride is dialyzable (with a clearance of up to 170 mL/min under good hemodynamic conditions),

prompt hemodialysis is recommended to correct the acidosis and remove the accumulated metformin. Such management often results in prompt reversal of symptoms and recovery.

Physicians should instruct their patients to recognize the symptoms which could be a signal of the onset of lactic acidosis. If acidosis of any kind develops, JANUMET™ should be discontinued immediately.

Change in clinical status of previously controlled diabetes patients: A diabetic patient previously well controlled on JANUMET™ who develops laboratory abnormalities or clinical illness (especially vague and poorly defined illness) should be evaluated promptly for evidence of ketoacidosis or lactic acidosis. Evaluation should include serum electrolytes and ketones, blood glucose and, if indicated, blood pH, lactate, pyruvate and metformin levels. If acidosis of either form occurs, JANUMET™ must be stopped immediately and appropriate corrective measures initiated.

Loss of control of blood glucose: When a patient stabilized on any diabetic regimen is exposed to stress such as fever, trauma, infection, or surgery, a temporary loss of glycemic control may occur. At such times, it may be necessary to withhold JANUMET™ and temporarily administer insulin. JANUMET™ may be reinstituted after the acute episode is resolved.

The effectiveness of oral antidiabetic drugs in lowering blood glucose to a targeted level decreases in many patients over a period of time. This phenomenon, which may be due to progression of the underlying disease or to diminished responsiveness to the drug, is known as secondary failure, to distinguish it from primary failure in which the drug is ineffective during initial therapy.

Should secondary failure occur with JANUMET™, therapeutic alternatives should be considered.

Vitamin B_{12} levels: Impairment of Vitamin B_{12} absorption has been reported in some patients. Therefore, measurements of serum Vitamin B_{12} are advisable at least every one to two years in patients on long-term treatment with JANUMET™.

A decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, is observed in approximately 7% of patients receiving metformin in controlled clinical trials of 29 weeks duration. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation. Measurement of hematologic parameters on an annual basis is advised in patients on JANUMET™ and any apparent abnormalities should be appropriately investigated and managed. Certain individuals (those with inadequate Vitamin B_{12} or calcium intake or absorption) appear to be predisposed to developing subnormal Vitamin B_{12} levels.

Hypoglycemia: Hypoglycemia does not occur in patients receiving metformin alone under usual circumstances of use, but could occur when caloric intake is deficient, when strenuous exercise is not compensated by caloric supplementation, or during concomitant use with other glucose-lowering agents (such as sulfonylureas and insulin) or ethanol. Elderly, debilitated, or malnourished patients, and those with adrenal or pituitary insufficiency or alcohol intoxication are particularly susceptible to hypoglycemic effects. Hypoglycemia may be difficult to recognize in the elderly, and in people who are taking ß-adrenergic blocking drugs.

The patients should be warned about driving a vehicle or operating machinery under these conditions where risk of hypoglycemia is present.

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women; therefore, the safety of JANUVIA® or JANUMET™ in pregnant women is not known. JANUVIA® or JANUMET™ are not recommended for use in pregnancy

Nursing Women: In studies performed with sitagliptin and metformin, both sitagliptin and metformin are secreted in the milk of lactating rats. It is not known whether sitagliptin and/or metformin are secreted in human milk. Therefore, JANUVIA® or JANUMET™ should not be used by a woman who is nursing.

Geriatrics (≥65 years of age):

Sitagliptin and Metformin

Because sitagliptin and metformin are substantially excreted by the kidney and because aging can be associated with reduced renal function, JANUVIA® or JANUMET™ should be used with caution as age increases. Care should be taken in dose selection and should be based on careful and regular monitoring of renal function.

Cardiovascular - Patients with Congestive Heart Failure:

Sitagliptin

A limited number of patients with congestive heart failure participated in clinical studies of sitagliptin. In studies of sitagliptin in combination with metformin, patients with congestive heart failure requiring pharmacological therapy or NYHA Class III or IV congestive heart failure were excluded. Patients with Classes I and II were included in small number. Use in this population is not recommended.

Metformin

Hypoxic States: Cardiovascular collapse (shock) from whatever cause, acute congestive heart failure, acute myocardial infarction and other conditions characterized by hypoxemia have been associated with lactic acidosis and may also cause prerenal azotemia. When such events occur in patients on JANUMET™ therapy, the drug should be promptly discontinued.

Hepatic Insufficiency:

Sitagliptin

There are limited clinical experiences in patients with moderate hepatic insufficiency and no clinical experience in patients with severe hepatic insufficiency. Use in patients with severe hepatic insufficiency is not recommended.

Metformin

Since impaired hepatic function has been associated with some cases of lactic acidosis, JANUMET™ should generally be avoided in patients with clinical or laboratory evidence of hepatic disease.

Renal Insufficiency:

Sitagliptin

Clinical study experience with sitagliptin in patients with moderate or severe renal insufficiency including those with ESRD is limited. Use in these patients is not recommended.

Metformin

Metformin is known to be substantially excreted by the kidney, and the risk of metformin accumulation and lactic acidosis increases with the degree of impairment of renal function. Thus, patients with serum creatinine levels above the upper limit of the normal range for their age should not receive JANUMET™. In patients with advanced age, JANUMET™ should be carefully titrated to establish the minimum dose for adequate glycemic effect, because aging is associated with reduced renal function. In elderly patients, particularly those ≥80 years of age, renal function should be monitored regularly.

Before initiation of JANUVIA®/JANUMET™ therapy and every 6 months while on JANUMET™ therapy, renal function should be assessed and verified as being within normal range.

In patients in whom development of renal dysfunction is anticipated, renal function should be assessed more frequently and JANUMET™ discontinued if evidence of renal impairment is present.

Special caution should be exercised in situations where renal function may become impaired, for example when initiating antihypertensive therapy or diuretic therapy and when starting therapy with an NSAID.

Use of concomitant medications that may affect renal function or metformin disposition:

Concomitant medication(s) that may affect renal function or result in significant hemodynamic change or may interfere with the disposition of metformin, such as cationic drugs that are eliminated by renal tubular secretion, should be used with caution.

Radiologic studies involving the use of intravascular iodinated contrast materials (for example, intravenous urogram, intravenous cholangiography, angiography, and computed tomography (CT) scans with intravascular contrast materials): Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin. Therefore, in patients in whom any such study is planned, JANUMET™ should be temporarily discontinued at the time of or prior to the procedure, and withheld for 48 hours subsequent to the procedure and reinstituted only after renal function has been re-evaluated and found to be normal.

Peri-Operative Consideration

Metformin

JANUMET™ therapy should be temporarily suspended for any surgical procedure (except minor procedures not associated with restricted intake of food and fluids). JANUMET™ should be discontinued 2 days before surgical intervention and should not be restarted until the patient's oral intake has resumed and renal function has been evaluated as normal.

Alcohol Intake

Alcohol is known to potentiate the effect of metformin on lactate metabolism. Patients, therefore, should be warned against excessive alcohol intake, acute or chronic, while receiving JANUMET™.

ADVERSE REACTIONS

(see Supplemental Product Information for full listing)

Adverse Drug Reactions Overview

Sitagliptin

Sitagliptin was generally well tolerated in controlled clinical studies as monotherapy and as part of combination therapy with metformin, with the overall incidence of side effects similar to that reported with placebo.

The incidences of serious adverse experiences and discontinuation of therapy due to clinical adverse experiences were also similar to placebo. The most frequent adverse reaction in trials of sitagliptin as monotherapy (placebo-controlled) and as add-on combination therapy with metformin (reported regardless of causality, and more common with sitagliptin than other treatments) was nasopharyngitis.

Metformin

The adverse events most commonly associated with metformin (sitagliptin/metformin) are diarrhea, nausea, and upset stomach. Lactic acidosis is a rare, but serious side effect. Lactic acidosis is fatal in approximately 50% of cases.

Lactic Acidosis: very rare (<1/10, 000 and isolated reports).

Gastrointestinal Reactions: very common: (>1/10) Gastrointestinal symptoms (diarrhea, nausea, vomiting, abdominal bloating, flatulence, and anorexia) are the most common reactions to metformin and are approximately 30% more frequent in patients on metformin monotherapy than in placebo-treated patients, particularly during initiation of metformin therapy. These symptoms are generally transient and resolve spontaneously during continued treatment. Occasionally, temporary dose reduction may be useful.

Because gastrointestinal symptoms during therapy initiation appear to be dose-related, they may be decreased by gradual dose escalation and by having patients take metformin (metformin HCl) with meals.

Because significant diarrhea and/or vomiting can cause dehydration and prerenal azotemia, metformin should be temporarily discontinued, under such circumstances.

For patients who have been stabilized on metformin, nonspecific gastrointestinal symptoms should not be attributed to therapy unless intercurrent illness or lactic acidosis have been excluded.

Special Senses: common (≥1/100): During initiation of metformin therapy complaints of taste disturbance are common, i.e. metallic taste.

Dermatologic Reactions: very rare (<1/10,000 and isolated reports): The incidence of rash/dermatitis in controlled clinical trials was comparable to placebo for metformin monotherapy and to sulfonylurea for metformin /sulfonylurea therapy. Reports of skin reactions such as erythema, pruritus, and urticaria are very rare.

Hematologic: During controlled clinical trials of 29 weeks duration, approximately 9% of patients on metformin monotherapy and 6% of patients on metformin /sulfonylurea therapy developed asymptomatic subnormal serum vitamin B_{12} levels; serum folic acid levels did not decrease significantly. However, only five cases of megaloblastic anemia have been reported with metformin administration (none during U.S. clinical studies) and no increased incidence of neuropathy has been observed.

Decrease of vitamin B_{12} absorption with decrease of serum levels during long-term use of metformin is rare (≥1/10,000 and <1/1,000). Consideration of such aetiology is recommended if a patient presents with megaloblastic anemia.

Hepatic: very rare (<1/10,000 and isolated reports): Liver function tests abnormalities or hepatitis resolving upon metformin discontinuation has been documented in isolated reports.

To report a suspected adverse reaction, please contact Merck Frosst Canada Ltd. by:

Toll-free telephone: 1-800-567-2594
Toll-free fax: 1-877-428-8675
By regular mail:
Merck Frosst Canada Ltd.
P.O. Box 1005
Pointe-Claire – Dorval, QC H9R 4P8

DRUG INTERACTIONS

(see Supplemental Product Information for full listing)

Overview

Sitagliptin and Metformin

Co-administration of multiple doses of sitagliptin (50 mg) and metformin (1000 mg) given twice daily did not meaningfully alter the pharmacokinetics of either sitagliptin or metformin in patients with type 2 diabetes. Pharmacokinetic drug interaction studies with JANUMET™ have not been performed; however, such studies have been conducted with the individual components of JANUMET™ (sitagliptin and metformin).

Sitagliptin is not an inhibitor of CYP isozymes CYP3A4, 2C8, 2C9, 2D6, 1A2, 2C19 or 2B6, and is not an inducer of CYP3A4. Sitagliptin is a p-glycoprotein substrate, but does not inhibit p-glycoprotein mediated transport of digoxin. Based on these results, sitagliptin is considered unlikely to cause interactions with other drugs that utilize these pathways. Sitagliptin is not extensively bound to plasma proteins. Therefore, the propensity of sitagliptin to be involved in clinically meaningful drug-drug interactions mediated by plasma protein binding displacement is very low.

Metformin

The simultaneous administration JANUMET™ and a sulfonylurea could produce a hypoglycemic reaction, especially if they are given in patients already receiving other drugs which, themselves, can potentiate the effect of sulfonylureas. These drugs can be: long-acting sulfonamides, tubercolostatics, phenylbutazone, clofibrate, monoamine oxidase inhibitors, salicylates, probenecid and propanolol.

In healthy volunteers, the pharmacokinetics of propranolol and ibuprofen were not affected by metformin when co-administered in single-dose interaction studies. Metformin is negligibly bound to plasma proteins and is therefore, less likely to interact with highly protein-bound drugs such as salicylates, sulfonamides, chloramphenicol and probenecid.

Drug-Drug Interactions

Sitagliptin

In clinical studies, sitagliptin did not meaningfully alter the pharmacokinetics of metformin, glyburide, simvastatin, rosiglitazone, warfarin, or oral contraceptives, providing *in vivo* evidence of a low propensity for causing drug interactions with substrates of CYP3A4, CYP2C8, CYP2C9, and organic cationic transporter (OCT).

Digoxin: Sitagliptin had a minimal effect on the pharmacokinetics of digoxin. Following administration of 0.25 mg digoxin concomitantly with 100 mg of sitagliptin daily for 10 days, the plasma AUC of digoxin was increased by 11%, and the plasma C_{max} by 18%. These increases are not considered likely to be clinically meaningful. No dosage adjustment of digoxin, or JANUVIA® or JANUMET™ is recommended.

Cyclosporine: A study was conducted to assess the effect of cyclosporine, a potent inhibitor of p-glycoprotein, on the pharmacokinetics of sitagliptin. Coadministration of a single 100-mg oral dose of sitagliptin and a single 600-mg oral dose of cyclosporine increased the AUC and C_{max} of sitagliptin by approximately 29% and 68%, respectively. These modest changes in sitagliptin pharmacokinetics were not considered to be clinically meaningful. The renal clearance of sitagliptin was also not meaningfully altered. Therefore, meaningful interactions would not be expected with other p-glycoprotein inhibitors. No dosage adjustment for JANUVIA® or JANUMET™ is recommended when co-administered with cyclosporine or other p-glycoprotein inhibitors (e.g., ketoconazole).

Metformin

Glyburide: In a single-dose interaction study in type 2 diabetes patients, co-administration of metformin and glyburide did not result in any changes in either metformin pharmacokinetics or pharmacodynamics. Decreases in glyburide AUC and C_{max} were observed, but were highly variable. The clinical significance of this interaction is uncertain.

Furosemide: A single-dose, metformin-furosemide drug interaction study in healthy subjects demonstrated that pharmacokinetic parameters of both compounds were affected by co-administration. Furosemide increased the metformin plasma and blood C_{max} by 22% and blood AUC by 15%, without any significant change in metformin renal clearance. When administered with metformin, the C_{max} and AUC of furosemide were 31% and 12% smaller, respectively, than when administered alone, and the terminal half-life was decreased by 32%, without any significant change in furosemide renal clearance. No information is available about the interaction of metformin and furosemide when co-administered chronically.

Nifedipine: A single-dose, metformin-nifedipine drug interaction study in normal healthy volunteers demonstrated that co-administration of nifedipine increased plasma metformin C_{max} and AUC by 20% and 9%, respectively, and increased the amount excreted in the urine. T_{max} and half-life were unaffected. Nifedipine appears to enhance the absorption of metformin. Metformin had minimal effects on nifedipine.

Cationic drugs: Cationic drugs (e.g., amiloride, digoxin, morphine, procainamide, quinidine, quinine, ranitidine, triamterene, trimethoprim, or vancomycin) that are eliminated by renal tubular secretion theoretically have the potential for interaction with metformin by competing for common renal tubular transport systems. Such interaction between metformin and oral cimetidine has been observed in normal healthy volunteers in both single- and multiple-dose metformin-cimetidine drug interaction studies, with a 60% increase in peak metformin plasma and whole blood concentrations and a 40% increase in plasma and whole blood metformin AUC. There was no change in elimination half-life in the single-dose study. Metformin had no effect on cimetidine pharmacokinetics. Although such interactions remain theoretical (except for cimetidine), careful patient monitoring and dose adjustment of JANUMET™ and/or the interfering drug is recommended in patients who are taking cationic medications that are excreted via the proximal renal tubular secretory system.

Other: Certain drugs tend to produce hyperglycemia and may lead to loss of glycemic control. These drugs include the thiazides and other diuretics, corticosteroids, phenothiazines, thyroid products, estrogens, estrogen plus progestogen, oral contraceptives, phenytoin, nicotinic acid, sympathomimetics, calcium channel blocking drugs, isoniazid and beta-2-agonists. ACE-inhibitors may decrease the blood glucose levels. When such drugs are administered to a patient receiving JANUMET™ the patient should be closely observed to maintain adequate glycemic control.

Elimination rate of the anticoagulant phenprocoumon has been reported to be increased by 20% when used concurrently with metformin. Therefore, patients receiving phenprocoumon or other antivitamin K anticoagulants should be monitored carefully when both types of drugs are used simultaneously. In such cases, an important increase of prothrombin time may occur upon cessation of JANUMET™ therapy, with an increased risk of hemorrhage.

Drug-Food & Drug-Herb Interactions

There are no known interactions with food, and interactions with herbal products have not been established.

Drug-Laboratory Interactions

Intravascular contrast studies with iodinated materials can lead to acute alteration of renal function and have been associated with lactic acidosis in patients receiving metformin.

Drug-Lifestyle Interactions

Sitagliptin and Metformin

JANUMET™ is not expected to affect the ability to drive and use machines under usual circumstances. However, patients should be warned about driving a vehicle or operating machinery under conditions where a risk of hypoglycemia is present.

Metformin

Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JANUMET™, since alcohol intake potentiates the effect of metformin on lactate metabolism.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations:

JANUVIA® (sitagliptin) can be taken with or without food.

JANUMET™ should be given with meals.

Recommended Dose and Dosage Adjustment:

JANUVIA®: The recommended dose of JANUVIA® is 100 mg once daily. No dosage adjustment is necessary

for geriatric patients. Use of JANUVIA® in patients with moderate or severe renal insufficiency, or severe hepatic insufficiency is not recommended. Use of JANUVIA® in pediatric patients younger than 18 years is not recommended.

JANUMET™: The starting dose of JANUMET™ should be based on the patient's current regimen. JANUMET™ should be given twice daily with meals. The following doses are available:

50 mg sitagliptin/500 mg metformin hydrochloride

50 mg sitagliptin/850 mg metformin hydrochloride

50 mg sitagliptin/1000 mg metformin hydrochloride

Patients inadequately controlled on metformin monotherapy: For patients inadequately controlled on metformin alone, the usual starting dose of JANUMET™ should provide sitagliptin dosed as 50 mg twice daily (100 mg total daily dose) plus the dose of metformin already being taken.

Patients switching from co-administration of sitagliptin and metformin: For patients switching from sitagliptin co-administrated with metformin, JANUMET™ may be initiated at the dose of sitagliptin and metformin already being taken.

Patients with Renal Insufficiency: JANUMET™ should not be used in patients with renal failure or renal dysfunction e.g., serum creatinine levels ≥ 136 µmol/L [males], ≥ 124 µmol/L [females] or abnormal creatinine clearance.

Patients with Hepatic Insufficiency: Use of JANUMET™ in patients with severe hepatic insufficiency is not recommended.

Geriatrics: As metformin and sitagliptin are excreted by the kidney, JANUMET™ should be used with caution as age increases. Monitoring of renal function is necessary to aid in prevention of metformin-associated lactic acidosis, particularly in the elderly.

Pediatrics: There are no data available on the use of JANUMET™ in patients younger than 18 years of age. Therefore, use of JANUMET™ in pediatric patients is not recommended.

Missed Dose:

If a dose of JANUVIA® or JANUMET™ is missed, it should be taken as soon as the patient remembers. If he/she does not remember until it is time for the next dose, the missed dose should be skipped and returned to the regular schedule. Two doses of JANUVIA® or JANUMET™ should not be taken at the same time.

OVERDOSAGE

For management of suspected drug overdose, contact your regional Poison Control Center.

Sitagliptin

During controlled clinical trials in healthy subjects, single doses of up to 800 mg sitagliptin were generally well tolerated. Minimal increases in QTc, not considered to be clinically relevant, were observed in one study at a dose of 800 mg sitagliptin.

There is no experience with doses above 800 mg in humans. In phase I multiple-dose studies, there were no dose-related clinical adverse reactions observed with sitagliptin with doses of up to 600 mg per day for 10 days and 400 mg per day for periods of up to 28 days.

In the event of an overdose, it is reasonable to employ the usual supportive measures, e.g., remove unabsorbed material from the gastrointestinal tract, employ clinical monitoring (including obtaining an electrocardiogram), and institute supportive therapy if required.

Sitagliptin is modestly dialyzable. In clinical studies, approximately 13.5% of the dose was removed over a 3- to 4-hour hemodialysis session. Prolonged hemodialysis may be considered if clinically appropriate. It is not known if sitagliptin is dialyzable by peritoneal dialysis.

Metformin

Available information concerning treatment of a massive overdosage of metformin hydrochloride is very limited. It would be expected that adverse reactions of a more intense character including epigastric discomfort, nausea and vomiting followed by diarrhea, drowsiness, weakness, dizziness, malaise and headache might be seen. Should those symptoms persist, lactic acidosis should be excluded. The drug should be discontinued and proper supportive therapy instituted.

Overdose of metformin hydrochloride has occurred, including ingestion of amounts greater than 50 grams. Hypoglycemia was reported in approximately 10% of cases, but no causal association with metformin hydrochloride has been established. Lactic acidosis has been reported in approximately 32% of metformin overdose cases.

Metformin is dialyzable with a clearance of up to 170 mL/min under good hemodynamic conditions. Therefore, hemodialysis may be useful for removal of accumulated drug from patients in whom metformin overdosage is suspected.

Supplemental Product Information

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the 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.

Monotherapy: Two placebo-controlled monotherapy studies, one of 18- and one of 24-week duration, included patients treated with JANUVIA® 100 mg once daily and patients given placebo. The 10 most frequent adverse reactions, reported regardless of causality assessment, in ≥ 1% of patients in these two studies pooled are shown below.

Upper respiratory tract infection 29 (6.5%) vs. 24 (6.6%); Nasopharyngitis 23 (5.2%) vs. 12 (3.3%); Influenza 19 (4.3%) vs. 16 (4.4%); Diarrhea 19 (4.3%) vs. 10 (2.8%); Headache 18 (4.1%) vs. 14 (3.9%); Back pain 14 (3.2%) vs. 12 (3.3%); Constipation 13 (2.9%) vs. 5 (1.4%); Urinary tract infection 8 (1.8%) vs. 9 (2.5%); Cough 8 (1.8%) vs. 10 (2.8%); Hypertension 8 (1.8%) vs. 7 (1.9%).

In a 24-week placebo-controlled double blind clinical study of patients receiving sitagliptin (100 mg daily) as add-on combination therapy with metformin (n=464) vs. placebo and metformin (n=237), the incidence of the 10 most frequent adverse reactions, reported regardless of causality assessment, in ≥1% of patients are shown below.

Upper respiratory tract infection 34 (7.3%) vs. 22 (9.3%); Influenza 19 (4.1%) vs. 12 (5.1%); Nasopharyngitis 19 (4.1%) vs. 7 (3.0%); Back pain 15 (3.2%) vs. 6 (2.5%); Arthralgia 14 (3.0%) vs. 1 (0.4%); Cough 14 (3.0%) vs. 4 (1.7%); Bronchitis 12 (2.6%) vs. 6 (2.5%); Headache 12 (2.6%) vs. 7 (3.0%); Diarrhea 11 (2. 4%) vs. 6 (2.5%); Urinary tract infection 9 (1.9%) vs. 2 (0.8%).

In a pre-specified analysis, the incidence of hypoglycemia in patients treated with sitagliptin plus metformin (1.3%) was similar to patients treated with placebo and metformin (2.1%). The incidence of selected gastrointestinal adverse experiences in patients treated with sitagliptin and metformin was also similar to placebo and metformin.

In pooled studies of up to one year duration which compared sitagliptin added to metformin (n=979) or a sulfonylurea agent (glipizide) (n=748) added to metformin, the 10 most frequent adverse reactions, reported regardless of causality assessment, in ≥1% of patients are shown below.

Upper respiratory tract infection 78 (8.0%) vs. 70 (9.4%); Nasopharyngitis 75 (7.7%) vs. 49 (6.6%); Diarrhea 42 (4.3%) vs. 36 (4.8%); Urinary tract infection 41 (4.2%) vs. 21 (2.8%); Back pain 39 (4.0%) vs. 32 (4.3%); Influenza 35 (3.6%) vs. 32 (4.3%); Arthralgia 34 (3.5%) vs. 29 (3.9%); Headache 34 (3.5%) vs.31 (4.1%); Hypertension 33 (3.4%) vs. 29 (3.9%); Hypoglycemia 32 (3.3%) vs. 217 (29.0%).

For Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <1% (Drug-Related and Greater than Placebo) please refer to the Product Monograph for complete information

In two monotherapy studies, diarrhea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving JANUVIA® 100 mg (1.1%) and greater than in patients receiving placebo (0.3%).

In a combination therapy study with metformin, nausea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving sitagliptin (1.1%) and greater than in patients receiving placebo (0.4%).

Abnormal Hematologic and Clinical Chemistry Findings

Sitagliptin

The incidence of laboratory adverse experiences was similar in patients treated with sitagliptin 100 mg compared to patients treated with placebo. In most clinical studies, a slight decrease in alkaline phosphatase and small increases in uric acid and white blood cell count (due to an increase in neutrophils) were observed. In active comparator studies versus a sulfonylurea agent (glipizide) similar changes were seen in alkaline phosphatase and uric acid.

Metformin

In controlled clinical trials of metformin of 29 weeks duration, a decrease to subnormal levels of previously normal serum Vitamin B_{12} levels, without clinical manifestations, was observed in approximately 7% of patients. Such decrease, possibly due to interference with B_{12} absorption from the B_{12}-intrinsic factor complex, is, however, very rarely associated with anemia and appears to be rapidly reversible with discontinuation of metformin or Vitamin B_{12} supplementation

Post-Marketing Adverse Drug Reactions

The following additional adverse reactions have been identified during post-marketing use of JANUMET™ or sitagliptin, one of the components of JANUMET™. Because these reactions are reported voluntarily from a population of uncertain size, it is generally not possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Hypersensitivity reactions include anaphylaxis, angioedema, rash, urticaria, cutaneous vasculitis and exfoliative skin conditions, including Stevens-Johnson syndrome.

Pancreatitis.

JANUVIA®: last revised: December 14, 2009.
09,12-a_127029

JANUMET™: last revised: September 23, 2009.
09,09-a_123245

Januvia®

(sitagliptin phosphate monohydrate)

Incretin enhancer
Powerful glucose lowering

Recommended as a First-Line Add-On to Metformin[1]

In the CDA 2008 Clinical Practice Guidelines
Please see guidelines for complete recommendations

More than 12 million prescriptions worldwide[2,*]

Now Available

Janumet™

(sitagliptin phosphate monohydrate and metformin hydrochloride)

A powerful course to glucose control.

More than 3.2 million prescriptions worldwide[2,*]

JANUVIA® (sitagliptin) is indicated in combination with metformin in adult patients with type 2 diabetes mellitus to improve glycemic control when diet and exercise, plus metformin do not provide adequate glycemic control.

SELECTED IMPORTANT SAFETY INFORMATION

Post-marketing reports of serious hypersensitivity reactions in patients treated with JANUVIA® included anaphylaxis, angioedema, and exfoliative skin conditions including Stevens-Johnson syndrome.

In controlled clinical trials, JANUVIA® was generally well tolerated as a combination therapy with metformin, with overall incidence of side effects similar to placebo. Discontinuation of therapy due to clinical adverse experiences was similar to placebo. Nasopharyngitis, the most frequently reported adverse event in clinical trials, was reported in 4.1% of patients receiving JANUVIA® (n=464) vs 3.0% of patients receiving placebo (n=237) in a 24-week study. The only drug-related adverse reaction that occurred in ≥1% of patients receiving JANUVIA® and more frequently than in patients receiving placebo was nausea (1.1% vs 0.4%, respectively).

JANUMET™ (sitagliptin/metformin) is indicated as an adjunct to diet and exercise to improve glycemic control in adult patients with type 2 diabetes mellitus inadequately controlled on metformin or in patients already being treated with the combination of sitagliptin and metformin.

SELECTED IMPORTANT SAFETY INFORMATION

- Lactic acidosis is a rare, but serious, metabolic complication that can occur due to metformin accumulation during treatment with JANUMET™
- Patients should be cautioned against excessive alcohol intake, either acute or chronic, when taking JANUMET™, since alcohol intake potentiates the effect of metformin on lactate metabolism.

CONTRAINDICATIONS

Unstable and/or insulin-dependent (Type I) diabetes mellitus; acute or chronic metabolic acidosis, including diabetic ketoacidosis, with or without coma, history of ketoacidosis with or without coma. Diabetic ketoacidosis should be treated with insulin. In patients with a history of lactic acidosis, irrespective of precipitating factors. In the presence of renal impairment or when renal function is not known, and also in patients with serum creatine levels above the upper limit of normal range. Renal disease or renal dysfunction, e.g., as suggested by serum creatinine levels ≥136 µmol/L [males], ≥124 µmol/L [females], or abnormal creatinine clearance (< 60 mL/min), which may also result from conditions such as cardiovascular collapse (shock), acute myocardial infarction, and septicemia (see WARNINGS AND PRECAUTIONS). In excessive alcohol intake, acute or chronic. In patients suffering from severe hepatic dysfunction, since severe hepatic dysfunction has been associated with some cases of lactic acidosis, JANUMET™ should generally be avoided in patients with clinical or laboratory evidence of hepatic disease. In cases of cardiovascular collapse and in disease states associated with hypoxemia such as cardiorespiratory insufficiency, which are often associated with hyperlactacidemia. During stress conditions, such as severe infections, trauma or surgery and the recovery phase thereafter. In patients suffering from severe dehydration. During pregnancy and breastfeeding. Known hypersensitivity to sitagliptin, metformin or to any ingredient in the formulation.

JANUMET™ should be temporarily discontinued in patients undergoing radiologic studies involving intravascular administration of iodinated contrast materials, because the use of such products may result in acute alteration of renal function

BEFORE PRESCRIBING **JANUVIA®** OR **JANUMET™** OR ANY OTHER PRODUCT MENTIONED, PLEASE CONSULT THE APPROPRIATE PRESCRIBING INFORMATION.

PRESCRIBING INFORMATION FOR **JANUVIA®** AND **JANUMET™** ENCLOSED.

For complete details, please refer to the respective product monographs, available for download at www.merckfrosst.ca

*excluding Canada

References: 1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Management of Type 2 Diabetes. Can J Diabetes 2008; 32 (Suppl 1):S53-S61.
2. IMS Health, NPA™ Weekly; week-ending October 20, 2006 through week-ending July 24, 2009.

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See prescribing summary on page 140