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Perioperative Considerations in Kidney Disease
Brian Forzley and William Ghali

Lynch Syndrome
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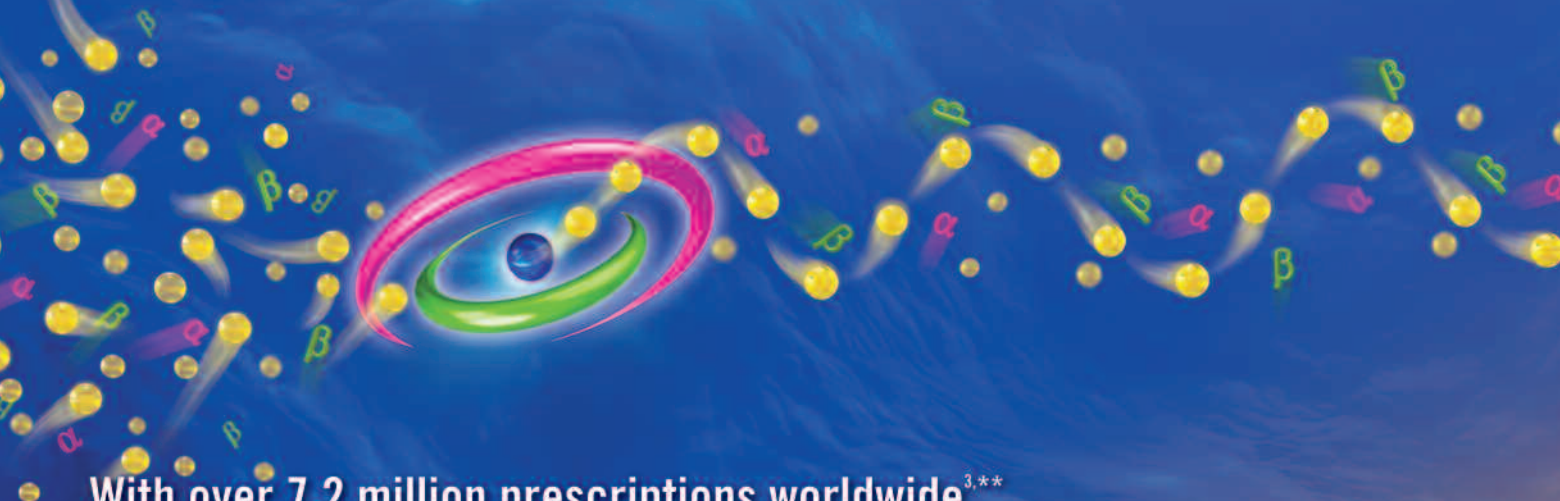

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1. Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. Canadian Diabetes Association 2008 Clinical Practice Guidelines for the Prevention and Management of Diabetes in Canada: Pharmacologic Management of Type 2 Diabetes. Can J Diabetes 2008; 32 (Suppl 1):S53-S61.
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3. IMS Health, NPA™ Weekly; 10-20-08.

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See prescribing summary on page 47.

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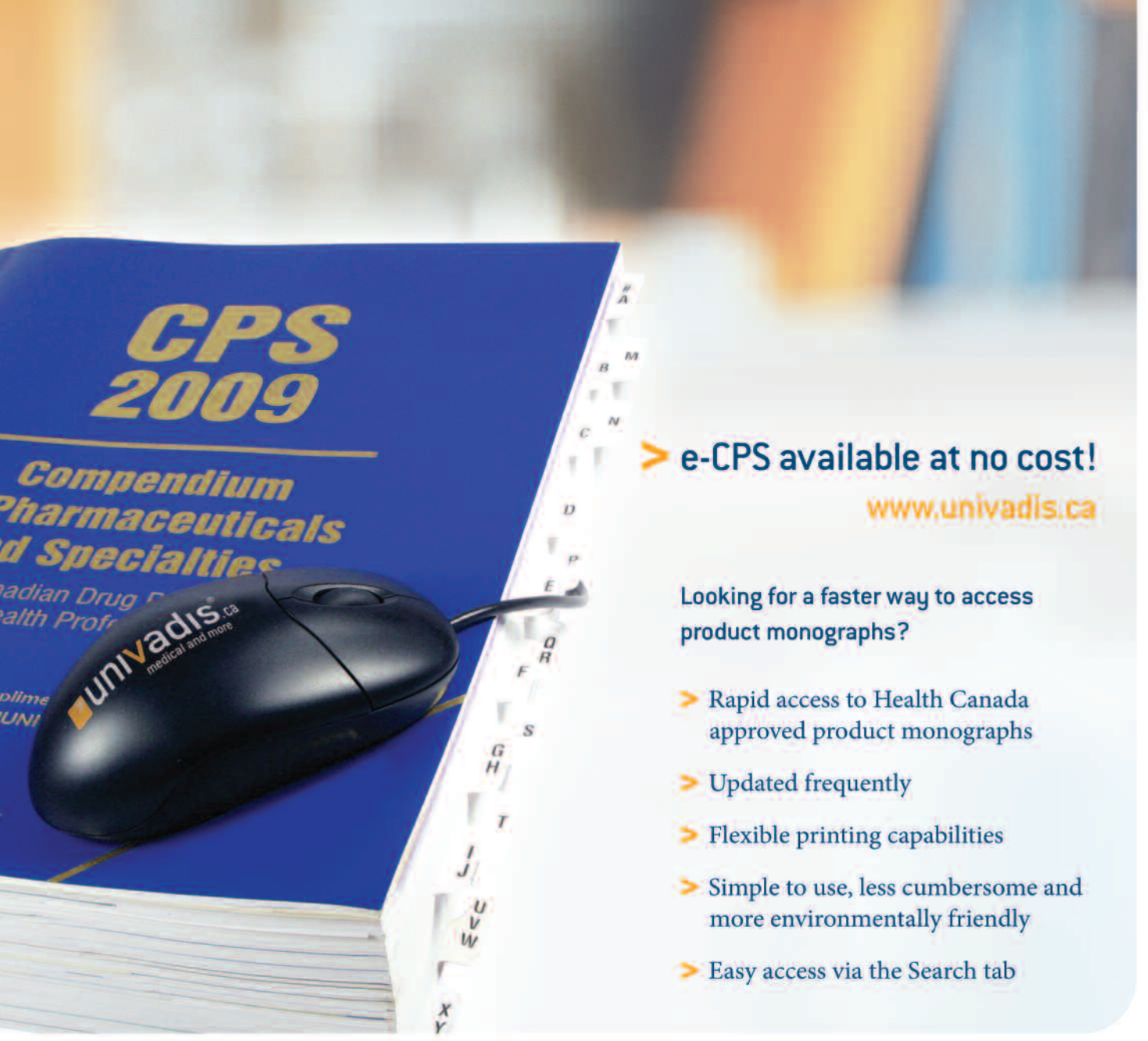
ABOUT THE COVER

The windows of the Royal Bank Plaza in downtown Toronto are covered with 24-karat gold, which makes them ideal mirrors for reflecting the morning sun.

This photo was taken by Robert Wallace. Since retiring from York University in Toronto, where he taught English and drama for 35 years, Robert now devotes much of his free time to photography.



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A Case for Generalism

Bert Govig, MD

About the Author

Bert Govig is with the Department of Internal Medicine at CSSS Les Eskers de L'Abitibi, Amos; is physician in chief with Coalition pour L'Acquisition de Saines Habitudes (CASH); and is with the Department of Internal Medicine at McGill University, Montréal, Québec.

Should every patient with a heart attack be seen by a cardiologist? This is a rhetorical question, and the answer is obvious to most people. What is interesting is that the answer to this question is different depending on where you ask it.

To a cardiologist or health care worker at a university hospital in a large Canadian city, the answer is almost certain to be "yes." Yet, it my town in Northwest Québec, the answer is equally clear. There are no cardiologists here, so general internists are the consultant of choice for heart attack victims. An hour or so away from my place, there are no internists, and acute care is managed by GPs. If you continue further north, you find the same care being administered by some extremely savvy and talented nurses.

I could quote the literature and make a case that one group provides better care than another, but these are divisive, tribalistic, and moot arguments. The reality is, you cannot provide the care if you are not there.

So, why don't we have more cardiologists? This question has been asked before – guess which specialty asks it most often? It is human nature to root for your own team, but clearly the opportunity costs of a having a cardiologist in every hamlet would be unacceptable not only to patients and the health care system, but to cardiologists. Put a cardiologist in a village of 500 people and you will create a bored cardiologist whose skills are on the wane. Put a nurse practitioner in the same setting and you are more likely to match the level of challenge to the skill level of the nurse, and create what social science researcher Mihaly Csikszentmihalyi calls "flow" – an engaged and energized state of heightened concentration and absorption with the task at hand.

To answer the question above in a very personal way, should I get a tight feeling in the chest and my STs go skyward, I will not run looking for a cardiologist. After all, I can read my own ECG. But I will sincerely hope that the person in front of me will be able to get near that state between bored and overwhelmed that is associated with high performance.

All Canadian patients deserve a high performance health care system, and the prescription for that is more complex than just adding more experts who know more about less. It requires that we promote a culture where most health care workers are working near their highest levels of competency – near that state called flow. In a spread out country like Canada, where 30% of the population lives in rural settings, this is the pitch for generalism. An army of subspecialists could never meet the needs of our population without the network of nurses, GPs, pediatricians, and general internists and surgeons (to name but a few) that are the foundation of our health care system.

We need to be promoting generalism throughout the health care system. It is worthwhile to promote the techniques, knowledge, and skill sets that are disease specific, but the crucial investment in health care lies in promoting evidence-based medicine, the maintenance of competence, team building, systems change, health promotion, and the fundamental concepts and principles that underlie all good care.

Why do we get such different answers to the question at the top of this page? Because the respondents genuinely believe that their answer will give the best care to a patient in their setting, and they are probably right. However, you do not judge a health care system by the outcome of the patient that got the best care. You judge a system by the outcomes of all patients. The best outcomes will be achieved when there is the most efficient balance of generalists and subspecialists. Finding that balance point will not be easy, but it seems fairly clear that the pendulum has swung to the extreme of a subspecialty-dominated world. Generalism is back on the rise in Canada, and this is good for both patients and for generalists.

Faces Of Deep Vein Thrombosis...

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

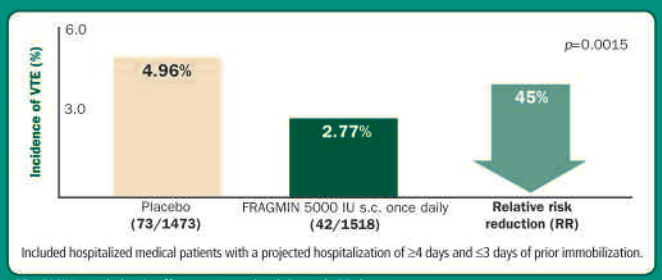
Based on composite patient data. May not be representative of all patients.

FRAGMIN demonstrated a 45% reduction in VTE, including verified DVT.[1,2]

*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).[3] In fact, 50% to 70% of symptomatic VTE occurs among patients who have not undergone surgery.[3]

FRAGMIN Significantly Reduced VTE, Including Verified DVT Compared to Placebo (p=0.0015)[1,2,†,‡]



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[1,2]

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

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

- Study investigators also reported a low incidence of thrombocytopenia with FRAGMIN[2]
- Day 21: Thrombocytopenia 0.54% (10/1848) FRAGMIN vs. 0.44% (8/1833) Placebo

- FRAGMIN offers simple, once daily dosing – 5000 IU s.c. In clinical trials, the usual duration of administration was 12 to 14 days.[2]
- FRAGMIN is eligible for reimbursement under many provincial formularies.[4]

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 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; 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; or 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.

† 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 End Point: 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 and study parameters on page 44.

Plaidoyer en faveur du généralisme

Bert Govig, MD

Au sujet de l'auteur
Bert Govig œuvre au sein du Service de médecine interne au CSSS Les Eskers de l'Abitibi à Amos; il est médecin en chef de la Coalition pour l'acquisition de saines habitudes (CASH); il enseigne au Département de médecine interne de l'Université McGill à Montréal (Québec).

Est-ce que toutes les personnes ayant subi un infarctus du myocarde devraient être prises en charge par un cardiologue? C'est une question de pure forme, et la réponse est évidente pour la plupart des gens. À souligner, cependant, que la réponse varie selon le lieu où la question est posée.

Dans un hôpital universitaire d'une grande ville canadienne, le cardiologue ou le travailleur de la santé répondront sans doute par « oui ». Chez-moi, dans le nord-ouest du Québec, la réponse est tout aussi claire, pourtant elle est différente. Aucun cardiologue n'exerce ici, et ce sont des internistes généralistes qui interviennent à titre de médecins consultants auprès des victimes d'infarctus. À environ une heure d'ici, il n'y a pas d'internistes, et les soins de courte durée sont l'affaire d'omnipraticiens. Plus loin au nord, ces mêmes soins sont dispensés par des infirmières chevronnées et talentueuses. M'appuyant sur la documentation pertinente, je pourrais faire valoir qu'un groupe est mieux qualifié qu'un autre pour prodiguer ces soins, mais la discussion deviendrait vite ségrégationniste et théorique. Force est de constater que vous ne pouvez dispenser des soins si vous n'êtes pas là.

Alors, pourquoi n'y a-t-il pas plus de cardiologues? La question a déjà été posée à maintes reprises – quelle est, selon vous, la spécialité qui la pose le plus souvent? C'est dans l'ordre des choses de mousser sa propre équipe, mais, à l'évidence, le coût d'affectation d'un cardiologue dans chaque hameau de la province serait inacceptable non seulement pour les patients et le système de santé, mais également pour les cardiologues. Que deviendrait un cardiologue dans un village de 500 habitants? Un médecin spécialiste qui s'ennuie ferme et dont les compétences s'émoussent. Remplacez-le par une infirmière praticienne et celle-ci y trouvera des défis à sa mesure, et elle oeuvrera dans ce que le chercheur en sciences sociales Mihaly Csikszentmihalyi appelle un « flot », l'état mental qui naît de l'absorption dans une tâche au point de ne plus sentir le temps passer et qui procure un sentiment d'intense satisfaction.

Si je répondais à la question de mon point de vue bien personnel, je dirais que, advenant que l'étau se resserre dans ma poitrine et que les segments ST de mon ECG fassent des folies, je ne serais pas à la recherche d'un cardiologue. Après tout, je peux interpréter moi-même l'ECG. Mais je souhaiterais de tout cœur que la personne qui prendra soin de moi ne prenne pas mon cas à la légère par ennui, ni ne se sente dépassée, mais fasse preuve de diligence éclairée.

Tous les Canadiens malades méritent des soins de qualité du système de santé, et l'ordonnance à cette fin est bien plus complexe que le seul fait d'ajouter ça et là des experts qui en savent plus sur un moins grand nombre de sujets. Elle devra être axée sur la promotion d'une culture voulant que les travailleurs de la santé tendent vers la mise en application optimale de leurs compétences – dans cet état de « flot » justement. Dans ce pays aux vastes horizons qu'est le Canada, où 30 % de la population habitent dans les régions rurales, c'est le généralisme qui serait propice à une telle culture. Une armée de surspécialistes serait bien incapable de répondre aux besoins de la population s'il n'y avait ce réseau d'infirmières, d'omnipraticiens, de pédiatres, d'internistes généralistes et de chirurgiens, entres autres, qui ensemble forment l'assise du système de santé.

Nous devons promouvoir le généralisme à la grandeur du système de santé. Il est bon de favoriser les techniques, les connaissances et les compétences propres à chacune des maladies, mais l'investissement crucial dans les soins de santé réside dans l'expansion de la médecine factuelle, le maintien des compétences, le travail d'équipe, le changement systémique, la promotion de la santé et le respect des concepts et principes fondamentaux garants de l'excellence dans les soins.

Pourquoi y a-t-il des réponses si différentes à la question qui fait l'objet de mon message. Par ce que les répondants ont l'intime conviction que leur réponse est celle qui offre au patient les meilleurs soins qui soient dans leur milieu, et ils ont probablement raison. Toutefois, un système de santé n'est pas évalué sur la foi de l'état de santé du patient qui a bénéficié des meilleurs soins. Il est jugé en fonction des résultats obtenus chez tous les patients. Ces résultats seront optimaux quand le système sera parvenu au juste équilibre entre les généralistes et les surspécialistes. Y parvenir ne sera pas chose aisée, mais le pendule a certes accompli toute sa course jusqu'à l'extrême d'un système dominé par les surspécialistes. Il redescend maintenant, en faveur du généralisme qui, lui, est en hausse partout au Canada, pour le bien des patients et des généralistes.

Internal Medicine in Mexico

Donald Echenberg, MD

About the Author
Donald Echenberg practices and teaches general internal medicine at the University Hospital in Sherbrooke, Quebec.

PHOTOS COURTESY OF CARMEN PLAMONDON

Last March *l'Association des spécialistes en médecine interne au Québec* (ASMIQ) held their first-ever meeting outside of Quebec. Come with me for a short tour of what we saw, did, and learned in Riviera Maya, Mexico.

First, a few words about ASMIQ. Many of you have already come into contact with this vibrant body of internists during our own CSIM annual meeting in June 2004, held in Quebec City and again in Montreal last October. ASMIQ promotes a general internal medicine (GIM) training program suited to the changing needs of the community; supports its members' professional and scientific needs; and emphasizes the value of internists' cognitive and procedural skills. ASMIQ is incorporated as an association under the law governing the professional unions of Quebec. All general internists in Quebec are ASMIQ members, with fees deducted from annual dues paid to the *Fédération des médecins spécialistes du Québec* (FMSQ). It has 386 members and is probably the best organized provincial group of medical specialists in Canada.

After numerous annual meetings held in all corners of the province, the organizing committee decided to hold the latest meeting in Mexico. In the lush setting of the Yucatan Peninsula of Southern Mexico, 82 attending members were treated to a rich scientific program. There were sessions on obstetrical medicine, tropical medicine, venous thrombosis, coronary disease, perioperative medicine, diabetes, and others. The venue provided members and their families a much-needed break from the severe winter weather that Quebec suffered last year. The timing could not have been better.

One of the high points of the meeting was a session on acute mountain sickness and other high-altitude illnesses, given by Dr. Marc-André Laberge, an internist from the Abitibi region in Quebec. The spectrum of this intriguing syndrome, first recognized over 2,000 years ago, extends from mild symptoms such as headaches, insomnia, and anorexia to severe manifestations such as high-altitude cerebral and pulmonary edema.

Another highlight of the meeting was the chance to hear the presentation of the president of the *Colegio de medicina interna de México* (CMIM), Dr. Heríberto A. Martinez Camacho, and then to chat casually with him on the beach later that afternoon, a beer in hand. We learned that after several decades of national de-emphasis of the importance of general internal medicine skills, a long overdue revival began in 1974, when what is now known as the Mexican College of Internal Medicine was formed with 80 members. There are now 8,307 members, 18% of whom are women.

To be a doctor in Mexico, one must complete medical school and a 1-year hospital internship, and then work for a year in a needy community. To become an internist, one competes for a place in a hospital to practice the specialty and to sit a national examination. In Mexico, it is possible to have "double certification," but this is uncommon.

In Mexico, internists can practise in office or hospital settings. They provide consultant services in the emergency room and the intensive care unit. The domain of a Mexican internist is similar to our own, with an emphasis on diagnostic skills, undifferentiated medical problems, and an interdisciplinary approach to the management of adults with complex medical problems. Dr. Camacho used the metaphors of a warrior against the power of sickness, a multi-faceted diamond.

However, the last lines of his presentation best sum up the Mexican view of internal medicine:

> "When a person works with his hands he is a goldsmith, with his voice he is a singer, with his soul he is a philosopher, with his heart he is a leader, with his strength he is an athlete; but when he works with all this at once … there is no doubt that he is an internist."

ASMIQ is planning its next out-of-province meeting in 2 years. Would you like to join us?

Did you know?

- Although the Fio_2 at altitude remains constant (21%), the partial pressure of oxygen decreases with barometric pressure.
- High-altitude sickness is rare under 2,500 m.
- In La Paz (3,853 m), the Pio_2 at 86.4 mm Hg is the equivalent of breathing 12% oxygen at sea level.
- The highest level of natural human habitation is 5,300 m.

Internal Medicine in Europe

Rosalie-Selene Meunier, MD

About the Author
Rosalie-Selene Meunier is a fifth-year internal medicine resident at Université de Montréal. She plans an academic career in internal medicine.

The 11th annual meeting of the European School of Internal Medicine (ESIM) was held in Estoril, Portugal, from August 31 to September 7, 2008. ESIM is a summer school uniting residents and speakers from different European countries and is a project fully supported by the European Federation of Internal Medicine and each of the national federations. The school first began in Alicante, Spain, and the meeting was held there for 8 consecutive years. It then moved to Portugal under the presidency of Dr. Baptista, with the help of the Portuguese Society of Internal Medicine. The first two meetings held in Portugal were so successful that it was decided to extend his presidency for a third and final term.

For the first time this year, Canada was invited to join 71 other residents from 25 different countries – including the United States, Turkey, and Israel. During the week, one speaker and one resident from each country were invited to give a presentation on various aspects of internal medicine. Time was also spent discussing different aspects of training and practice of internal medicine. For instance, in most of the Scandinavian countries, internal medicine does not exist as an area of practice, but each resident undertaking medical specialty training is required to complete a 5-year program of internal medicine. In the United Kingdom, one field of internal medicine in development is called "acute medicine." Internists are involved as first-line physicians, taking global care of the patient and guiding them through the health care process. These physicians have a practice that, in Canada, would sit somewhere between emergency medicine and intensive care. There is growing interest in this approach, and other European countries have started to implement similar projects.

The program also tackled medical ethics. We discussed interesting topics such as organ transplantation. Different European countries have quite different criteria for organ allocation, making it difficult to for countries to share donor tissues with each other. Another subject that generated very animated debate involved the notion of revealing patients' human immunodeficiency virus status to their relatives for their own health security. While in certain countries confidentiality cannot be breached for any reason, in other countries such disclosure is allowed after a reasonable effort has been made to have the patients do it themselves.

Dr. Linda Snell (McGill University, Montreal) gave an excellent and dynamic talk on improving our teaching skills, in general terms and in our presentations. Other speakers compared European guidelines, which in general were quite similar to ours. Some gave presentations on their area of expertise, sharing their knowledge and experience.

We seized the chance to enjoy our host country, taking a day off to see the sights of Lisbon, searching for wild dolphins by boat, and eating delicious charcoal-broiled fresh fish. We finished our week with a wonderful evening by the seashore, with magnificent fireworks and live music.

The most rewarding aspect of this meeting was the opportunity to make friends and exchange ideas. In a time when we question the future of our health system and the role of internal medicine, I was able to reflect on new ideas and perspectives. The friendships that were made during this week will last a lifetime, and I hope represent the beginning of a collaboration that will strengthen and improve the medicine we practise.

For those of you who would like to read more on the subject, you can consult the official website of ESIM 11 at http://esim.spmi.pt/esim11/index.asp. CSIM has two travel scholarships available for residents interested in attending ESIM. The next meeting will be held in England and will be a fantastic opportunity for residents to share their experiences. I hope that this first year of Canadian participation in ESIM marks the beginning of an enriching tradition.

Perioperative Medical Considerations in Patients with Chronic Kidney Disease

Brian R. Forzley, MD, William A. Ghali, MD

About the Authors

Brian Forzley is an internist and nephrologist, presently working toward a master's degree in Health Services Research at the University of Calgary, Calgary, Alberta. William Ghali is a professor in the Departments of Medicine and Community Health Sciences at the University of Calgary, with interests in health sciences research related to cardiovascular disease. Correspondence may be directed to Brian.Forzley@albertahealthservices.ca.

In 2003, over 1.5 million Canadians underwent nonemergency surgery. The demand may increase as our population ages. Chronic kidney disease (CKD) is an increasingly recognized comorbidity, commonly defined as an estimated creatinine clearance <60 mL/min/1.73 m^2. CKD affects approximately 7% of adults and up to 35% of Canadians over age 60.[1] Internists must be aware of how the medical needs of a surgical patient with CKD may differ from those of other patients. In many of these domains, recently published evidence should inform management decisions. Examples include a recent meta-analysis estimating the perioperative risk of death associated with CKD,[2] and recent randomized controlled trials including Coronary Artery Revascularization Prophylaxis (CARP),[3] Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE),[4] and Perioperative Ischemic Evaluation (POISE),[5] which help clarify the role of medical interventions to reduce cardiovascular (CV) events. Other domains, such as management of uremic bleeding diathesis, may need to become part of the standard knowledge base of the general internist. This narrative review focuses on several elements of the preoperative medical consultation and highlights instances where conventional practice may differ in the surgical patient with CKD.

Cardiac Assessment

Many algorithms that estimate perioperative cardiac risk account for CKD. However, estimation of risk is not synonymous with assessing the need for a revascularization procedure since risk of death or a CV event accrues from lesions other than coronary atherosclerosis. Risk stratification may help us decide whether to postpone or cancel an elective procedure when the risks outweigh the benefits. In contrast, a cardiac assessment may result in an intervention (e.g., medication, angioplasty, cardiac surgery) that reduces the likelihood of an adverse cardiac event with subsequent surgery. Preoperative evaluation for cardiac disease in patients with CKD should proceed with three themes in mind: the spectrum of cardiac disease in CKD, the evidence to support an altered threshold for seeking out modifiable coronary artery disease (CAD), and the role of beta-blockers.

Spectrum of Cardiac Disease in CKD

CV disease is the most frequent cause of death among patients with CKD. Surprisingly, only 10% of deaths in the United States Renal Data System (USRDS) and 4-D study were due to myocardial infarction.[6] Although the prevalence of obstructive CAD in asymptomatic patients may exceed 35%, the majority of deaths in the 4-D study were attributed to cardiac arrest, heart failure, and valvular disease. Left ventricular hypertrophy is observed in up to 72% of adults with CKD[6] and may be responsible for a large number of sudden deaths due to undiagnosed arrhythmias and heart failure. Among CKD patients with angina, 30% of patients had normal coronary arteries,[6] suggesting the presence of underlying microvascular disease (endothelial dysfunction with impaired vessel relaxation, intimal-medial thickening and calcification).[7] As such, the majority of CV events may be due to cardiac disease that cannot be improved with a revascularization procedure.

Estimating Risk

Estimating the postoperative risk of death or a CV event is a key aspect of a medical consult and can guide decisions to postpone or recommend against surgery. Many risk assessment tools account for renal dysfunction. Recently, the adverse impact of CKD on survival after noncardiac surgery was systematically reviewed by Mathew et al.[2] These authors considered a broad range of surgeries and defined CKD as either a serum creatinine >177 µmol/L or an estimated glomerular filtration rate <60 mL/min/1.73 m^2. The pooled probability of death in patients with CKD undergoing surgery was 4.7% (95% CI 1.6–13%), almost triple the mortality of individuals without CKD. This risk persisted after adjusting for comorbidities as well as surgery type. CKD imparts a tangible risk of perioperative death, which should be considered when deciding between surgical and nonsurgical management of patients.

Risk Modification

Recommendations for reducing perioperative CV risk do not differ for patients with CKD. This is due to a lack of CKD-specific data to recommend a different management approach. In this domain, we are not aware of a compelling a priori argument against generalizing results to the CKD population.

Prophylactic preoperative revascularization in patients with stable CAD was addressed by the recent CARP trial,[3] where patients scheduled for peripheral vascular surgery were selectively screened with angiography. Patients found to have CAD amenable to surgical repair were randomized to medical management with or without revascularization; no long-term improvement in mortality was gained by revascularization. The recent COURAGE trial, a nonperioperative trial, provides further insight to this issue. This large, randomized, multicentre study of stable CAD patients (without conventionally operable disease) showed no improvement in mortality or CV events

with the addition of a percutaneous coronary intervention (PCI).[4] This result, together with the need for post-stent antiplatelet therapy, might argue against a lowered threshold for cardiac workup in the preoperative setting.

Perioperative beta-adrenergic blockade remains controversial. The POISE trial investigated whether metoprolol would prevent CV events and death in moderately high-risk patients undergoing noncardiac surgery.[5] The results included a reduction in myocardial infarction but an increase in all-cause mortality by 0.8% ($p = .03$) that appeared to be driven by fatal strokes plausibly related to excess hypotension and bradycardia. In general, the results caution against an overly aggressive beta-blockade strategy in surgical patients. A recent large observational study investigated beta-blockade in patients with CKD undergoing noncardiac surgery and reported a reduced risk of death (HR 0.82, 95% CI 0.71–0.93).[8] This study did not find an excess of hypotension, bradycardia, or stroke. Taken together, a beneficial effect from the conservative use of beta-blockers cannot be excluded and may be appropriate in selected patients. However, a dosing strategy that avoids hypotension and bradycardia is clearly important.

In summary, these studies provide general evidence for the management of CV risk perioperatively. Each of these studies included some patients with CKD, but the studies generally do not provide CKD-specific information to suggest that the management of CKD patients needs to be different than that of other patients, despite the increased CV risk that CKD patients have.

Intravenous Fluids

Patients with CKD have been excluded from the majority of perioperative fluid studies. Studies of healthy volunteers receiving fluid boluses have shown an adverse impact on respiratory function. However, studies employing fluid restriction in patients undergoing bowel preparation for colon surgery have shown preserved blood pressure, heart rate, and renal function. Randomized blinded clinical trials of fluid restriction compared with aggressive fluid support for patients undergoing mainly elective colorectal surgeries generally show either a reduced length of stay or less fluid overload complications, but at the expense of more frequent nausea and pain. Of note, major complication rates correlate positively with patient weight gain.[9] The balance of evidence appears to favour perioperative fluid restriction, which would intuitively hold all the more for patients with oliguric renal failure.

Although seemingly obvious on the surface of things, it is important to explicitly mention that care should be taken in patients with advanced CKD who may require an arteriovenous fistula. Efforts to preserve veins in the fistula arm require that nurses avoid needling the arm that will eventually have a fistula, which is usually the nondominant side.

Pharmacotherapeutic Issues

Patients with CKD have an altered clearance of many medications commonly used in the perioperative setting and may also be predisposed to adverse side effects. Adjusting medications is therefore an important aspect of medical management of the surgical patient with CKD.

Low Molecular Weight Heparin

Deep venous thrombosis (DVT) prophylaxis and bridging anticoagulation are routine aspects of medical management of the surgical patient. Major bleeding associated with low molecular weight heparins (LMWHs) has been reported in patients with CKD. A recent meta-analysis reported a clear excess of bleeding among patients with CKD receiving full anticoagulation from LMWHs compared with unfractionated heparin (UFH).[10] The authors reported on patients receiving an empirical dose adjustment of LMWHs. While harm was not conclusively demonstrated, wide confidence intervals hampered the ability to exclude harm in this subgroup. Studies have shown that the bleeding risk in CKD patients receiving LMWH does not correlate with factor Xa levels. In the absence of a reliable monitoring assay for LMWH efficacy, and given the difficulty of reversing anticoagulation in actively bleeding patients, we recommend the use of an infusion of UFH. The safety and efficacy of LMWH compared with UFH for postoperative DVT prophylaxis has not been tested in a randomized controlled trial. Small uncontrolled studies in critically ill patients suggest this strategy is safe.

Renal Dose Adjustment

The majority of beta-lactam antibiotics (penicillins, cephalosporins, carbapenems), fluoroquinolone antibiotics (levofloxacin, ciprofloxacin), aminoglycoside antibiotics (gentamicin, tobramycin), and vancomycin require dose adjustment for patients with CKD. Other medications commonly used perioperatively, such as H_2 receptor blockers (e.g., ranitidine), narcotics, and digoxin also require empirical dose adjustment. Specific guidance on how to dose adjust each drug is available in various reference manuals.

Avoidance of Nephrotoxins

Clinicians are generally well aware of the adverse effects of nonsteroidal anti-inflammatory drugs (NSAIDs), aminoglycosides, and radiocontrast dye on renal function. Clinicians may be unaware that many patients already on dialysis have residual renal function (RRF), which is a potent predictor of patient survival on dialysis. Since patients are commonly exposed to nephrotoxins perioperatively, it is worth emphasizing that avoiding these substances is equally important for patients on dialysis with RRF.

Bleeding Diathesis

The association between coagulopathy and uremia is well described and even can be observed with mild reductions in renal function. Bleeding risk in patients with CKD is multifactorial and includes alterations in von Willebrand's factor (vWF) binding, a low hematocrit affecting platelet flow and function, and dysfunction of several important cytokines related to the uremic milieu.[11] These aspects of uremic coagulopathy have led to several management strategies that relate to acute management as well as prophylaxis (Table 1).

Management of active bleeding may include the following measures. Desmopressin (DDAVP) binds to V2 receptors on vascular endothelium leading to the release of vWF, permitting platelet binding through IIb/IIIa receptors as well as Ib/IX receptors.[12] The latter receptor is felt to be dysfunctional in uremia. Desmopressin reduces bleeding time within 1 hour and is appropriate in the management of

Table 1. Medical Management of Bleeding Diathesis

Treatment	Dose	Time to Peak Effect	Notes
Desmopressin	0.3 µg/kg IV over 30 minutes	1 hour	Tachyphylaxis
Cryoprecipitate	10 units	4 hours	Caution if oliguria
Estrogen	0.6 mg/kg/d IV, 4 doses	5 days	Males or females
Erythropoietin	50 U/kg SQ/IV given 3x/wk	Weeks	Titrate to hematocrit >30%
Dialysis	By guidelines	Weeks	

acute hemorrhage.[11] Observational studies demonstrate that cryoprecipitate improves bleeding in uremia, presumably by supplying the patient with factor VIII/vWf.[12] Supportive measures, including adequate blood and volume resuscitation, as well as discontinuation of antiplatelet agents and anticoagulants, are also important.

Strategies to prevent bleeding may include the following measures. Erythropoietin is thought to reduce platelet dysfunction by several means. These include alterations in platelet flow due to a restored hematocrit, an increased supply of thromboxane A_2 from erythrocytes, and the generation of new and hemostatically active platelets.[11,12] Several studies, including a randomized clinical trial, support a role for erythropoietin to attain a hematocrit >0.30,[11] which is achieved by the hemoglobin range of 100–120 gm/L recommended by recent Canadian guidelines. Conjugated estrogens act in a multifactorial fashion, with effects on nitric oxide. Bleeding time is reduced at 6 hours using intravenous preparations, but the peak effect on bleeding time takes up to 1 week.[12] As such, estrogen is less useful for acute hemorrhage. Finally, several studies support the importance of adequate dialysis to avoid uremic platelet dysfunction.[11] However, no data exist to support intervening with dialysis for renal failure to avoid bleeding complications in patients who would otherwise not require dialysis.

Conclusion

General internists, nephrologists, anesthesiologists, and surgeons can expect CKD and the medical management of the surgical patient to intersect with increasing frequency. Therefore, medical issues unique to this patient population (Table 2) must become part of the working knowledge base of all physicians who care for surgical patients. Attention to these aspects will help optimize outcomes in this complex and growing patient population.

Table 2. Summary of a Medical Consult on a Surgical Patient with CKD

1. Nonsurgical management should be carefully considered where possible as the presence of chronic kidney disease (CKD) imparts a threefold higher rate of perioperative death (4.7%).
2. Assessment of coronary artery disease (CAD) should probably not differ from that in patients without CKD and may include a cautious use of beta-blockers in selected patients. It does not indicate a lower threshold to obtain an angiogram with a view to revascularization prior to surgery.
3. Fluid restriction on balance likely benefits the patient and should be prescribed for the oliguric patient with renal failure.
4. Assessing medication doses, in light of reduced renal clearance, and avoiding nephrotoxins remain important in the patient on dialysis. A preference for unfractionated heparin is reasonable for most anticoagulant needs.
5. Acute bleeding can be managed with desmopressin or cryoprecipitate, in addition to blood transfusion and discontinuation of antiplatelet agents and anticoagulants.

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Lynch Syndrome

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Case

A colonoscopy on your 38-year-old male patient identifies an adenocarcinoma in the right colon, together with three polyps. His mother had colon cancer at 53 and uterine cancer at 58. His uncle had kidney cancer at 47. A maternal cousin had colon cancer at age 45 and another had uterine cancer at age 49. Would you recognize this as Lynch syndrome?

Background

Lynch syndrome[1] is named after Dr. Henry Lynch, who described this collection of cancers as a hereditary condition. It has also been called hereditary non-polyposis colon cancer (HNPCC), but since the condition definitely has some colonic polyps and involves more than colon cancer, the eponymous designation is preferred.

Lynch syndrome is the most common of the hereditary colon cancer syndromes (Table 1) and accounts for approximately 5% of all colon cancers. Individuals with Lynch syndrome have a risk[2] for cancer of the colon and other organs of the abdominopelvic cavity (Table 2). Liver cancer is generally considered a metastatic site. Prostate and cervical cancers are not included. Hematological malignancies and cancers outside the abdomen and pelvis (excepting Turcot's and Muir-Torre syndromes) are not part of this syndrome.

Mutations in four genes – *MLH1, MSH2, MSH6,* and *PMS2* – are associated with Lynch syndrome. These genes are responsible for deoxyribonucleic acid (DNA) mismatch repair. Some families with Lynch syndrome do not have mutations in any of these genes, and it is assumed that there are rare genes for Lynch syndrome that have not yet been identified.

Lynch syndrome is inherited in an autosomal dominant fashion. That is, anyone with a Lynch mutation has a 50-50 chance of passing on the mutation in any reproductive event, regardless of the sex of the parent or offspring.

Some individuals represent a new mutation in a mismatch repair gene. Any individual under the age of 50 who presents with colon cancer, regardless of family history, should be considered suspicious for harboring a Lynch mutation.

Identification of Patients with Lynch Syndrome

Diagnostic criteria[3] are based on personal and family histories (Table 3). Families who meet the Amsterdam criteria[4] have a 50% chance of having a mutation in *MLH1* or *MSH2*. Those who meet modified Amsterdam criteria have a 26% chance of having such a mutation. Genetic testing based on family history alone requires that the family meet Amsterdam or modified Amsterdam criteria.

Individuals who meet Bethesda criteria have an 8% chance of having a mutation in *MLH1* or *MSH2*. Therefore, individuals who meet only Bethesda criteria should undergo further pathological testing before germline genetic testing is considered.

Tumour Features

In general, colon cancers are right sided and the individual may have a few polyps.[5] The age of diagnosis of cancer is often less than 50. The

Table 1. Etiology of Colon Cancers

Syndrome	Genes	Percentage of Colon Cancers
Familial adenomatous polyposis (FAP), including attenuated FAP and 2/3 of Turcot's syndrome	*APC, MYH*	1
Hamartomatous polyps – Peutz-Jeghers syndrome, juvenile polyposis, Cowden disease	*STK1, SMAD4, BMPR1A, PTEN*	<1
Lynch syndrome, including 1/3 of Turcot's syndrome, and Muir-Torre syndrome	*MLH1, MSH2, MSH6, PMS2,* other	5
Non-syndromic		**Percentage of Colon Cancers**
Associated with inflammatory bowel disease		1
Remainder*		90+

*The majority of colon cancers are multifactorial. That is, the cancers are due to a combination of small, nonspecific, additive factors of a genetic, environmental, and personal nature.

Data from Lynch HT and Lynch JF, 2004.[1]

Table 2. Cancers in Lynch Syndrome

Cancer	Risk (%)
Colon (male)	28–75
Colon (female)	24–52
Uterine	27–71
Ovarian, gastric, upper urinary tract	1–13
Biliary tract, small bowel	2–7
Glioblastoma	Rare
Sebaceous gland adenoma/ carcinoma: keratocanthomas	Extremely rare

Data from Vasen HFA et al., 2007.[2]

Table 3. Diagnostic Criteria

Amsterdam (aka Amsterdam I)
3 or more relatives with colorectal cancer with pathological verification
1 should be of first-degree relation to the other 2
2 or more generations affected
At least 1 colorectal cancer before age of 50
Familial adenomatous polyposis ruled out
Modified Amsterdam (aka Amsterdam II)
As above but other Lynch-type tumours may be included
Modified Bethesda
Colorectal cancer <50 years
Synchronous or metachronous cancers, Lynch type, in a single individual, regardless of age
Colorectal cancer with MSI-H associated histology in patient <60
Family history of Lynch-type tumour but not meeting Amsterdam I or II criteria

MSI = microsatellite instability.

Data from National Comprehensive Cancer Network, 2008.[3]

Table 4. Screening Recommendations

To individuals identified with a Lynch mutation *or* a first-degree relative of anyone with a Lynch mutation:

1. Screening colonoscopy starting at the age of 20–25, to be done every other year to the age of 40 and then yearly
2. Colonoscopy yearly on remaining colon after colectomy
3. Gynecological screening* should be considered yearly from age 30–35: (i) pelvic examination, (ii) ultrasonography of uterus and ovaries, (iii) CA125, and (iv) endometrial biopsy
4. Yearly urinalysis with cytology starting at age 30–35
5. Yearly ultrasonography of kidneys starting at age 30–35
6. Yearly upper gastroscopy starting at age 30–35

*Ovarian screening by ultrasonography and CA125 is extremely controversial as there are many false-positives and false-negatives.

Data from Vasen HFA et al., 2007.[2]

cancer may have a nodular or Crohn's-like peri-tumour lymphocytic infiltration. The finding of more than two tumour infiltrating lymphocytes (TILs) should raise suspicion. Lynch colon cancers exhibit pathological features, such as microsatellite instability (MSI) and abnormal immunohistochemistry, that may help identification.[5]

Importance of Identification of a Lynch Mutation for Patient and Family

The patient with a proven Lynch mutation might be considered for more extensive colonic surgery[2] in situations where there are multiple or widely distributed colonic polyps or an extremely difficult colonoscopy. Women with a Lynch mutation[6] may consider prophylactic total hysterectomy and bilateral salpingo-oophorectomy after child-bearing is complete. In the latter circumstance, there is no contraindication to hormonal replacement therapy to the average age of menopause.

Where a familial mutation has been identified, at-risk individuals in the family should consider genetic testing to identify their personal mutation status. All individuals with a Lynch mutation should be advised about the risk of developing these cancers, and screening issues should be discussed (Table 4).

Summary

Lynch syndrome has an extremely variable presentation. Many patients present to general internal medicine as intra-abdominal cancers. Suspicion should be raised by the age of onset or the presence of a family history of Lynch-type cancers. Routine and specialized pathological investigations may add further information. Finally, referral to medical genetics may allow the identification of the mismatch repair mutation and facilitate risk stratification for family members. While there is no prevention for Lynch syndrome cancers, early detection of cancers by aggressive screening can significantly reduce morbidity and mortality.

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The Usual Suspects

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In my last column (Volume 3, Issue 3), I promised to present an EKG that reinforces the concept that correct EKG interpretation requires memorization of the typical appearance of left and right bundle branch blocks.

A 69-year-old man with a history of hypertension called 9-1-1 because of the sudden development of palpitations and dizziness. When the paramedics arrived, he did not seem to be in any distress and his blood pressure was 100/70, while his pulse was 185 bpm. They recorded the EKG shown in Figure 1. What is the diagnosis?

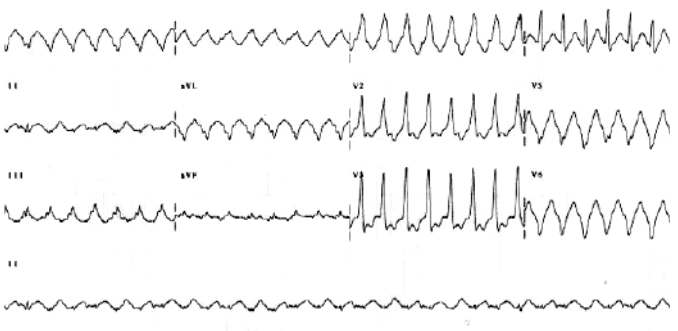

Figure 1

The EKG reveals a regular wide complex tachycardia. The broad differential diagnosis includes (1) ventricular tachycardia (VT), (2) supraventricular tachycardia (SVT) conducted aberrantly, (3) pre-excited SVT, and (4) paced rhythm. The latter two are very unlikely but always worthy of at least consideration. Pacemaker-mediated tachycardia (PMT) would be extremely unlikely because a sustained paced rhythm at 185 bpm is very unusual (upper rates on pacemakers are almost never that high) and there are no pacing stimuli preceding the QRS complexes. Most importantly, this patient has no pacemaker! A pre-excited SVT would also be extremely unlikely in an individual whose prior cardiology workup has never disclosed ventricular pre-excitation. And so, we are left with the usual suspects: VT or aberrantly conducted SVT?

The first step ought to be an examination for signs of AV dissociation (dissociated P waves, fusion beats, and capture beats), which would indicate a diagnosis of VT. Unfortunately, these findings are either absent or difficult to appreciate when the rate is >180 bpm. Dissociated P waves are hard to find because the entire EKG is composed of large-amplitude QRS complexes and T waves with virtually no isoelectric segments between beats in which small P waves might be seen. Fusion and capture beats rarely happen because the AV conduction system is either depolarized by retrograde penetration by the VT or refractory for the same reason.

In these situations, one is most often left studying the morphology of the QRS complexes to determine the likelihood of SVT versus VT. There are myriad morphology criteria, and clinicians, frustrated by too many details to memorize, sometimes carry laminated cards or algorithms in handheld computers to guide them in this common situation. It is noteworthy that the vast majority of these criteria point to a diagnosis of VT, which ought to be the default diagnosis when one is not sure anyway!

It has been proposed that if one knows what typical left bundle branch block (LBBB) and right bundle branch block (RBBB) look like, there is no need to ever memorize any morphology criteria, nor pull out any laminated card or handheld computer. Because aberrantly conducted SVT almost always conducts with either RBBB or LBBB, and VT rarely activates the ventricles the same way that LBBB and RBBB do, the following is usually true: the more the QRS complex resembles typical LBBB or RBBB, the more likely the rhythm is to be aberrantly conducted SVT. The corollary is equally true: the less the QRS complex resembles typical LBBB or RBBB, the more likely the rhythm is to be VT. This really is the basic message of all of the available morphology criteria.

The rhythm in question has an RBBB morphology, but does it look like a typical RBBB? In a typical RBBB, the R wave is not taller than the R′ in lead V1, and V5, V6, I, and aVL are not QS complexes. The QRS complex of this tachycardia does not resemble typical RBBB at all, so one ought to conclude that this is VT.

Relying on QRS complex morphology to make the diagnosis is not always exact, whether one uses memorized criteria or knowledge of the typical appearance of LBBB and RBBB. This is why signs of AV dissociation are more diagnostically firm. (Note that there are dissociated P waves seen in the relatively flat T waves after QRS complexes 3 and 6 in lead III.) Morphology examination can be particularly error fraught when true antiarrhythmic drugs are on board or other metabolic disturbances affect QRS complex morphology. Nevertheless, short of an electrophysiological study or pacemaker/ICD interrogation during the arrhythmia to provide intracardiac electrograms, the EKG really is the gold standard for this diagnosis.

To be good at EKG interpretation, one ought to be able to pull out a blank piece of paper and draw the QRS complexes of typical LBBB and RBBB in leads V1, V6, and aVL. If you cannot do that, just see how much better you get at EKG interpretation once you can (and how much lighter your pockets get too).

Takayasu's Arteritis

Chris Venner, MD, Nathan Janzen, Peter Wei, MD

About the Authors

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Takayasu's arteritis is a rare form of vasculitis with a predilection for the large arteries. It is in a similar category to giant cell arteritis, but because the small vessels are generally spared, it is distinct from the medium- and small-vessel vasculitides. Classically, it is described as a disease occurring predominantly in young adult females of Asian descent.[1]

Case Report

A 43-year-old Lebanese man presented to the emergency room with a 5-month history of malaise. His illness started with a headache of moderate severity, followed by fatigue, intermittent fevers, chills, and drenching night sweats. In the 6 weeks prior to admission, he had lost 9 kg. He did not complain of claudication, visual changes, or other focal neurological disturbances. He had been assessed by his family doctor and emergency room physicians on several occasions. At one point, he was given a brief course of oral steroids, possibly aimed at treating a presumed diagnosis of reactive airways disease, and his condition improved dramatically. However, he relapsed when the steroids were withdrawn. An outpatient abdominal ultrasound revealed mild splenomegaly and a pericardial effusion, and he was subsequently referred to our hospital.

His vital signs were normal, except for a temperature of 38.6°C. He had small palpable cervical lymph nodes bilaterally and in the left axilla, all small, mobile, and nontender. His cardiopulmonary examination was unremarkable. Specifically, he had no clinical signs of tamponade or congestive heart failure. There was dullness over the spleen, but it was not palpable. A peripheral examination did not reveal any arthritis, rashes, bruits, or arterial insufficiency.

His laboratory tests showed microcytic anemia (hemoglobin 104 g/L, MCV 77) with normal white cell and platelet counts. A peripheral blood smear was unremarkable. His erythrocyte sedimentation rate (ESR) was 108 mm/h, C-reactive protein (CRP) 196.3 mg/L, and ferritin 309 μg/L. Electrolytes, renal function, and liver enzymes were normal, as were serum and urine protein electrophoresis. Chest and abdominal radiographs were normal. Our initial concern was that of an underlying hematologic malignancy. Contrast computed tomography (CT) scans of the chest, abdomen, and pelvis were ordered.

Our patient's CT scan did not show signs of malignancy; however, a marked circumferential thickening of the wall of the aortic arch and descending thoracic aorta was seen. Additionally, there was circumferential thickening of the great vessels arising from the aortic arch, including the innominate artery, the right and left common carotid arteries, and the right and left subclavian and axillary arteries. With the exception of the left common carotid artery and the right subclavian artery, which were mildly attenuated, arterial calibre was maintained. Mild splenomegaly and a small pericardial effusion were also visualized. Based on this, a diagnosis of Takayasu's arteritis was suggested (Figure 1).

Discussion

The most recent diagnostic criteria for this condition were established in 1990 by the American College of Rheumatology.[2] Many of these criteria, however, reflect end-stage disease, which, pathologically, is a manifestation of the postinflammatory fibrosis. It has been recognized that the disease presents in two stages: an acute "pre-pulseless" phase characterized by nonspecific inflammation and a chronic phase characterized by end-organ damage due to arterial insufficiency. These phases may be separated by months to years. As well, intermittent acute inflammatory flares may occur throughout the chronic phase if left untreated.[1,2] Physical examination findings are described in Table 1. Symptoms of congestive heart failure may be seen secondary to hypertension, aortic regurgitation, or dilated cardiomyopathy. Neurological features such as postural dizziness, seizures, and amaurosis fugax may be related to ischemia or hypertension.[2,3]

Several imaging modalities may help in the diagnosis. Angiography has traditionally been the procedure of choice, typically showing long, smooth stenotic areas or occlusions. However, it is less effective at detecting the early signs of arteritis (changes in the vessel wall architecture) when compared with cross-sectional imaging.[4] CT/CT angiography is useful in early diagnosis as it is able to assess great vessel wall thickening, in addition to reductions in luminal diameter. One study of 25 patients with symptoms suggestive of Takayasu's arteritis found that CT angiography was 95% sensitive and 100% specific for the diagnosis.[5]

Magnetic resonance imaging (MRI) does not require the administration of radiation or contrast material; thus, it is ideal for serial evaluation of patients undergoing treatment. Additionally, one has the ability to view vessels in any plane and, as with CT, assess vessel wall thickness.[6] MRI of the thorax and neck of our patient was carried out to establish a baseline prior to the initiation of therapy. It showed concentric arterial wall thickening of the thoracic aortic arch (7 mm in

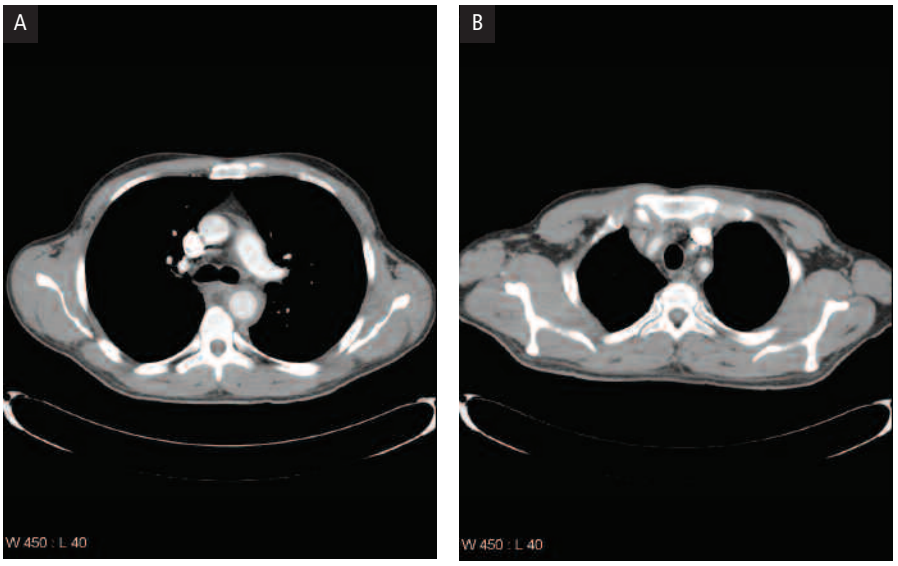

Figure 1. Computed tomography imaging of the thorax. *A*, Circumferential thickening of the wall of the aortic arch and descending thoracic aorta. *B*, Circumferential thickening of the great vessels arising from the aortic arch, including the innominate artery, the right and left common carotid arteries, and the right and left subclavian and axillary arteries.

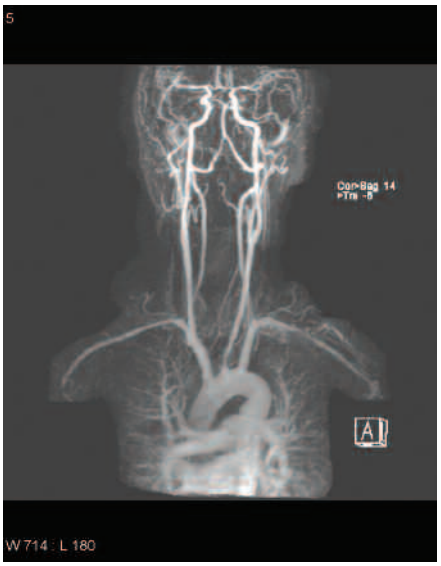

Figure 2. Magnetic resonance image of the thorax and neck showed concentric arterial wall thickening of the thoracic aortic arch (7 mm in maximum dimension), a proximal descending thoracic aorta, and supra-aortic arteries. Mild calibre reduction was evident in the proximal right subclavian and right vertebral arteries, and the left common carotid artery was stenosed approximately 35–40%.

maximum dimension), a proximal descending thoracic aorta, and supra-aortic arteries. Diffuse arterial wall enhancement was also present on T1 fat sat imaging post-gadolinium. Mild calibre reduction was evident in the proximal right subclavian and right vertebral arteries, and the left common carotid artery was stenosed approximately 35–40% (Figure 2).

Positron emission tomography (PET) scanning can also aid in the diagnosis of early disease by revealing areas of vessel wall inflammation, and data suggest that PET could be more sensitive and specific than inflammatory markers and CT in evaluating disease activity.[4] However, the use of PET is limited by its inability to assess wall structure and luminal flow, and by its high cost and restricted availability.

Our patient was started on pulse intravenous methylprednisolone 1 g, followed by prednisone 70 mg daily. Within 24 hours, his feelings of malaise and fatigue had resolved. Within 10 days, his CRP had decreased to 2.1, his ESR had fallen to 3 mm/h, and his hemoglobin had risen to 135g/L. Prior to discharge, he was started on methotrexate in addition to his oral steroid.

The medical treatment for Takayasu's arteritis consists primarily of traditional anti-inflammatory agents. In particular, high-dose steroids are used to induce remission. They are effective in up to 60% of patients,[7] but more than half subsequently relapse when the steroids are tapered. Other immunosuppressive agents, such as methotrexate, are used to forestall relapse and progression, as well as to reduce steroid-related morbidity.[8]

In the past, it was felt that this disease was chronic but self-limited. Many patients stopped treatment when their disease became quiescent. However, with the advent of noninvasive vascular imaging techniques, it is now known that new vascular lesions can be found in 61% of patients who were thought to be in clinical remission.[7] Other studies have shown that surgical specimens taken from patients in clinical remission show histological evidence of ongoing inflammation in 40%.[9] Therefore, most patients with this condition face a chronic and relapsing course.

Takayasu's arteritis is a challenging disease. Diagnostically, the paucity of signs and symptoms at presentation makes early detection difficult. In addition, although current medical therapy can often induce remission, most patients experience a relapse of their disease upon tapering of their immunosuppressive agents. Clinical signs and acute phase reactants may correlate poorly with disease activity. In the long term, imaging studies or biopsy are likely needed to track disease activity.

Table 1. Clinical Features of Takayasu's Arteritis

Clinical Finding	Percentage of Patients
Diminished or absent pulses ± limb claudication or blood pressure discrepancies	84–96
Bruits within the carotids, subclavian, and abdominal vessels	80–94
Aortic regurgitation	20–24
Hypertension	33–83
Hypertension reflecting renal artery stenosis	28–75

Acknowledgement

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Perspectives in GIM

Reperfusion Therapy for ST Elevation Myocardial Infarction: What Is Relevant to the General Internist?

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The management of acute ST elevation myocardial infarction (STEMI) has been extensively studied. The *American College of Cardiology/American Heart Association Guidelines for the Management of Patients with ST-Elevation Myocardial Infarction*, developed in collaboration with the Canadian Cardiovascular Society, were published in 2004[1] and subsequently updated in 2007.[2] One of the key components addressed by these guidelines was the area of reperfusion therapy.

Fibrinolytic therapy has been shown to reduce mortality in STEMI patients and has been accepted as a standard of care. Subsequent studies comparing fibrinolytic therapy to primary percutaneous coronary intervention (PCI) defined the role of primary PCI as highly effective, with lower rates of recurrence of myocardial infarction, a decreased incidence of stroke, and better short-term survival.[3]

Trials of reperfusion therapy using either fibrinolysis or PCI intervention have used the inclusion criteria of "chest pain" of at least 20 minutes' duration within 6 hours of presentation, and the presence of the standard ST elevation criteria on an electrocardiogram (EKG). However, it should be recognized that some patients with STEMI, especially the elderly, may present with atypical symptoms.[4,5] Nevertheless, the presence of the EKG diagnostic criteria for STEMI in this population still implies a total coronary artery occlusion. The association of ST elevation with total coronary artery occlusion is clearly documented.[6,7] Delays in instituting timely reperfusion therapy in patients with either typical or atypical symptoms result in ongoing myocardial necrosis with unfavourable ventricular remodelling in the subacute phase, and possibly left ventricular dysfunction over long term.

Should "pain free" patients with persistent ST segment elevation be thrombolyzed? Generally speaking, the answer is, Yes! In patients who present with atypical symptoms, the onset of their acute infarct may be difficult to identify. Consideration should be given to reperfusion if the predominant finding on EKG is ST elevation. In contrast, if the EKG shows significant Q waves, the process of myocardial necrosis may be

advanced and the reperfusion therapy may not be able to salvage a significant amount of myocardium.

What Are the ACC/AHA STEMI Recommendations for Reperfusion?

The ACC/AHA STEMI guidelines state: "The committee continues to endorse the concept that faster times to reperfusion and better systems of care are associated with important reductions in morbidity and mortality rates in patients with STEMI. An underutilized but effective strategy for improving systems of care for STEMI patients is to expand the use of pre-hospital 12 lead electrocardiogram programs by emergency medical systems (EMS) that provide advanced life support." The overarching goal is to keep ischemic time within 120 minutes. When primary PCI is available, the best outcomes are achieved by offering this strategy 24 hours per day, 7 days a week. The goal should be to achieve a "door to balloon" time within 90 minutes. With use of primary PCI, the recommendation is to have an ongoing program of outcome analysis and periodic review of the process of care. A national initiative has been put in place in the United States to improve quality of care and outcomes in STEMI patients.[8] Hospitals without PCI facilities should achieve a door-to-needle time of 30 minutes for STEMI patients. Patients with STEMI who present at a non-PCI hospital in cardiogenic shock or with contraindications to fibrinolysis should be transferred urgently to a PCI facility. Following use of fibrinolytic therapy, rescue PCI is suggested in the following situations: ongoing hemodynamic or electrical instability; persistent ischemic symptoms; or <50% resolution of ST elevation 90 minutes after therapy – in moderate to large-sized infarcts.

What Is Necessary to Implement These STEMI Guidelines in Canada?

Provinces need to enhance their "systems of care" for STEMI management. Every province in Canada is unique in regard to facilities for timely PCI for STEMI patients and their availability of pre-hospital 12-lead EKGs and prehospital fibrinolysis.

In the province of Nova Scotia, all ambulances have been equipped with 12-lead electrocardiogram services, and some of them have the capability of transmitting EKGs to the nearest emergency department. The use of prehospital fibrinolysis has been established in one region, with plans to gradually extend it to other regions of the province. The primary PCI area is being expanded to include cases where a door-to-balloon time would be achievable within 90 minutes. Within this area, the cardiac catheterization laboratory can be activated with a diagnostic prehospital EKG. Nova Scotia guidelines for ACS management prepared under the auspices of Cardiovascular Health Nova Scotia,[9] a provincial Department of Health program, have been disseminated to all regional hospitals in the province. These guidelines define the inclusion criteria for referral for primary and rescue PCI within the province.

Such efforts to enhance STEMI systems are likely ongoing across Canada. All emergency department physicians, internists, and cardiologists should be aware of systems in place within their region in order to improve the quality of care and outcomes of reperfusion therapy in STEMI patients.

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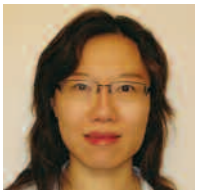
Atypical Presentation of Subcutaneous Panniculitis-Like T-Cell Lymphoma

Xiaolan Feng, MD, Iwona Auer-Grzesiak, MD, Ian Scott MD



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Case Report

A 69-year-old Vietnamese man presented to hospital with a 4-month history of high fever (39°C–40°C). This usually occurred in late afternoon, lasted for 2–3 hours, and could be transiently suppressed by acetaminophen. He also complained of general weakness and malaise. However, he denied any focal weakness or myalgia or significant weight loss in the previous 6 months. He had no other symptoms that might have suggested an underlying infection, malignancy, or rheumatoid disease. A review of systems was otherwise unremarkable. His medical history was significant for well-controlled hypertension. Interestingly enough, he had a remote history of hepatitis and malaria, which seemed to have been treated but details could not be recalled clearly by the patient or his family. He was taking irbesartan/hydrochlorothiazide for his hypertension and acetaminophen for his fever. He denied taking any other over-the-counter medications or herbal products. He is an ex-smoker with a 40 pack-year history. He immigrated to Canada 16 years previously. He went back to Vietnam and stayed in an urban area for 2 months in 2006, and he travelled to California in 2007 for 1–2 weeks. He denied any contact with ill people or animals during those stays. He denied having had a blood transfusion. He is a retired janitor.

On examination, his temperature fluctuated between 37.5°C and 40°C. His blood pressure was 140/80. However, he did not appear to be in acute distress. No jaundice, pallor, skin rash, or lymphadenopathy was appreciated. A single subcutaneous mass measuring 4 x 4.5 cm in diameter was noted in the anterior abdominal wall. Upon questioning, the patient vaguely recalled that this mass had been there for years and had not changed in size. It was soft, mobile, nontender, and without overlying erythema. The remainder of the physical examination produced normal results.

Extensive blood work was ordered. He was mildly anemic with a hemoglobin of 124 g/dL. His white blood cell counts were normal, except for a mild lymphopenia of 0.4 x 10^9/L. His platelet count was normal. His C-reactive protein and erythrocyte sedimentation rate were elevated at 75.7 mg/L and 56 mm/h, respectively. He was hypoalbuminemic at 26 g/L. Several liver enzymes were elevated: bilirubin 18 µmol/L, alanine aminotransferase (ALT) 98 U/L, alkaline phosphatase (ALP) 176 U/L, gamma-glutamyl transpeptidase (GGT) 120 U/L, and lactate dehydrogenase (LDH) 650 IU/L. The ALP normalized spontaneously during his hospitalization; however, his GGT, ALT, LDH, ESR, and CRP remained elevated and his albumin remained low.

He was also hyponatremic at 124–130 mmol/L. His urine sodium and osmolarity were consistent with the syndrome of inappropriate secretion of antidiuretic hormone (SIADH), even after his diuretic was held. The rest of his electrolytes, including calcium, were normal. He had normal serum creatinine, creatine kinase, antinuclear antibodies, extractable nuclear antigen, antineutrophil cytoplasmic autoantibodies, rheumatic factor, and complement levels. Several sets of blood cultures and urine cultures yielded no growth. Repeated thick peripheral blood smears were negative for malaria. Serologic studies were negative for hepatitis B, Epstein-Barr virus, human immunodeficiency virus, syphilis, filaria, *Bartonella henselae*, and Q fever. Anti-hepatitis C (HCV) and anti-hepatitis A (HAV) were positive (anti-HCV IgM and anti-HAV IgM were negative), consistent with his past history of hepatitis. A tuberculin skin test was negative. An examination for acid-fast bacilli in induced sputum and first morning urine samples was also negative.

A computed tomography scan of the chest, abdomen, and pelvis revealed mild splenomegaly and thickening in the posterior wall of the bladder. No other mass or significant lymphadenopathy was noted. Subsequent cystoscopy was normal. A transesophageal echocardiogram was normal. A bone marrow aspiration/biopsy as well as a fine-needle biopsy of his liver were performed, and the results were nonspecific. A bone scan revealed no metastatic bone disease. Magnetic resonance imaging of brain revealed no abnormality.

A biopsy of the abdominal wall mass was subsequently performed. The microscopic sections showed an incompletely excised mass with no overlying epidermis/dermis. The mass was composed of adipose tissue featuring septa thickened by an infiltrate of atypical convoluted lymphoid cells and a patchy infiltrate of CD68 positive foamy histiocytes (Figure 1). The atypical lymphoid cells were distinctly rimming individual adipocytes (Figure 2). Immunohistochemical stains revealed a marked predominance of dimCD45/CD45RO/-CD3/CD5/CD2/CD7/CD8-positive cytotoxic type T lymphocytes showing distinct granzyme B positivity (Figure 3). CD56/ALK-1/CD1a were negative. CD20 showed few scanty B lymphocytes, and CD68 decorated tumour-infiltrating histiocytes. Ki67 showed a proliferative rate of approximately 40%. ZN and Grocott stains were negative for microorganisms. PCR-based analysis revealed monoclonal T-cell receptor beta and gamma gene rearrangements. These morphological, immunohistochemical, and molecular findings were those of a T-cell non-Hodgkin's lymphoma with distinct features of subcutaneous panniculitis-like T-cell lymphoma.

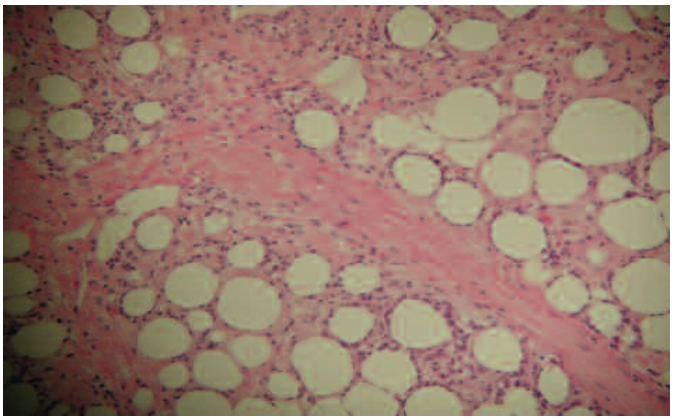

Figure 1. Thickened and hypercellular panniculitic septa.

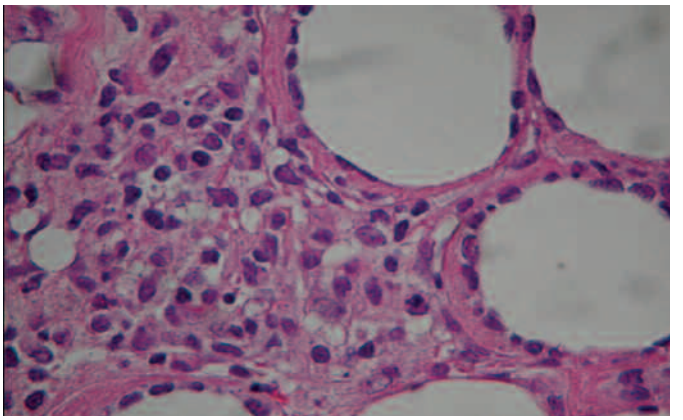

Figure 2. Neoplastic lymphoid cells expand the septa and line the adipocytes.

Discussion

Subcutaneous panniculitis-like T-cell lymphoma (SPTL) is a rare cytotoxic T-cell lymphoma that involves subcutaneous tissue. It was originally identified by Gonzalez et al. in 1991 as an uncommon subtype of lymphoma that pathomorphologically may mimic panniculitis.[1] Since then, more cases have been recognized globally, including in Asia, Europe, and North America,[1–4] and the condition is now considered a separate clinicopathological entity.[5] Both sexes are equally involved and usually present in their fourth and fifth decades; however, older and pediatric cases have been reported.[5]

Common presentations include multiple subcutaneous nodules or plaques on the trunk and extremities, which may mimic the pattern of panniculitis,[2,5,6] prompting initial consultation with a dermatologist. In nearly half of cases, the disease course is complicated by symptoms and signs of hemophagocytic syndrome, which heralds rapid disease progression.[1,5] In addition, elevated liver enzymes including ALT, AST, and LDH have also been reported.[3,5,6] Although constitutional symptoms such as fever, malaise, and weight loss are very common (40–50%), they are usually associated with extensive subcutaneous involvement.[5,6]

The clinical course of our patient was characterized by a relentless spiking fever (FUO) and profound constitutional symptoms despite limited tissue involvement. The small abdominal wall mass detected upon initial physical examination was thought to be a benign lipoma. We initially focused on investigating possible infectious causes, considering the patient's race, original nationality, and recent travel history. Malignancy including lymphoma was also considered due to his age, significant smoking history, marked elevation of LDH, and clinical picture of SIADH. However, the history, physical examination, and CT scan did not support this diagnosis. The benign-looking subcutaneous abdominal mass lacked typical characters of malignant or inflammatory lesions; therefore, it did not raise our suspicion and we did not initially biopsy the lesion. The mass lacked the appearance of SPTL, as previously reported. The only other clues in investigations that indicated that he might have SPTL were marked elevations of LDH, CRP, and ESR and mildly elevated liver enzymes, none of which are specific.

It has been reported that several factors, including old age, dermal or subdermal involvement, the presence of HPS, low WBC, high LDH, and an unfavourable immunophenotype of T cells (CD4–, CD8–, CD56+) negatively affect the prognosis of SPTL.[3,5] The mean 5-year survival rates have been reported at between 11 and 91%.[5,6] The treatments were highly individualized, ranging from focal surgical and radiation therapies to aggressive combined chemotherapy and stem cell transplantation. Other agents, such as prednisone, cyclosporine, and gemcitabine, have been used with variable success.[5–8] Since this disease

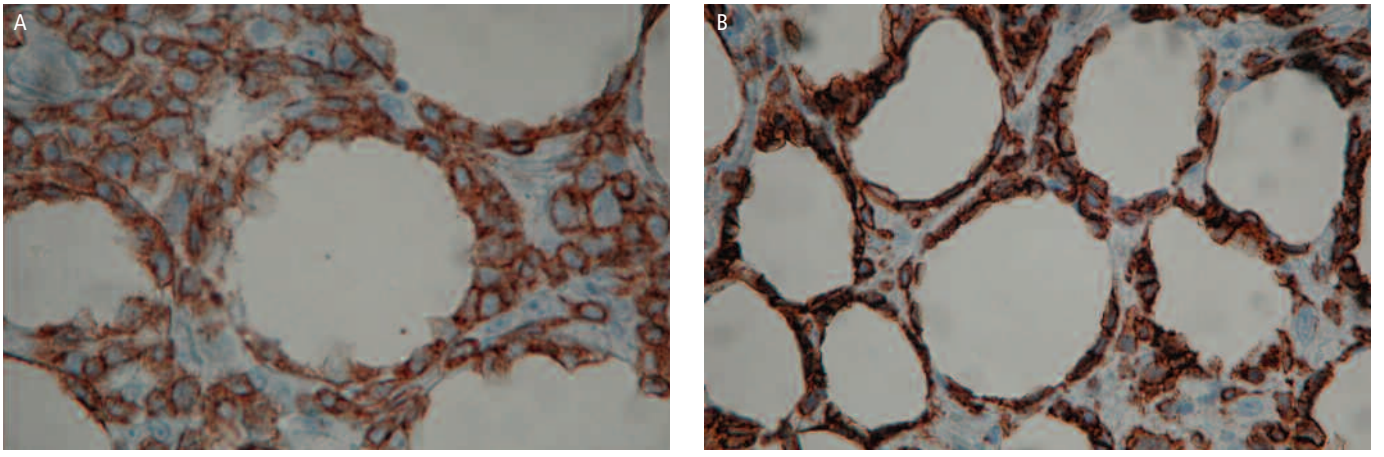

Figure 3. *A*, CD3 and CD8 stain. *B*, CD3/CD8-positive cytotoxic T cells form the majority of the neoplastic infiltrate.

is rare, therapeutic trials are lacking. Common treatments for comparable patients include doxorubicin-based chemotherapy (CHOP or similar). Recent studies using a combination of chemotherapy and bone marrow transplantation and/or long-term steroid therapy result in a better survival rate.[5]

Our patient received one cycle of standard CHOP chemotherapy soon after the diagnosis. His daily high fever diminished. His LDH, ALT, GGT, and ESR came down to normal ranges. He was dismissed from hospital and currently receives outpatient follow-up.

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Practice of GIM

Whom Are We Missing? Recognition and Treatment of Heart Failure with Preserved Ejection Fraction

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Heart failure (HF) is defined as a pathophysiological state in which the heart, with a normal filling pressure, is unable to pump blood at a rate sufficient to meet the metabolic needs of the body. It should be noted that the definition of HF does not require the measurement of ejection fraction (EF). HF is a syndrome characterized clinically by breathlessness, effort intolerance, fluid retention, and poor survival.[1]

Approximately 1–2% of the general population has symptomatic HF, and the prevalence increases with age.[1] This translates into over 400,000 people in Canada having HF, over 100,000 hospitalizations each year, an in-hospital mortality rate of approximately 16%, and over $1 billion per year in health care costs.[2,3] Although there are data to suggest there has been a decline in mortality over the past 20 years,[4] recent findings from Ontario demonstrate the 1-year mortality following an HF hospitalization is over 30%.[5] Since HF occurs predominately in the elderly, it is expected the prevalence will increase – by the middle of the 21st century, over 25% of the population in Canada will be over the age of 65 years.[6]

Heart Failure with Preserved Ejection Fraction

Although the diagnosis of HF does not require the measurement of EF, it has long been assumed that the presence of HF is associated with a reduced EF. Over 30 years ago, it was recognized that HF could occur in

the absence of left ventricular chamber dilatation.[7] However, until recently, this condition was somewhat ignored.

In more recent years, a number of population-based echocardiographic studies have examined the prevalence of HF with preserved ejection fraction (HFPEF).[8] These studies demonstrated that, on average, about 56% of HF patients had HFPEF.[8] A recent study from Ontario of 2,802 patients discharged from hospital with a diagnosis of HF demonstrated that 44% had HFPEF.[9] These data are consistent with the Euro Heart Failure Survey, which demonstrated that 46% of 6,806 HF patients had HFPEF.[10] Although the symptoms and signs in patients with HFPEF may appear very similar to those in patients with HF with reduced EF (HFREF), there are clinical features that distinguish them. HFPEF patients are older, are more often women, have a greater prevalence of hypertension and atrial fibrillation, and less often have ischemic heart disease.[8,10] A study by Ceia et al.[11] demonstrated that over the age of 70 years, HFPEF may represent even more than 50% of the HF cases.

Diagnosis of HFPEF

The diagnosis of HFPEF is challenging because often there is no one specific test that can be used. One proposed set of criteria involves categorizing the patients as having definite, probable, or possible HFPEF.[12] In this classification, all patients must have symptoms and signs of HF; patients who also have EF >50% measured within 72 hours of an HF event and cardiac catheterization showing diastolic dysfunction are classified as definite diastolic HF; patients with a probable diagnosis have an EF >50% measured within 72 hours of an HF event; and, finally, those with only HF symptoms and signs have a possible diagnosis.

A consensus statement from Europe has recently suggested a more detailed algorithm to diagnosis HFPEF.[13] Patients must have HF symptoms and signs, an EF >50%, and left ventricular end diastolic volume index <97 mL/m^2; then evidence of diastolic dysfunction is sought through the use of cardiac catheterization or specific echocardiographic findings in combination with an elevation of natriuretic peptide levels.

There are problems with these criteria for the diagnosis of HFPEF. Often the EF is not measured within 72 hours of an event, hemodynamic data are usually not available, measurement of diastolic function with echocardiography is at times difficult, and natriuretic peptides are not always available. A study by Zile et al.[14] examined whether an objective measurement of diastolic function is required in patients with typical HF symptoms and signs and a normal EF. They found that over 90% of the patients had evidence of diastolic dysfunction based on hemodynamic measurements made during cardiac catheterization. Thus, the diagnosis of diastolic HF can be made without the measurement of parameters that reflect diastolic function. Therefore, in practical terms, the diagnosis of HFPEF is usually made based on HF symptoms and signs with an EF ≥45–50%.

Mortality and Morbidity Associated with HFPEF

A variety of studies have not uniformly found a difference in mortality between HFPEF and HFREF, although most have found that mortality is slightly less in HFPEF.[8] Recently, two studies have compared the mortality of HFPEF with that of HFREF.[9,15] Owan et al.,[15] examining 4,594 HF patients, found that for HFPEF patients the mortality at 1 year was 29% and at 5 years was 65%, which was significantly less (p = .03) than those for HFREF – 32% and 68%, respectively. In another study of 2,802 HF patients, the 1-year mortality of 22% in HFPEF was not significantly different (p = .07) from the 26% mortality in HFREF.[9] Furthermore, although there was a significant (p = .005) improvement in mortality for HFREF from 1987 to 2001, there has been no improvement (p = .36) for HFPEF.[15]

Studies comparing the HF readmission rate in HFPEF with that in HFREF have generally found a slightly lower rate in HFPEF.[8] However, a recent study did not find a significant (p = .09) difference between the 1-year HF readmission rate for HFPEF (13.5%) compared with that for HFREF (16.1%).[9] There are data to suggest that while the HF readmission rate for HFREF did not change from 1986 to 2001, there has been a significant increase in the rate for HFPEF during that time period.[15]

Therapy for HFPEF

There have been many small studies evaluating various therapies for HFPEF.[16] These studies have generally demonstrated that angiotensin-converting enzyme inhibitors, beta-blockers, angiotensin receptor blockers, and calcium channel blockers have all been shown to relieve symptoms and improve exercise capacity. There have been a limited number of clinical trials examining the effect of a therapy on clinical end points in HFPEF patients. The Digitalis Investigation Group ancillary trial examined the effects of digoxin in 988 HF patients with an EF >45%.[17] The primary combined outcome of HF hospitalization or HF mortality was not reduced with digoxin (HR = 0.82; 95% CI 0.63–1.07; p = .136). Furthermore, digoxin had no effect on all-cause or cause-specific mortality or on all-cause or cardiovascular hospitalization. Digoxin was associated with a trend to a reduction of HF hospitalizations (HR = 0.79; 95% CI 0.59–1.04; p = .94) but also to a trend toward an increase in hospitalizations for unstable angina (HR = 1.37; 95% CI 0.99–1.91; p = .061).

The Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) – Preserved study evaluated the effects of candesartan in 3,023 HF patients with an EF >40%.[18] The primary outcome of cardiovascular death or HF hospitalization was not reduced by candesartan compared with placebo (HR = 0.89; 95% CI 0.77–1.03; p = .118; covariate adjusted HR = 0.86; 95% CI 0.74–1.0; p = .051). There was a trend to reduction in HF hospitalizations with candesartan (HR = 0.85; 95% CI 0.72–1.01; p = .072; covariate adjusted HR = 0.84; 95% CI 0.70–1.00; p = .047).

The Perindopril in Elderly People with Chronic Heart Failure (PEP-CHF) study examined the effects of perindopril in 850 HF patients with an EF >40%.[19] The primary combined outcome of all-cause mortality and unplanned HF hospitalization was not significantly reduced with perindopril compared with placebo (HR = 0.92; 95% CI 0.70–1.21; p = .545).

The Irbesartan in Patients with Heart Failure and Preserved Ejection Fraction (IPRESERVE) study examined the effects of irbesartan in 4,128 HF patients with an EF ≥45%.[20] The primary combined outcome

of all-cause mortality and protocol-specified cardiovascular hospitalizations (for HF, myocardial infarction, unstable angina, stroke, ventricular or atrial arrhythmia) was not significantly reduced by irbesartan compared with placebo (HR = 0.95; 95% CI 0.86–1.05; $p = .35$).

Summary

The data strongly support that HFPEF is a clinical entity. HFPEF is common as it occurs in approximately 50% of all HF patients and appears to be more prevalent with increasing age. Although the degree of mortality and morbidity associated with HFPEF may not be as great as those with HFREF, the clinical event rate is still unacceptably high. To date, the published clinical trials in this patient population have essentially been neutral. The guidelines deal with the management of HFPEF patients by recommending treating the comorbidities (e.g., hypertension) that exist in these patients. In order for this field to move forward, we need a better understanding of the mechanisms underlying this syndrome and to gain additional potential targets for treatment.

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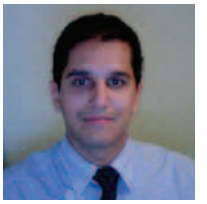
Smoking and CREST Syndrome

Christopher Labos, MD, Joseph Schuster, MD



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This 62-year-old woman has been followed up in the immunology clinic for long-standing CREST (*c*alcinosis cutis, *R*aynaud's phenomenon, *e*sophageal dysfunction, *s*clerodactyly, *t*elangiectasia) syndrome. Interestingly, the vasospasm from her Raynaud's phenomenon was noticeably worse during periods when she was smoking. Upon presentation to clinic she had numerous cutaneous ulcers (Figure 1) as well as marked sclerodactyly and calcinosis consistent with her history of CREST syndrome. Radiographs showed resorption of the distal phalanges (Figure 2).

She was treated conservatively by our wound care team and counselled to stop smoking. The ulcers gradually resolved, and her Raynaud's phenomenon became less severe. Whenever she resumes smoking, the cutaneous ulcers return within 3 months. The cycle of compliance and relapse has repeated itself many times, demonstrating the synergistic effect of nicotine-induced vasospasm in this condition.

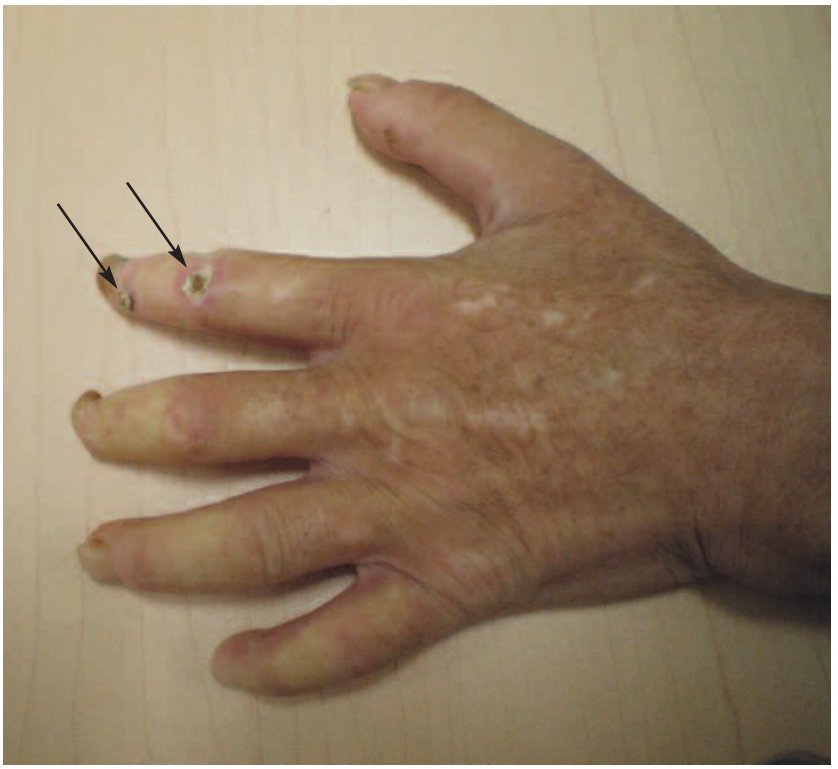

Figure 1. Cutaneous ulcers (*arrows*).

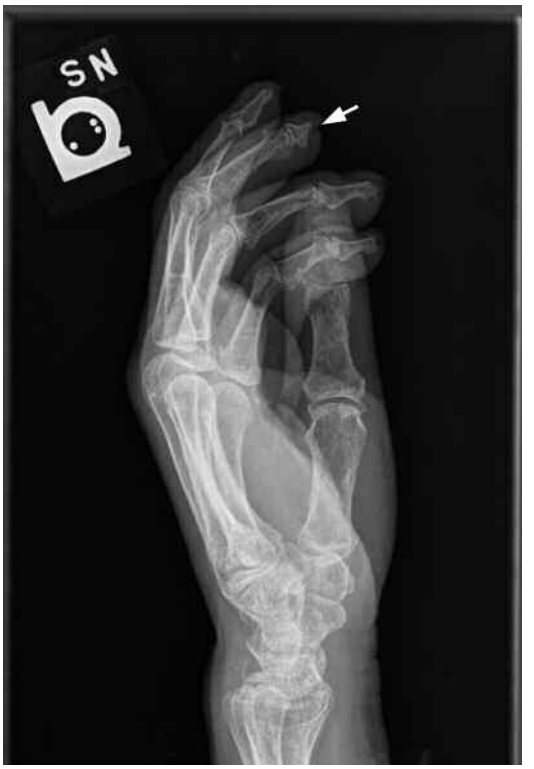

Figure 2. Resorption of the distal phalanges (*arrow*).

Généralisation des études de bêta-bloquants péri-opératoires de Mangano et POISE dans une clinique d'évaluation pré-opératoire

Odile Paquette, MD, Catherine St-Georges, MD, Matthieu Touchette, MD, Luc Lanthier MD

Au sujet des auteurs
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Les chirurgies non cardiaques sont associées à une mortalité et morbidité cardiaque significative et l'utilisation de bêta-bloquants en péri-opératoire pourrait prévenir les événements cardio-vasculaires.[1–3] Les bénéfices reliés à l'usage de cette médication en péri-opératoire demeurent toutefois controversés dans la littérature.[2–9]

Deux études récentes ont évalué les bénéfices des bêta-bloquants en péri-opératoire. L'étude de Mangano a évalué l'impact de l'administration d'aténolol en péri-opératoire chez une population à risque de maladie coronarienne subissant une chirurgie majeure non cardiaque alors que l'étude POISE s'est adressée à évaluer l'efficacité de l'utilisation du métoprolol CR chez des patients à risque cardiovasculaire modéré et élevé.[2,6,10] Les critères d'éligibilité à la participation à ces deux études étaient par ailleurs différents.

La généralisation de ces études dans une population pré-opératoire hétérogène demeure inconnue, aucune étude n'ayant évalué ce sujet. Nous avons donc réalisé une étude de cohorte rétrospective dans une clinique d'évaluation pré-opératoire afin d'évaluer l'applicabilité des études de Mangano et POISE en révisant les indications et contre-indications relatives à la prescription de bêta-bloquants dans chacune de ces études.

Méthode

Il s'agit d'une étude de cohorte rétrospective regroupant les patients ayant été évalués à la clinique pré-opératoire de médecine interne du CHUS (Centre hospitalier universitaire de Sherbrooke) entre novembre 2005 et novembre 2006. Les patients inclus dans notre étude devaient avoir eu une chirurgie non-urgente nécessitant une hospitalisation. Les dossiers incomplets, les patients dont les chirurgies ont été annulées ou réalisées en chirurgie d'un jour ont été exclus.

La collecte de donnée a été effectuée par la révision de dossiers médicaux informatisés. Les caractéristiques générales des sujets, de la chirurgie ainsi que les données relatives aux critères d'inclusion et d'exclusion des études de Mangano et POISE ont été recueillies (Tableau 1).

L'objectif principal était de déterminer le nombre de patients

Tableau 1. Critères des études MANGANO et POISE

Mangano	
Indication : 1 des 2 critères	
1.	MCAS (IM, angine typique ou angine atypique avec épreuve de stress +)
2.	≥ 2 facteurs de risque : âge ≥ 65 ans, HTA, tabagisme actif, cholestérol ≥ 6,2 mmol/L, diabète mellitus
Contre-indication	
	TA systolique < 100 mm Hg, pouls < 55/min, BAV 3e degré, insuffisance cardiaque, bronchospasme
POISE	
Indicationuivant : Patient âgé >45 ans avec une hospitalisation de >24h qui présente 1 des 6 critères suivant :	
1.	MCAS (angine, IM, épreuve de stress à l'exercice/nucléaire/échographique +, sténose > 50% à l'angio ou ECG avec onde Q ds 2 dérivations continues)
2.	MVAP (claudication intermittente, ITH ≤ 0,90 au repos ou sténose > 70% au doppler ou à l'angio)
3.	AVC causé par maladie athérothrombotique
4.	Hospitalisation pour insuffisance cardiaque dans les 3 dernières années
5.	Chirurgie vasculaire majeure
6.	3/7 facteurs de risque suivant : chirurgie à haut risque, insuffisance cardiaque, diabète sous hypoglycémiant oral ou insuline, créatinine préop > 175 µmol/L, âge > 70 ans, ICT
Contre-indication	
	Pouls < 50/min, BAV 2–3e degré sans pacemaker, asthme actif, MPOC bronchospastique, effet secondaire aux bêta-bloquants, PAC avec revascularisation complète < 5 ans et sans évidence d'ischémie depuis, chirurgie à faible risque, prise de vérapamil

AVC = accident vasculaire cérébral; BAV = bloc auriculo-ventriculaire; ICT = ischémie cérébrale transitoire; IM = infarctus du myocarde; ITH = index tibio-huméral; MVAP = maladie vasculaire artérielle périphérique; PAC = pontage aorto-coronarien.

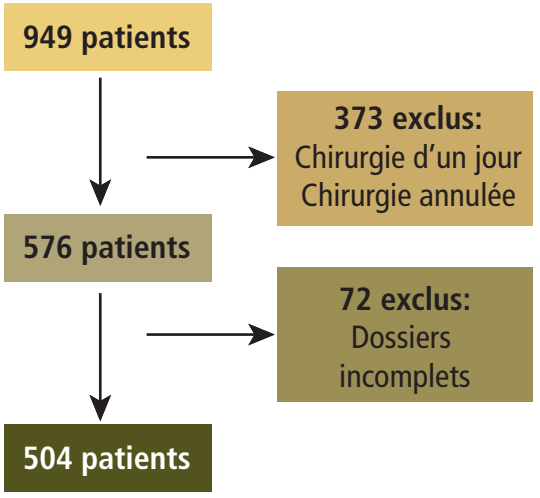

Figure 1. Schéma de l'étude.

possédant une indication de bêta-bloquant tout en l'absence de contre-indication ou d'une prise quotidienne de cette médication selon les différents critères des études de Mangano et POISE. Ces variables catégoriques ont été analysées avec le test de Chi-carré à l'aide du logiciel SPSS (version 14.0). Les résultats sont présentés sous la forme de fréquence et de pourcentage. Une valeur de p inférieure à 0.05 a été considérée comme statistiquement significative.

Résultats

Des 949 sujets évalués, 72 ont été exclus parce que les dossiers étaient incomplets et 373 car l'intervention a été annulée ou réalisée en chirurgie d'un jour. 504 patients rencontraient donc les critères d'inclusion de l'étude (Figure 1). Près de la moitié des patients étaient des hommes (49%) ; l'âge était de 67 ± 12 ans (Tableau 2). La majorité des patients étaient connus pour de l'hypertension artérielle (65%) et de la dyslipidémie (53%). Le tiers des patients présentait une maladie cardiaque athérosclérotique (32%). Plus du tiers des patients avaient parmi leur médication anti-hypertensive un diurétique (35%), un bêta-bloquant (34%), un bloquant des canaux calciques (32%) et/ou un IECA (31%) (Figure 2).

Selon les critères de l'étude de Mangano, 396 (79%) sujets présentaient une indication à la prescription de bêta-bloquants, mais 187 (47%) de ceux-ci présentaient une contre-indication ou prenaient déjà cette médication quotidiennement (Tableau 3). Au total, 209 des 504 sujets (42%) étaient donc éligibles à l'administration de bêta-bloquants en péri-opératoire selon ces critères.

Avec l'utilisation des critères de l'étude POISE, 208 (41%) sujets présentaient une indication alors que 160 de ceux-ci (77%) avaient une contre-indication à la médication ou étaient déjà sous bêta-bloquant. Ainsi, selon les critères de POISE, 48 des 504 sujets (10%) étaient donc éligibles à l'administration de bêta-bloquants en péri-opératoire.

Il y a une différence significative entre les critères des études de Mangano et POISE en ce qui concerne les indications (79% vs 41%, $p < 0{,}001$) et les contre-indications (7% vs 28%, $p < 0{,}001$) de bêta-bloquants. Une différence statistiquement significative a aussi été démontrée quant au nombre de sujets étant éligibles à l'administration de bêta-bloquants selon les critères de Mangano et POISE (42% vs 10%; $p < 0{,}0001$).

Discussion

Il n'y a pas de données disponibles dans la littérature jusqu'à présent concernant la généralisation des études de bêta-bloquants en péri-opératoire. Il s'agit en fait de la première étude portant sur ce sujet.

Tableau 2. Caractéristiques de base des patients

Variables	Patients
	***n* = 504**
Âge (ans)	67 ± 12
Sexe masculin	249 (49%)
Prise d'alcool	35 (7%)
MCAS	164 (32%)
Facteur de risque cardiovasculaire	
Tabac	85 (17%)
HTA	329 (65%)
Diabète	126 (25%)
Dyslipidémie	294 (53%)
Autres comorbidités	
FA/Flutter	58 (11%)
Insuffisance cardiaque	16 (3%)
ICT/AVC	39 (7%)
MVAP	48 (9%)

AVC = accident vasculaire cérébral; ICT = ischémie cérébrale transitoire; FA = fibrillation auriculaire; MVAP = maladie vasculaire artérielle périphérique.

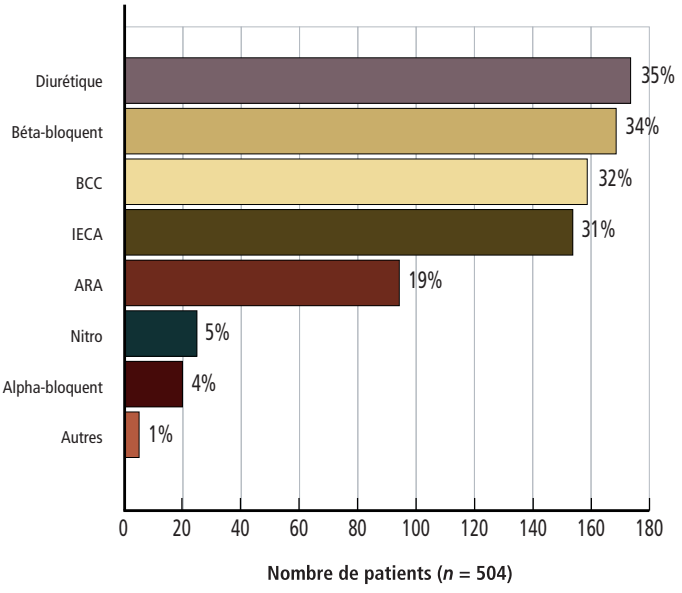

Figure 2. Médication à la clinique pré-opératoire. ARA = antagoniste des récepteurs de l'angiotensine; BCC = bloquant des canaux calciques; IECA = inhibiteur de l'enzyme de conversion de l'angiotensine.

Tableau 3. Administration de bêta-bloquants selon les critères des études de Mangano et POISE

Variables	Mangano	POISE	*p*
Indication de BB	396/504 (79%)	208/504 (41%)	<0,001
Contre-indication ou sous BB	187/396 (47%)	160/208 (77%)	0,005
Contre-indication	26/396 (7%)	58/208 (28%)	<0,001
Sous bêta-bloquant	161/396 (41%)	102/208 (48%)	0,048
Indication de BB et absence de contre-indication ou prise de BB	209/504 (42%)	48/504 (10%)	<0,001

BB = bêta-bloquant.

L'utilisation des critères de l'étude POISE restreint grandement la prescription de bêta-bloquants en péri-opératoire en comparaison à ceux de l'étude de Mangano. Les critères d'inclusion de cette étude ciblent préférentiellement les patients à risque de maladie cardiaque et d'événements cardiaques péri-opératoires. Les différentes contres-indications associées à l'usage des bêta-bloquants sont aussi beaucoup plus détaillées dans l'étude POISE et limitent donc la prescription de cette médication. Il est aussi intéressant de constater que même si les critères de POISE ciblent un groupe plus précis de patients à risque, les résultats de cette étude demeurent mitigés puisque la réduction de décès cardiaque, d'infarctus non-fatal et d'arrêt cardiaque se fait au prix d'une augmentation la mortalité totale et des accidents cérébraux-vasculaires, ce qui risque de limiter grandement l'utilisation des bêta-bloquants dans le contexte péri-opératoire.[6,9]

En conclusion, l'utilisation des critères d'administration de bêta-bloquants en péri-opératoire de l'étude POISE permettent d'orienter l'administration de cette médication à une population beaucoup plus ciblée. La généralisation des études de Mangano et POISE sur l'utilisation de bêta-bloquants en péri-opératoire est donc très différente.

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Generalization of Perioperative Beta-Blocker Studies by Mangano and POISE in a Preoperative Assessment Clinic

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Noncardiac surgery is associated with significant cardiac mortality and morbidity. The use of perioperative beta-blockers has been proposed to reduce or prevent cardiovascular events,[1–3] but there is significant controversy in the literature.[2–9]

The benefits of perioperative beta-blockers have been evaluated in two recent studies. Mangano et al. evaluated the impact of atenolol as a perioperative treatment in a population at risk of coronary artery disease undergoing major noncardiac surgery, whereas the POISE study was designed to evaluate the efficacy of metoprolol CR on patients with moderate or high cardiovascular risk.[2,6,10] Moreover, the eligibility criteria for participation in these two studies were different. The generalization of these studies in a heterogeneous preoperative population is still unknown as no study has addressed this question.

Method

We conducted a retrospective cohort study of the patients assessed at the internal medicine preoperative clinic at Sherbrooke University Hospital between November 2005 and November 2006. The cohort criteria included having had nonurgent surgery requiring hospital admission. Patients whose files were incomplete or whose surgeries were cancelled or performed as a day surgery were excluded.

The data were collected by reviewing computerized medical files. The general characteristics of the patients and the surgery and data pertinent to the inclusion and exclusion criteria of the Mangano and POISE studies were tabulated (Table 1).

The main objective was to determine the number of patients for whom beta-blocker treatment would have been indicated by applying the various criteria used in the Mangano and POISE studies, less those who were already taking this medication daily or for whom it was contraindicated. We used version 14.0 of the SPSS software to analyze these categorical variables with the chi-square test. The results are presented as a frequency and percentage. A p value <.05 was deemed statistically significant.

Table 1. MANGANO and POISE Criteria

Mangano	
Indication: 1 of 2 criteria	
1.	CHD (MI, typical or atypical angina with positive stress test)
2.	≥2 risk factors: age ≥65 years, HBP, active smoker, cholesterol ≥6.2 mmol/L, diabetes
Contraindication	
	Systolic BP <100 mm Hg, pulse <55 bpm, third-degree AVB, heart failure, bronchospasm
POISE	
Indication: Age >45 years, plus hospitalization >24 hours, plus 1 of the following 6 criteria:	
1.	CHD (angina, MI, exercise/nuclear/echocardiographic stress test + stenosis >50% by angiography, or ECG with Q waves in two continuous leads)
2.	PAD (intermittent claudication, ABI ≤0.90 at rest, or stenosis >70% by Doppler or angiography)
3.	Stroke caused by atherothrombotic disease
4.	Hospitalization for heart failure in the past 3 years
5.	Major vascular surgery
6.	Three of the seven following risk factors: emergent/urgent surgery, high-risk surgery, heart failure, diabetes treated with oral hypoglycemic agents or insulin, preoperative creatinine >175 µmol/L, age >70 years, TIA
Contraindication	
	Pulse <50 bpm, 2nd- or 3rd-degree AVB without pacemaker, active asthma, bronchospastic COPD, beta-blocker side effects, CABG with complete revascularization <5 years and with no evidence of subsequent ischemia, low-risk surgery, use of verapamil

ABI = ankle-brachial index; AVB = atrioventricular block; CABG = coronary artery bypass graft; CHD = coronary heart disease; COPD = chronic obstructive pulmonary disease; ECG = electrocardiography; HBP = high blood pressure; MI = myocardial infarction; PAD = peripheral arterial disease; stroke = cerebrovascular accident; TIA = transient ischemic attack.

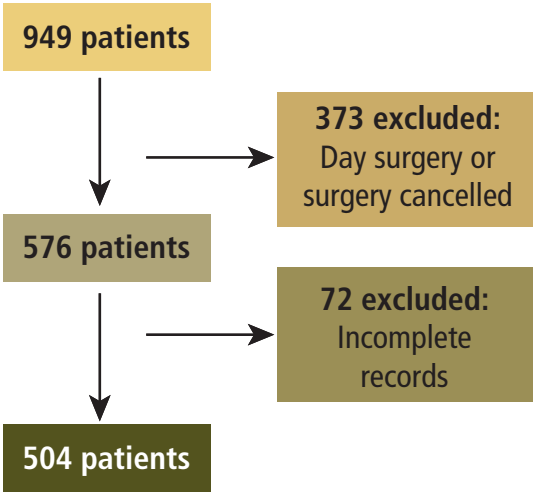

Figure 1. Study sample.

Results

Of the 949 patients assessed, 72 were excluded because their files were incomplete and 373 were excluded because their surgery was cancelled or performed as a day surgery. In total, 504 patients satisfied the study's inclusion criteria (Figure 1). Nearly half of the patients were male (49%); the age was 67 ± 12 years (Table 2). Most of the patients had high blood pressure (65%) and dyslipidemia (53%). A third of the patients had coronary heart disease (32%). More than one third of the patients were on antihypertensive therapy, such as a diuretic (35%), beta-blocker (34%), calcium channel blocker (32%), or angiotensin-converting enzyme (ACE) inhibitor (31%) (Figure 2).

Applying the criteria used in the Mangano study, 396 (79%) of the patients had an indication for a beta-blocker prescription, but 187 (47%) of these patients had a contraindication or were already taking this medication on a daily basis (Table 3). In all, with these criteria, 209 of the 504 patients (42%) were therefore eligible for perioperative beta-blocker treatment.

Applying the criteria used in the POISE study, 208 (41%) of the patients had an indication for beta-blockade, but 160 (77%) of these patients had a contraindication for the medication or were already taking a beta-blocker. With the POISE criteria, 48 (10%) of the 504 patients were therefore eligible for perioperative beta-blocker treatment.

There is a significant difference between the criteria used in the Mangano and POISE studies as regards the indications (79% versus 41%, $p < .001$) and contraindications (7% versus 28%, $p < .001$) for beta-blocker treatment. A statistically significant difference was also found in the number of patients eligible for beta-blocker treatment in applying the Mangano and POISE criteria (42% versus 10%; $p < .001$).

Discussion

To date, there are no data in the literature on the generalization of perioperative beta-blocker studies. In fact, this is the first study on this topic.

Applying the POISE study criteria greatly restricted the prescription of perioperative beta-blockers compared with the Mangano-study criteria. The criteria for inclusion in this study preferentially targeted patients at risk of perioperative heart disease and cardiac events. The various contraindications associated with the use of beta-blockers are also much more detailed in the POISE study, and they therefore limit the prescription of this medication. It is also interesting to observe that although the POISE criteria target a more precise group of patients at risk, the results of that study are still inconclusive because the reduction

Table 2. Patient Characteristics

Variables	Patients
	***n* = 504**
Age (years)	67 ± 12
Male	249 (49%)
Consumes alcohol	35 (7%)
CHD	164 (32%)
Cardiovascular risk factors	
Tobacco	85 (17%)
HBP	329 (65%)
Diabetes	126 (25%)
Dyslipidemia	294 (53%)
Other comorbidities	
AF/Flutter	58 (11%)
Heart failure	16 (3%)
TCI/stroke	39 (7%)
PAD	48 (9%)

AF = atrial fibrillation; CHD = coronary heart disease; HBP = high blood pressure; PAD = peripheral arterial disease; stroke = cerebrovascular accident; TCI = transient cerebral ischemia.

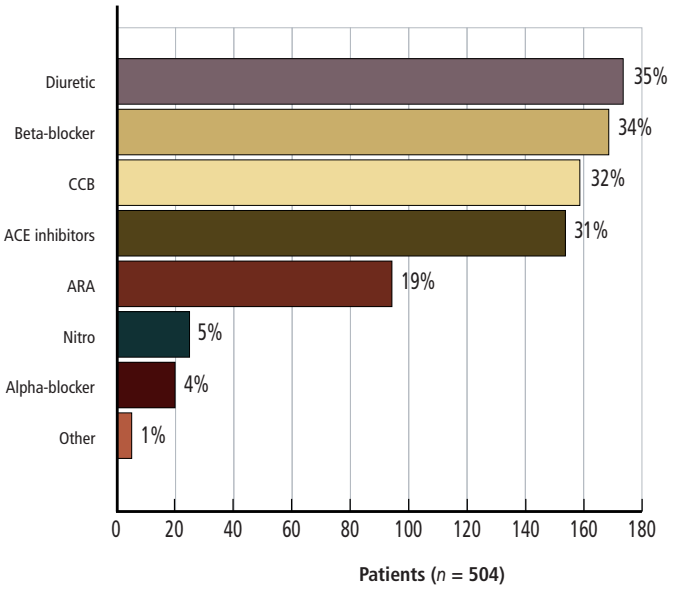

Figure 2. Medication at preoperative clinic. ACE = angiotensin-converting enzyme; ARA = angiotensin receptor antagonist; CCB = calcium channel blocker.

Table 3. Administration of Beta-Blockers When Applying the Mangano and POISE Criteria

Variables	Mangano	POISE	*p* Value
BB indicated	396/504 (79%)	208/504 (41%)	<.001
Contraindication or use of BB	187/396 (47%)	160/208 (77%)	.005
Contraindication	26/396 (7%)	58/208 (28%)	<.001
Use of BB	161/396 (41%)	102/208 (48%)	.048
BB indicated and absence of contraindication or use of BB	209/504 (42%)	48/504 (10%)	<.001

BB = beta-blocker.

in cardiac death, nonfatal heart attacks, and cardiac arrest was achieved at the cost of an increase in total mortality and strokes, which may well greatly limit the use of beta-blockers as a perioperative treatment.[6,9]

In conclusion, an application of the POISE criteria for prescribing perioperative beta-blockers makes a case for using this medication in a much more targeted population. Generalizing the Mangano and POISE studies on the use of perioperative beta-blockers therefore produces very different results.

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Future Developments in GIM

Medical Simulation: Part 2 – Present and Future

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Part 1 of this series (*CJGIM Volume 3, Issue 3*, pp. 172–174) addressed the unique opportunities offered by simulation and the challenges that must be overcome. Part 2 reviews existing programs and identifies research issues likely to dominate the future.

Introduction

This is an exciting time for medical simulation! The cutting-edge of simulation now appears to be collaborative simulation, evidence-based simulation, and developing the science of simulation. National

organizations now exist such as the Society for Simulation in Healthcare (SSIH),[1] the Canadian Resuscitation Institute (CRI),[2] and the Society in Europe for Simulation Applied to Medicine (SESAM).[3] Widespread collaboration can promote national standards, spearhead national advocacy, germinate multicentre trials, and lead to the development of evidence-based educational initiatives. A few of these are discussed below.

Acute Critical Events Simulation

The Acute Critical Events Simulation (ACES) program was designed by CRI,[4] specifically to reduce the incidence of recurrent errors in patient resuscitation efforts. This 2-day course was designed by a nationwide faculty to enhance knowledge and procedural skills and to improve the understanding of team behaviour and communication. It has been delivered to hundreds of candidates and has been highly rated. ACES is one of the first courses to focus on crisis resource management (CRM) skills (see Part 1) and, as such, offers a unique and important supplement to other excellent life support courses.

Simulating Telephone Calls

The large distances and low population density we have in Canada result in the frequent transport of acutely ill patients to higher-care centres. Much of this is coordinated by telephone, but communication skills are rarely addressed. As such, acute care teleconference calls have been simulated to help develop the "verbal-dexterity" and problem-solving abilities required in this setting. Little research has been done regarding how best to transition care from one group to another (for example, from prehospital to the emergency room) or how to safely transport unstable patients across enormous distances. Qualitative evaluation suggests this exercise has been valuable: participants felt this strategy was superior to didactic sessions and complementary to clinical experience. Simulated calls within the same hospital could be performed just as easily, and plans are under way to train both referring and receiving staff using this method.[5]

Simulating Transportation of the Acutely Ill

Wright et al.[6] studied the impact on resuscitation procedures of an air ambulance helicopter environment. With the craft idling on the ground, they were able to simulate the noise and vibration of an in-flight transport, and found this had profound implications for resuscitation efforts. Alarms were missed and monitors seemed blurred, making this environment particularly difficult to work in.

Once again evaluations were very positive.[6] One can easily imagine other difficult scenarios that health care workers might find themselves working in, such as in the confined spaces one finds in the back of ambulances or in elevators. Optimizing transportation and transition between teams is a poorly studied area, but one with huge potential.

Simulating Disaster Response

High-fidelity simulation has been used to develop (and refine) complex disaster plans. These recommendations are often extensively discussed, but are filed away in binders and rarely practised. Without testing and refinement, experience suggests they will not be properly applied during the chaos of an evolving crisis. Equally, it is not appropriate to learn through trial and error when the consequences of error could be to worsen an already desperate situation. Furthermore, while patient safety is now receiving long overdue attention, similar efforts are needed to ensure the safety of the health care worker. An example of such a challenge was the outbreak of severe acute respiratory syndrome (SARS) in Toronto in 2002–2003.

Abrahamson et al. used simulation to teach resuscitation during SARS.[7] This syndrome presented new paradigms that previously could not be addressed by standard protocols. For example, hospital workers needed to re-train *not* to vigorously bag-ventilate patients (given the risk of dispersing the SARS virus). Furthermore, workers needed to learn how to put on a personal protective suit (PPS) before they could attend to a patient. Intubation of the SARS patient required suiting up in order to mitigate exposure and transmission. However, this seriously hampered communication and procedural dexterity. Simulation "provided insights that had not been considered in earlier phases."[7] Expressed another way, if you plan in a boardroom, you will typically come up with boardroom solutions! Abrahamson et al. had initially timed individuals at 1.5–2.5 minutes to don these suits, and designed their protocols around this assumption. However, during simulation, the actual time was 3.5–5.5 minutes. Using results from the actual simulation, they revised their protocol and corrected unanticipated errors in infection control. Impressively, these authors were able to train 275 health care workers within 2 weeks.[7] These same opportunities exist whether for training in mass casualty, avian flu, or just another disastrous day in an overcrowded emergency room.

Rapid Response Team Training

Busy medical staff often fail to recognize when inpatients show early clinical deterioration.[9,10] Even when deterioration is recognized, health care workers often fail to initiate treatment.[10,11] There is little doubt that, for many acute illnesses, the outcome is far better with early intervention compared to waiting for full cardiovascular collapse.[9–12] However, there is equally still considerable debate as to the best way to institutionalize rapid response.[10,11] Different jurisdictions have implemented rapid response teams. In Canada, by far the most common model is the medical emergency team (MET).[11]

In theory, MET is activated when inpatients reach predetermined aberrant vital signs. MET usually consists of a physician, respiratory therapist, and a nurse. These professionals must be able to work together in an efficient and collegial way despite stressful situations and disparate training. Equally, despite numerous patients competing for their attention, ward nurses are expected to remember to activate MET in a timely manner. Medical simulation has therefore been recommended as a way to train all the personnel involved in these calls.[2]

DeVita et al.[13,14] used simulation to enhance multidisciplinary team skills during evolving medical crises. Following this training, simulated survival (following predetermined criteria for death) increased from 0 to 89%. A similar Medical Outreach Program has been developed by the CRI and has trained health care workers throughout Ontario.[2] These initiatives suggest that simulation has enormous potential to help in both triage and resuscitation.

While few argue with the idea of responding rapidly, the current research has not shown an unequivocal benefit following MET

implementation.[9] Simulation has a vital, but currently underutilized, role in this debate. It may be invaluable in the study of how best to introduce rapid response, and in understanding the complexities of the hospital culture within which it functions. Over time, simulation can be used to train personnel, to finesse rapid response, and to individualize programs for different care environments.

Simulation Research

Lord Kelvin stated that if knowledge could not be expressed in numbers, then it was meagre and unsatisfactory. This "Kelvin's curse"[15] complicates quantitative research of qualitative skills such as *communication* and *teamwork*. Whether didactic lecturing is beneficial has never been held to similar scrutiny, nor have other professions demanded proof before mandating widespread simulation. The skills addressed through simulation are not meagre or unimportant; we know that poor communication and teamwork are the principal causes of preventable medical error (see Part 1). Such outcomes are often difficult to quantify.

An intriguing question is that, given all the potential benefits of medical simulation (and the lack of any obvious downside), just what level of proof is needed? Most simulation research does not reach the level of proof expected of traditional research. For example, in a review of over 670 articles covering 34 years, McGaghie et al. identified that only 5% of simulation research publications met or exceeded minimum quality standards.[16]

Proponents of simulation have cited aviation industry standards that mandate regular simulation training for pilots entrusted with passenger's lives; therefore, standards for medical staff, entrusted with a patient's lives, should be no different. Equally, if simulation were regarded in the same light as a pharmaceutical agent, with the potential to improve outcomes and no clear side effects, practitioners would demand widespread access. These common sense arguments are worth making but cannot be confused with definitive proof.

We may indeed be approaching a state where medical simulation will become accepted based upon its face validity. However, it must be acknowledged that data are powerful allies when looking to change practice or redirect funding in times of fiscal restraint.

In short, simulation is almost certainly here to stay, but how rapidly accepted or widely integrated it becomes will be influenced by how well it grows into a scientific discipline. Obstacles to research exist, but the opportunities for benefit are too great not to persevere.

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Thrombolysis in Pulmonary Embolism

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Case Report

A 62-year-old hypertensive man presented to the emergency room with sudden-onset retrosternal chest pain and shortness of breath that began abruptly while working on a construction site. The pain had a mild pleuritic component. There was no history of antecedent angina symptoms. His past medical history was unremarkable. He had no known cardiovascular risk factors and was not taking any regular medications.

On examination, the patient was diaphoretic. His pulse was 110 bpm, blood pressure 100/70 (no gradient between arms), and respiratory rate 25 breaths/min, and he had an O_2 saturation of 92% on 4 L/min of oxygen by nasal cannula. His JVP was not elevated. A precordial examination revealed a normal apex with no abnormal pulsations. Cardiac auscultation revealed normal heart sounds, with no extra sounds or murmurs. Crackles and wheezes were not present on auscultation of the chest. The abdomen was normal, and there was no peripheral edema or clinical signs suggestive of deep vein thrombosis.

His blood tests were normal, with the exception of a troponin I level of 0.60 μg/L (normal value <0.05 μg/L) and a D-dimer of >4,000 μg/L (normal value <500 μg/L). Twelve-lead electrocardiography showed sinus tachycardia with an inferior T wave inversion.

Given the small troponin rise and the high D-dimer, a computed tomography (CT) of the chest was performed to rule out other etiologies of chest pain with associated troponin elevation, such as a pulmonary embolus or thoracic aortic dissection. The CT scan revealed large pulmonary emboli in the right and left main pulmonary arteries with extension into the lower lobe vasculature (Figure 1). An emergent bedside echocardiography was performed, which demonstrated moderate right ventricular (RV) hypokinesis and left ventricular septal flattening consistent with an acute elevation of the RV pressure. The pulmonary pressure, estimated from the TR jet, was elevated at 61 mm Hg (normal <30 mm Hg).

Given the radiographic and echocardiographic evidence of RV hemodynamic compromise, the patient he was treated with intravenous tissue plasminogen activator (t-PA) in a monitored critical care setting, with good initial results. Repeat echocardiography the following day showed a significant improvement in his RV function, with a normalization of his pulmonary artery pressure. Further investigations did not reveal the source or etiology of his pulmonary emboli. He was discharged home on a low molecular weight heparin as a bridge to warfarin therapy, and outpatient workup of a hypercoagulable state.

Discussion

Pulmonary embolism (PE) is a relatively common clinical problem encountered by almost all physicians across the spectrum of clinical medicine. The annual incidence of PE is estimated at 0.5 per 1,000 people, with an estimated mortality of 15% at 3 months.[1] Although the diagnosis may be elusive due to atypical clinical presentations, the overall prognosis is favourable for normotensive patients in whom anticoagulation is promptly initiated. For those 5% with clinically massive PE – as manifested by failure of the right ventricle and hemodynamic instability – the prognosis is dismal, with up to a 50% risk of in-hospital mortality, often within hours of presentation. Given the poor survival in this subset of patients, urgent recanalization of the obstructed pulmonary artery is necessary.

Treatment options include mechanical recanalization with surgical

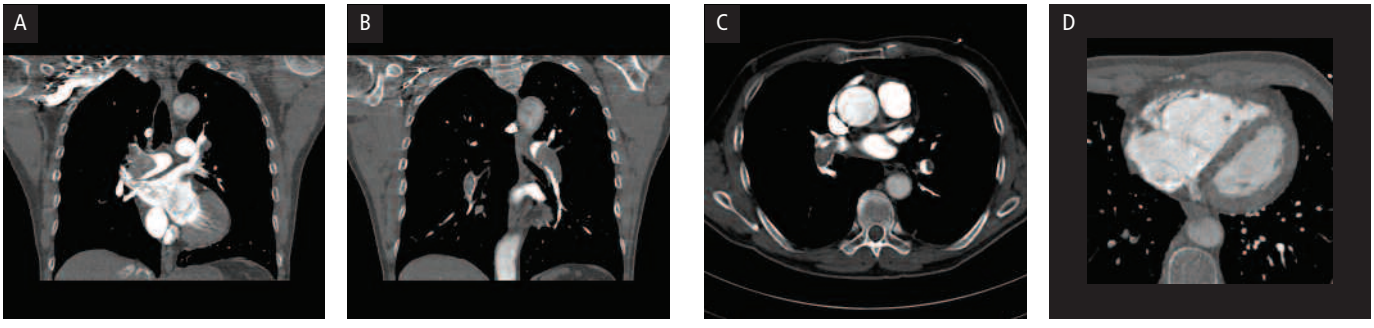

Figure 1. Computed tomography scans showing bilateral main pulmonary artery pulmonary emboli with extension into the left lower lobe segmental branch (panels A, B, and C). There was also right ventricular enlargement with contrast reflux into the IVC and hepatic arteries, suggesting right ventricular dysfunction (panel D).

embolectomy, a procedure revisited in light of favourable results of a recent surgical trial.[2] However, the primary therapeutic option is thrombolytic therapy. In five trials that included patients with hemodynamically unstable (massive) PE, there was a significant reduction in recurrent PE or death (9.4% versus 19.0%; odds ratio [OR] 0.45) with a number needed to treat (NNT) of 10.[3] Thrombolysis is therefore the preferred treatment in this group.

Although early thrombolysis (within 48 hours) has been shown to result in rapid resolution of the thrombotic obstruction and improvement in echocardiographic hemodynamic parameters, there is no evidence suggesting a benefit of thrombolysis compared with heparin for the initial treatment of acute PE *without* hemodynamic compromise.[3] Hence, thrombolysis should be reserved for those patients in whom a high risk of early PE-related death is anticipated.

For the normotensive patients with submassive PE, the standard of care involves treatment with intravenous heparin followed by long-term low molecular weight heparin or oral warfarin. Recent analyses have confirmed that his cohort may not be as homogeneous as previously thought. Analyses of registry data have suggested that the presence of subclinical RV dysfunction, even in normotensive patients, confers a poor prognosis with an increased risk of a fatal outcome.[4,5] Given the aforementioned potential benefit of thrombolysis, it has been suggested that this subpopulation would derive benefit from early thrombolysis compared with heparin.[6]

Currently available methods of identifying this subgroup include laboratory biomarker-based methods and cardiac imaging. For patients with hemodynamically stable submassive PE, the presence of a normal troponin has been shown to accurately rule out an adverse outcome in patients with PE.[6] In a study by Becattini et al., the authors concluded that elevated troponin levels were significantly associated with short-term mortality (OR 5.24, 95% CI 3.28–8.38), PE-related death (OR 9.44, 95% CI 4.14–21.49), and adverse outcome events (OR 7.03, 95% CI 2.42–20.43). Interestingly, these results remained significant for multiple isozymes (I and T) as well as multiple assays. Likewise, this association with mortality held true in a subgroup of hemodynamically stable patients (OR 5.90, 95% CI 2.68–12.95).[7]

Echocardiography and CT remain the two most common tests to identify patients with RV dysfunction. In addition to quantifying thrombus burden, CT imaging can also provide a static assessment of RV dimensions and, by extension, function. For example, one study from 2004 showed that in patients with acute PE, RV enlargement ($RV_{DIMENSION}/LV_{DIMENSION}$ >0.9) on a reconstructed four-chamber view was a predictor of early death with a hazard ratio of 3.36 for 30-day mortality.[8] This finding was also shown to have a good negative predictive value, with a 92% survival for those without RV enlargement. As most CT is not currently gated to the cardiac cycle, both overestimation and underestimation of the CT-derived RVD-LVD ratio may occur.

ECG gating offers the advantage of minimizing or eliminating motion artifact – allowing for more precise measurements of ventricular diameters. As well, retrospective ECG gating with CT acquisition throughout the cardiac cycle allows cine evaluation of wall motion and RV function. However, this technique involves significant cost and radiation exposure and adds little to the specificity of predicting 30-day mortality; it is not justified for routine clinical use.[9]

Transthoracic echocardiography (TTE) is the modality of choice for assessing RV function. Kucher et al. demonstrated that TTE evidence of RV hypokinesis within 24 hours of presentation is correlated with an increased 30-day mortality.[10] Several registries and cohort studies have confirmed this finding.

To date, there have been only two randomized controlled trials specifically examining the outcome of thrombolysis in normotensive patients with submassive PE and RV dysfunction.[11,12] Kucher et al.[10] randomized 101 patients with submassive PE and echocardiographic RV dysfunction to alteplase or heparin. At 24 hours, significant improvement was seen in RV wall motion (39% versus 17%; $p = .005$), RV end-diastolic area ($p = .01$), and pulmonary perfusion (14.6% versus 1.5%; $p < .0001$). Goldhaber et al.[13] examined 256 patients with submassive PE and pulmonary hypertension or RV dysfunction. Although echocardiography was performed in >90% of subjects, only 31% were found to have RV dysfunction. Alteplase was shown to be a safe treatment for hemodynamically stable patients with acute submassive PE and reduced subsequent treatment escalation (i.e., the use of vasopressors, respiratory support). In the accompanying editorial, it was suggested that "*we should seriously consider expanding the indications for thrombolysis [to] carefully selected, normotensive patients with pulmonary embolism who have moderate or severe right ventricular dysfunction*."[13]

Summary

In this case, we describe a patient who presented with chest pain, shortness of breath, and a mild troponin elevation suggesting an initial diagnosis of acute coronary syndrome. However, the pleuritic component to his chest pain and the absence of antecedent angina or cardiovascular risk factors suggested the alternative diagnosis. Once the diagnosis of PE was confirmed, the next step was to assess its severity. Submassive PE with poor prognosis was suggested by (1) elevated troponin, (2) normotension but significant tachycardia, (3) a large thrombus burden as seen on CT, and (4) RV dysfunction seen on echocardiography. These points argued in favour of a more aggressive approach, with thrombolytics. In patients with fewer points of concern, the risk of thrombolysis needs to be weighed against the potential for benefit. This article argues that the benefits may be more significant than previously appreciated.

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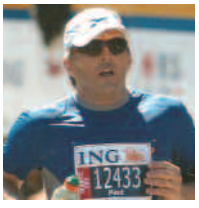
Practice of GIM

Heart Rates and Hydration Status Measured in the Cape Breton Fiddlers Marathon

Paul MacDonald, MD



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Legend has it that Pheidippides was an Athenian runner who, in 490 BC, ran from Marathon, where the Greeks had defeated the Persian invasion, to Athens to announce their victory. After covering the 26 miles, he collapsed dead.

Despite this, in 2006 there were 410,000 runners completing a marathon in the United States alone. Heart attacks and sudden death are extremely rare, but reports certainly raise the concern of extreme levels of exercise in the general population.[1–7]

The benefits of physical activity in preventing cardiovascular disease are well established.[8] However, the triggering of myocardial infarction or sudden cardiac death with heavy physical exertion has also been widely noted.[9–12] The risk for sudden cardiac death associated with marathons has been reported to range from 1 in 50,000 to 1 in 80,000.[13] This is much higher than the 1 in 1.5 million deaths with vigorous exercise reported in the Physicians' Health Study.[14]

The causes for most cardiac-related events are underlying, unrecognized coronary artery disease. Less common causes include unrecognized cardiomyopathies and congenital heart disease.[1,2] A study of the 2002 Boston Marathon reported a surprisingly high rate of hyponatremia and overhydration occurring in 13% of runners tested.[15]

We sought to analyze high heart rates as a potential trigger for acute myocardial infarction and sudden cardiac death, as well as to screen for hydration status using blood pressure and hypernatremia and hyponatremia in a community marathon comprised of both experienced and inexperienced runners.

Methods

We conducted a descriptive cross-sectional study of runners in the inaugural Cape Breton Fiddlers Run held in Sydney, Nova Scotia, on October 30, 2005. Volunteers were recruited prior to the race, with no exclusion criteria.

Table 1. Details of Participants Wearing a Holter Monitor

Runner	Age	Gender	Full or Half-Marathon	Time
1	48	F	Half	2:01:16
2	64	M	Half	1:54:16
3	35	M	Half	1:42:26
4	47	F	Half	2:20:53
5	51	M	Half	1:47:18
6	56	M	Full	4:00:11
7	45	M	Full	3:08:03

Table 2. Target, Maximum, and Average Heart Rates for Participants Wearing a Holter Monitor

Runner	Max. THR	Max. HR	Average HR	>85%	>100%	N/E
1	172	184	160	85%	57%	N
2	156	186	149	88%	66%	E
3	185	203	162	82%	70%	N
4	177	177	149	73%	<1%	N
5	166	159	145	87%	0	E
6	164	177	151	73%	43%	E
7	175	175	154	87%	0	E

E = experienced; HR = heart rate; N = novice; THR = target heart rate (220 – Age).

Eight volunteers were fitted with Holter electrocardiographic monitors (General Electric SEER Light monitors) placed with a shoulder strap and leads attached in a standard five-lead fashion. Monitors were placed approximately 30–60 minutes before the race and removed after the race. Data were analyzed using a General Electric version C software and reviewed by cardiologist (P.M.) to determine maximum heart rate as well as average heart rate and number of heart beats above 85% age-predicted maximum and above 100% age-predicted maximum. Age-predicted maximum heart rate was calculated as 220 minus age, with standard recommended heart rates for exercise between 55 and 85% of maximum heart rate.[16]

A second group of postrace volunteers also completed questionnaires on their racing experience, and baseline measurements were made by registered nurses (using arm sphygmomanometers) including age, height, waist circumference, weight, heart rate, resting blood pressure, race times, types of fluids consumed during the race, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs). Race volunteers were also asked whether they voided, which may indicate adequate hydration. After giving informed consent, race volunteers had blood samples drawn to measure sodium and potassium levels. A Johnson & Johnson/Ortho Clinic 950 Vitros analyzer (dry technology) was used. Mean standard deviations for baseline demographics were calculated using an SPS statistical package. A Spearman correlation was used to further assess data.

Results

The race began at 8 a.m. in a temperature of 7°C (45°F), 78% humidity, under cloudy skies. Results were available from seven of eight Holter monitors, with one failing to properly record (Table 1). All seven runners spent most of the race at approximately 85% of their maximum age-predicted heart rate (Table 2). However, four runners spent between 43 and 70% of the race above their calculated 100% maximum heart rate. There did not seem to be any significant correlation in this small group between novice and experienced runners, male and female, age or race time.

For the hydration portion of our study, blood samples were obtained from 78 runners (35% of total participants; Table 3). No cases of severe hyponatremia (<130 mmol/L) were found. Our normal range for sodium is 137–145. Two participants' sodium levels were reported

Table 3. Hydration Results

	Half-Marathon	Full Marathon
Winning time	1:23:02	2:45:29
Total finishers	134	89
No. in study	41	37
Novice (%)	29	27
Age (yr)*	42.8	45.7
Male (%)	64	70
Hyponatremia (<137)	0	2
Severe hyponatremia (<130)	0	0
Hypernatremia (>145)	4	5
Hyperkalemia (K >5.0)	6	9
Void during race	6	13
Postrace low BP (<90)	2	7
Postrace high HR (>100)	9	9

BP = blood pressure; HR = heart rate.

*Range 16–69 yr.

below normal at levels of 135 and 136 in the full marathon. Five of 37 (13.5%) in the full marathon and 4 of 41 (9.7%) in the half-marathon showed high sodium, suggesting dehydration as being much more common.

There was no correlation between high potassium and sodium levels. Hyperkalemia occurred in participants aged 40–58, in the absence of renal disease or NSAID use. There was no difference in the types of fluids consumed, or whether the runner was novice or experienced. However, 8 of 9 (89%) cases of hypernatremia occurred in male participants, which is more than expected. Furthermore, a history of voiding did not predict hydration status. Runners were asked if they drank enough: only 2 of 9 dehydrated runners said they had not.

Not surprisingly, there is a moderately positive correlation between age and race time in the full marathon ($R = 0.48$, $p = .006$). There was also a correlation with postrace heart rate and race times found in the full marathon ($R = 0.54$, $p < .001$). Finally, there was also a correlation between lower blood pressures and longer race times ($R = –0.36$, $p < .05$). Higher heart rates and low blood pressure may

represent more dehydration, poorer physical conditioning, or a combination of both. Race times over 4 hours had the most increased heart rates and blood pressures in the full marathon.

Interpretation

We have previously reported excessive heart rates during adult recreational hockey,[17] with concern that this may trigger acute ischemic events and heart attack or death. We expected better heart rate control among distance runners; but, in a small sample size, some runners still exhibited very high heart rates and for prolonged periods of time while competing in a community-level half- or full marathon.

Previous recommendations from the American College of Sports Medicine regarding exercise and fluid replacement encouraged increasing consumption of fluids before and during long-distance running.[13] While this strategy may be responsible for the hyponatremia reported by Almond et al.,[15] we did not see any significant hyponatremia and were much more likely to see cases of hypernatremia and dehydration. Also, our study noted that men were more prone to dehydration, where men would have shorter race times and a greater body surface area. The Boston study by Almond et al. noted that women are more prone to overhydration. Further, we did not find any significant risk with the types of fluids consumed, anti-inflammatories used, whether participants had voided during the race, or their perception of adequate hydration.

Sudden cardiac death with running remains rare but important. As was seen with gentlemen hockey players, our study showed a high range of heart rate responses in a half- and full marathon among both novice and experienced runners. We also showed that dehydration seemed much more common, with no cases of overhydration seen in our community race. Again, individual monitoring and caution would allow the vast majority of recreational athletes to enjoy such competitive events as safely as possible.

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Pronostic cérébrovasculaire d'une scintigraphie myocardique normale

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La maladie cardiovasculaire (cardiopathie et accident vasculaire cérébral) constitue la première cause de décès au Canada (36%). Elle est la principale cause d'hospitalisation et elle impose un lourd fardeau économique tant au niveau collectif qu'au système de santé.[1] Ces données sont d'autant plus alarmantes vu le vieillissement de la population.

Plusieurs études ont démontré qu'une scintigraphie myocardique normale est associée à un faible risque d'événements cardiaques et ce, pour au moins 12 à 24 mois suivant la tenue de l'examen.[2–4] Puisque l'athérosclérose est un phénomène systémique,[5] un examen normal pourrait conférer également un bon pronostic cérébrovasculaire.

Le but de notre étude était de déterminer le pronostic cardiaque et cérébrovasculaire des patients avec scintigraphie myocardique de stress normale chez l'homme et chez la femme. Notre objectif secondaire était d'évaluer l'influence de l'âge et du type d'examen sur la venue d'événements. L'analyse des données permettra ainsi une meilleure compréhension du risque vasculaire global.

Méthodes

Nous avons sélectionné de façon rétrospective les dossiers de patients avec scintigraphie myocardique (Technicium^{99m} Sestamibi ou Thallium-201) réalisée sous stress pharmacologique (Dipyridamole) ou à l'exercice, au Centre Hospitalier Universitaire de Sherbrooke. Les données ont été obtenues pour la période de janvier 1998 à décembre 2000 inclusivement, à l'aide de la banque dénominalisée « CIRESSS » (Centre informatisé de recherche évaluative en services et soins de santé).

Cette étude a été autorisée par la direction des services professionnels du Centre Hospitalier de Sherbrooke.

Population

La population comprend tous les patients ayant eu un rapport de scintigraphie myocardique normale entre janvier 1998 et décembre 2000 inclusivement. Une scintigraphie était également considérée normale si le nucléiste faisait mention d'un phénomène probablement dû à l'atténuation mammaire ou diaphragmatique en l'absence d'autres anomalies rapportées.[6] Nous avons rejeté les procédures où il y avait tout autre anomalie ou si un effort insuffisant était mentionné.

Nous avons compilé l'âge, le sexe et type d'examen pour chaque patient. Si plus d'un examen était disponible durant la période choisie, nous conservions le premier réalisé.

Issues

Parmi les patients avec scintigraphie myocardique normale, nous avons sélectionné toutes les hospitalisations pour un événement cardiaque ou neurologique pour les 5 années suivant la tenue de l'examen. Les événements cardiaques incluaient tout infarctus avec élévation du segment ST / infarctus sans élévation du segment ST / infarctus avec onde Q / infarctus sans onde Q. Les événements neurologiques incluaient tout accident vasculaire cérébral / occlusion artérielle avec infarctus cérébral. Le décompte de ces événements a été fait en questionnant la banque informatisée avec les mots-clefs ci-dessus. Advenant le cas où un même patient avec plus d'un événement, le premier de chaque catégorie (cardiaque ou neurologique) était conservé.

Statistiques

Les comparaisons entre les groupes de patients ont été faites à l'aide du test de chi carré pour les variables catégoriques. Une erreur alpha inférieure à 0,05 était considérée significative.[7] Les variables catégoriques ont été décrites selon leur fréquence et les variables continues selon leur moyenne ± DS.

Les facteurs prédictifs d'événements ont été déterminés avec un modèle de régression de Cox.[8] Les variables analysées dans le modèle sont le sexe, l'âge et le type d'examen (effort ou stress pharmacologique). Des courbes de Kaplan-Meier pour les deux types d'événements à 5 ans furent construites en fonction des caractéristiques des patients.[9] Toutes les analyses statistiques ont été réalisées à l'aide du logiciel SPSS version 14.0.

Les auteurs avaient libre accès aux données et prennent la responsabilité de l'intégrité du contenu.

Résultats

Un total de 5499 scintigraphies myocardiques de stress ont été complétées dans la période déterminée, 2292 femmes (41,7%) et 3207 hommes (58,3%). De ce total, 1607 (29,2%) étaient dictées normales, 981 femmes (42,8%) et 626 hommes (19,5%). Il y a une différence statistiquement significative entre les sexes ($p < 0{,}001$) (Tableau 1).

Un plus grand nombre d'examen a été fait sous stress pharmacologique plutôt que par le biais d'une épreuve d'effort et ce, pour les 2 sexes. L'âge moyen était de 62,3 ± 11,4 ans (Tableau 1).

Issues

Le nombre total d'événements a été de 95 sur un suivi de 5 ans, correspondant à environ 5,9% de la population étudiée. Un seul patient a présenté à la fois un événement cardiaque et neurologique. La

Tableau 1. Caractéristiques des patients

	Femmes	Hommes	Total	Différences statistique entre les sexes, *p*
Scintigraphies au total (%)	2292 (41,7)	3207 (58,3)	5499	
Normales (%)	981 (42,8)	626 (19,5)	1607 (29,2)	<0,0001
Scintigraphies à l'effort (%)	224 (22,8)	236 (37,7)	460	
Scintigraphies sous stress pharmacologique (%)	757 (77,2)	390 (62,3)	1147 (714)	<0,0001
Âge moyen	63,5 ± 11,4	60,5 ± 11,1	62,3 ± 11,4	

proportion d'accidents vasculaires cérébraux par rapport au nombre total d'événements a été d'environ un tiers dans les deux groupes (35,4 % vs. 27,7%, p = NS) (Tableau 2).

Par analyse de régression logistique, le fait d'être un homme est associé à la survenue d'infarctus du myocarde (p = 0,006), mais il n'en va pas de même pour les accidents vasculaires cérébraux (p = 0,066). L'âge ne semble pas prédictif d'événements cardiaques suivant une scintigraphie myocardique normale (p = 0,300). Par contre, l'âge est un facteur prédictif d'événements neurologiques (p = 0,003). Le type de stress sous lequel était réalisé l'examen n'a pas eu d'influence sur la type d'événements (p = 0,680 pour les infarctus vs. p = 0,057 pour les accidents vasculaires cérébraux).

L'analyse des courbes de Kaplan-Meier comparant le sexe avec l'apparition d'infarctus du myocarde démontre une nette démarcation entre les courbes et celle-ci s'accentue avec le temps. Cependant, le taux d'événements demeure tout de même faible (Figure 1).

Discussion

Dans notre établissement, il y a un plus grand nombre de scintigraphies

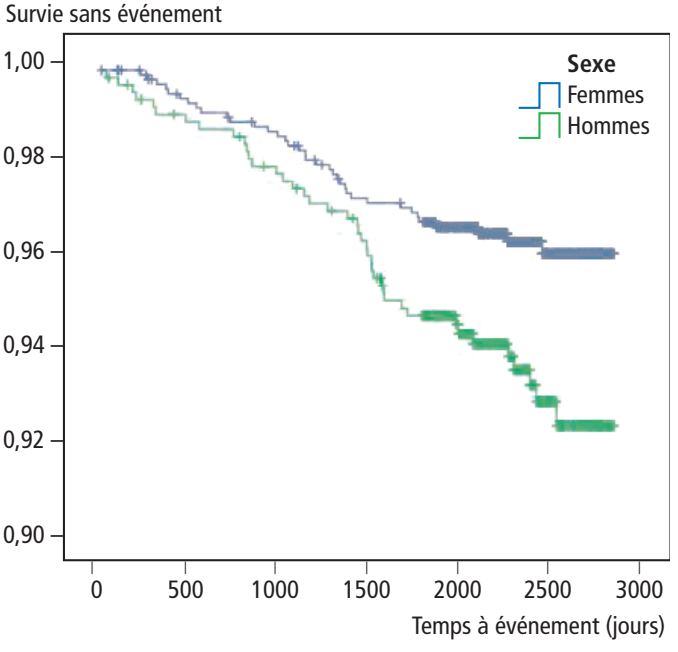

Figure 1. Courbe de survie sans infarctus du myocarde.

myocardiques de stress normales chez les femmes que chez les hommes. Bien sûr, les phénomènes d'atténuation constituent une source de perte de sensibilité et de spécificité diagnostic,[10] d'autant plus fréquents chez la femme vu la présence du tissu mammaire. Cependant, les techniques de prise d'images et d'interprétation se sont beaucoup améliorées au fil des années,[11,12] et nous savons qu'un examen démontrant des anomalies mineures demeure de bon pronostic cardiovasculaire.[6] C'est pourquoi les phénomènes d'atténuation ne peuvent que partiellement expliquer la différence entre les sexes dans le nombre d'examens normaux et le devenir des patients. Une hypothèse plausible est que la population étudiée diffère. En effet, les hommes bénéficiant d'une scintigraphie pourraient représenter une population à plus haut risque, la probabilité pré-test étant plus élevée ou l'examen étant plutôt pronostic que diagnostic. De plus, l'interprétation d'un tapis roulant chez la femme comporte un bon nombre de faux-positifs qui ont pu justifier un examen diagnostic supplémentaire.[13,14]

Le taux d'événements demeure faible dans notre population. La faiblesse majeure de notre étude est son caractère rétrospectif ayant pu mené à la perte d'événements. En revanche, les données quant à la survenue d'infarctus du myocarde correspondent à la littérature actuelle[4] tout comme la proportion d'accidents vasculaires cérébraux.[1] Il semble ainsi très rassurant et logique qu'une scintigraphie myocardique normale soit d'un bon pronostic vasculaire global. Étant le seul centre tertiaire de la région, il est à noter que notre centre traite la majorité des patients, surtout lorsqu'une investigation cardiaque ou neurologique est de mise.

Les hommes ont plus d'événements cardiaques que les femmes et les courbes de Kaplan- Meier semblent davantage se dissocier au fil des années. Ces données correspondent aux statistiques actuelles. L'analyse des accidents vasculaires cérébraux ne permet pas de conclure si le sexe influence différemment l'évolution des patients. Ce phénomène s'explique probablement par le faible nombre d'événements puisque le sexe féminin est déjà corrélé à la survenue d'accidents vasculaires cérébraux.[15] Seul l'âge semble être un facteur significatif pour les

Tableau 2. Événements à 5 ans

	Cardiaques	Neurologiques	Total
Femmes (%)	31 (3,2)	17 (1,7)	48 (4,9)
Hommes (%)	34 (5,4)	13 (2,1)	47 (7,5)
Total (%)	65 (4,0)	30 (1,9)	95 (5,9)

accidents vasculaires cérébraux.

Il est certain que notre étude comporte quelques limitations. Plusieurs facteurs confondants n'ont pu être évalués tels les antécédents vasculaires, le tabac, le diabète, la dyslipidémie, l'hypertension, la médication, la variabilité inter observateurs dans l'interprétation de l'examen. La banque informatisée CIRESSS est un outil d'interrogation puissant mais qui est basé sur les diagnostics au congé de l'hôpital, ce qui limite le nombre de variables analysées. De plus, notre population représente celle d'un seul centre tertiaire. Cependant, la taille de notre échantillon est importante et tous nos résultats concordent avec la littérature actuelle. Il s'agit d'une première étude sur ce sujet et d'autres études seront nécessaires pour mieux évaluer ces associations.

Conclusions

L'âge et le sexe influencent de façon différente le type d'événement. Cependant, un examen normal semble associé à la fois à un bon pronostic cardiaque et neurologique et pourrait permettre de discriminer une population qui bénéficierait peu d'une prévention pharmacologique primaire.

Remerciements

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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
- 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

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

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 of venous 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 sc or placebo once daily for 14 days and followed for up to 90 days. Primary end point was incidence of VTE on day 21; Secondary end points 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 2006.

3. Geerts W, Pineo G, Heit J *et al.* Prevention of venous thromboembolism: The Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest* 2004;126:338S–400S.

4. Drug Coverage.ca: A Guide to Reimbursement. Available at: www.drugcoverage.ca/. Accessed February 23, 2008.

Januvia™

(sitagliptin phosphate monoydrate)

Prescribing Summary

Patient Selection Criteria

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

INDICATIONS AND CLINICAL USE

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.

Geriatrics (≥65 years of age): No dosage adjustment is required base on age however, greater sensitivity of some older individuals cannot be ruled out (see WARNINGS AND PRECAUTIONS, DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY in the product monograph).

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

CONTRAINDICATIONS

Patients who are hypersensitive to this drug or to any ingredient in the formulation (see WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions and ADVERSE REACTIONS, Post-Marketing Adverse Drug Reactions in the Supplemental Product Information section). For a complete listing, see DOSAGE FORMS, COMPOSITION AND PACKAGING in the product monograph.

SPECIAL POPULATIONS

For use in special populations, see WARNINGS AND PRECAUTIONS, Special Populations.

Safety Information

WARNINGS AND PRECAUTIONS

General

JANUVIA™ 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 JANUVIA™. 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 JANUVIA™, with some reports occurring after the first dose. If a hypersensitivity reaction is suspected, discontinue JANUVIA™, 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).

Special Populations

Pregnant Women: There are no adequate and well-controlled studies in pregnant women; therefore, the safety of JANUVIA™ in pregnant women is not known. JANUVIA™ is not recommended for use in pregnancy (see also TOXICOLOGY in the product monograph).

Nursing Women: Sitagliptin is secreted in the milk of lactating rats. It is not known whether sitagliptin is secreted in human milk. Therefore, JANUVIA™ should not be used by a woman who is nursing.

Geriatrics (≥65 years of age): In clinical studies, no overall differences in safety or effectiveness were observed between subjects 65 years and over and younger subjects.While this and other reported clinical experience have not identified differences in responses between the geriatric and younger patients, greater sensitivity of some older individuals cannot be ruled out.

This drug is known to be substantially excreted by the kidney. Renal function should be assessed prior to initiating dosing and periodically thereafter in geriatric patients because they are more likely to have decreased renal function (see DOSAGE AND ADMINISTRATION, and ACTION AND CLINICAL PHARMACOLOGY in the product monograph).

Cardiovascular - Patients with Congestive Heart Failure: 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.

Hepatic Insufficiency: 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 (see ACTION AND CLINICAL PHARMACOLOGY in the product monograph).

Renal Insufficiency: Clinical study experience with JANUVIA™ in patients with moderate or severe renal insufficiency including those with ESRD is limited. Use in these patients is not recommended (see ACTION AND CLINICAL PHARMACOLOGY in the product monograph).

Monitoring and Laboratory Tests

Response to all diabetic therapies should be monitored by periodic measurements of blood blucose and HbA_{1c} levels, with a goal of decreasing these levels towards the normal range. HbA_{1c} is especially useful for evaluating long-term glycemic control. Sitagliptin is substantially excreted by the kidney. Renal function should be assessed prior to initiating dosing and periodically thereafter.

ADVERSE REACTIONS

(see Supplemental Product Information for full listing)

Adverse Drug Reactions Overview

JANUVIA™ was generally well tolerated in controlled clinical studies as a 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 JANUVIA™ as add-on combination therapy with metformin (reported regardless of causality, and more common with JANUVIA™ than other treatments) was nasopharyngitis.

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 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.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations: JANUVIA™ can be taken with or without food.

Recommended Dose and Dosage Adjustment: The recommended dose of JANUVIA™ is 100 mg once daily.

Missed Dose

If a dose of JANUVIA™ is missed, it should be taken as soon as the patient remembers. A double dose of JANUVIA™ should not be taken on the same day.

Study References

Supplemental Product Information

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

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. For more details on adverse reactions reported in ≥1% of patients in any treatment group, regardless of causality, during clinical trials see ADVERSE REACTIONS, Clinical Trial Adverse Drug Reactions, Tables 1 and 2 in the product monograph.

Less Common Clinical Trial Adverse Drug Reactions ≥0.1% and <1% (Drug-Related and Greater than Placebo)

Cardiac Disorders: bundle branch block

Gastrointestinal Disorders: abdominal discomfort, abdominal pain upper, diarrhea, dyspepsia, flatulence, reflux esophagitis disease, retching

General Disorders and Administration Site Conditions: face edema, malaise, peripheral edema, pain

Hepatobiliary Disorders: hepatic steatosis

Infections and Infestations: gastric ulcer helicobacter, helicobacter gastritis, upper respiratory tract infection

Investigations: blood glucose decreased

Metabolism and Nutrition Disorders: decreased appetite, hypoglycemia

Musculoskeletal and Connective Tissue Disorders: muscle tightness

Nervous System Disorders: migraine, neuropathy peripheral, parosmia, somnolence

Reproductive System and Breast Disorders: dysmenorrhea, erectile dysfunction

Respiratory, Thoracic and Mediastinal Disorders: cough

Skin and Subcutaneous Tissue Disorders: exanthem, rash, urticaria

Vascular Disorders: orthostatic hypotension

Nausea was the only drug-related adverse reaction reported by the investigator that occurred with an incidence ≥1% in patients receiving JANUVIA™ (1.1%) and greater than in patients receiving placebo (0.4%).

Abnormal Hematologic and Clinical Chemistry Findings

The incidence of laboratory adverse experiences was similar in patients treated with JANUVIA™ 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. For more details see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings in the product monograph.

Post-Marketing Adverse Drug Reactions

The following additional adverse reactions have been identified during post-marketing use of JANUVIA™: Hypersensitivity reactions including anaphylaxis, angioedema, rash, urticaria, and exfoliative skin conditions, including Stevens-Johnson syndrome.

DRUG INTERACTIONS

Drug-Drug Interactions: 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). For more details, see DRUG INTERACTIONS, Drug-Drug Interactions in the product monograph.

Drug-Food Interactions: There are no known interactions with food.

Drug-Herb Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with herbal products have not been established.

Drug-Laboratory Interactions: Interactions with laboratory tests have not been established.

Drug-Lifestyle Interactions: No studies of the effects of JANUVIA™ on the ability to drive and use machines have been performed. However, JANUVIA™ is not expected to affect the ability to drive and use machines.

OVERDOSAGE

During controlled clinical trials in healthy subjects, single doses of up to 800 mg JANUVIA™ 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 JANUVIA™ (see ACTION AND CLINICAL PHARMACOLOGY in the product monograph). There is no experience with doses above 800 mg in humans.

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.

(1125-a,3,08)
34501025, 34501025a, 34501025b, 34501025c, 34501025d

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PAAB

EZETROL®
ezetimibe

Prescribing Summary

Patient Selection Criteria

THERAPEUTIC CLASSIFICATION

Cholesterol Absorption Inhibitor

INDICATIONS AND CLINICAL USE

EZETROL® (ezetimibe) is indicated as an adjunct to lifestyle changes, including diet, when the response to diet and other non-pharmacological measures alone has been inadequate.

Primary Hypercholesterolemia

EZETROL®, administered alone or with an HMG-CoA reductase inhibitor (statin), is indicated for the reduction of elevated total cholesterol (total-C), low density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B), and triglycerides (TG) and to increase high density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia.

EZETROL®, administered in combination with fenofibrate, is indicated for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

Homozygous Familial Hypercholesterolemia (HoFH)

EZETROL®, administered with a statin, is indicated for the reduction of elevated total-C and LDL-C levels in patients with HoFH as an adjunct to treatments such as LDL apheresis or if such treatments are not possible.

Homozygous Sitosterolemia (Phytosterolemia)

EZETROL® is indicated for the reduction of elevated sitosterol and campesterol levels in patients with homozygous familial sitosterolemia.

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

When EZETROL® is to be administered with a statin or with fenofibrate, the contraindications to that medication should be reviewed before starting concomitant therapy.

The combination of EZETROL® with a statin is contraindicated in patients with active liver disease or unexplained persistent elevations in serum transaminases.

All statins and fenofibrate are contraindicated in pregnant and nursing women. When EZETROL® is administered with a statin or with fenofibrate in a woman of childbearing potential, refer to the product labeling for that medication (see WARNINGS AND PRECAUTIONS; Special Populations; Pregnant Women).

SPECIAL POPULATIONS

For use in special populations, see WARNING AND PRECAUTIONS, Special Populations.

Safety Information

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- hepatitis
- pancreatitis
- myopathy/rhabdomyolysis
- myalgia
- anaphylaxis (see ADVERSE REACTIONS; Post-Market Adverse Drug Reactions in the Supplemental Product Information section).

General

When EZETROL® is to be administered with a statin or with fenofibrate, please refer also to the Product Monograph for that medication.

Hepatic/Biliary/Pancreatic

Concomitant Administration with a Statin or Fenofibrate: When EZETROL® is initiated in a patient already taking a statin or fenofibrate, liver function tests should be considered at initiation of EZETROL® therapy, and then as indicated (see ADVERSE REACTIONS, Abnormal Hematologic and Clinical Chemistry Findings in the Supplemental Product Information section).

When EZETROL® is initiated at the same time as a statin or fenofibrate, liver function tests should be performed at initiation of therapy and according to the recommendations of that medication (see ADVERSE REACTIONS; Abnormal Hematologic and Clinical Chemistry Findings in the Supplemental Product Information section).

Liver Enzymes: In controlled monotherapy studies, the incidence of consecutive elevations (≥3 times the upper limit of normal [ULN]) in serum transaminases was similar between EZETROL® (0.5%) and placebo (0.3%).

In controlled co-administration trials in patients receiving EZETROL® with a statin, the incidence of consecutive transaminase elevations (≥3 X ULN) was 1.3% compared to 0.4% in patients on a statin alone.

Patients with Liver Impairment: The pharmacokinetics of ezetimibe were examined in patients with impaired liver function as defined by the Child-Pugh scoring system.

- In patients with mild hepatic insufficiency (Child-Pugh score 5 or 6), the mean area under the curve (AUC) for total ezetimibe (after a single 10 mg dose of EZETROL®) was increased approximately 1.7-fold compared to healthy subjects. No dosage adjustment is necessary for patients with mild hepatic insufficiency.
- In patients with moderate hepatic insufficiency (Child-Pugh score 7 to 9), the mean AUC for total ezetimibe (after multiple doses of 10 mg daily) was increased approximately 4-fold on Day 1 and Day 14 compared to healthy subjects. Due to the unknown effects of the increased exposure to ezetimibe in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score >9) hepatic insufficiency, ezetimibe is not recommended in these patients.
- No pharmacokinetic studies with ezetimibe have been carried out in patients with either active liver disease or unexplained and persistent elevations in serum transaminases. It is recommended that care be exercised in such patients.

Post-marketing reports of adverse events have included rare cases of hepatitis in patients taking EZETROL®, although causality has not been proven. If patients develop signs or symptoms of hepatitis, liver function should be evaluated.

Concomitant Administration with fibrates: The co-administration of ezetimibe with fibrates other than fenofibrate has not been studied. Therefore, co-administration of EZETROL® and fibrates (other than fenofibrate) is not recommended (see DRUG INTERACTIONS).

Fenofibrate: If cholelithiasis is suspected in a patient receiving EZETROL® and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered (see ADVERSE REACTIONS in the Supplemental Product Information section and the Product Monograph for fenofibrate).

Pancreatitis: Post-marketing reports of adverse events have included rare cases of acute pancreatitis occurring in patients taking EZETROL®, although causality has not been proven. The diagnosis of acute pancreatitis should be considered in patients taking EZETROL® who develop sudden acute abdominal pain.

Muscle Effects

Myopathy/Rhabdomyolysis: Myopathy and rhabdomyolysis are known adverse effects of statins and fibrates. Post-marketing reports of adverse events have included rare cases of myopathy/rhabdomyolysis occurring in patients taking EZETROL® with or without a statin, regardless of causality. Myopathy/rhabdomyolysis should be considered in patients presenting with muscle pain during treatment with EZETROL® with or without a statin or fenofibrate, and consideration given to discontinuation of the drugs. Most cases of myopathy/rhabdomyolysis resolved when drugs were discontinued.

Myalgia: In controlled clinical trials, the incidence of myalgia was 5.0% for EZETROL® vs 4.6% for placebo (see ADVERSE REACTIONS, Table 2 in the product monograph). Post-marketing reports of adverse events have included myalgia in patients taking EZETROL® with or without a statin, regardless of causality. Patients should be instructed to contact their physician if they experience persistent and severe muscle pains with no obvious cause.

A number of patients treated with EZETROL®, in whom myalgia occurred had previously experienced myalgia (with or without elevated CK levels) with statin therapy. Patients with a history of statin intolerance (myalgia with or without elevated CK levels) should be closely monitored for adverse muscle events during treatment with EZETROL®.

Renal

Renal Insufficiency: After a single 10 mg dose of EZETROL® in patients with severe renal disease, the mean AUC for total ezetimibe was increased approximately 1.5 fold, compared to healthy subjects. Accordingly, no dosage adjustment is necessary for renal impaired patients.

Special Populations

Pregnant Women: No clinical data on exposed pregnancies are available for EZETROL®. The effects of ezetimibe on labour and delivery in pregnant women are unknown. Note that all statins and fenofibrate are **contraindicated** in pregnant women (see the Product Monograph for that medication). Caution should be exercised when prescribing to pregnant women.

Nursing Women: Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL® should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant.

Pediatrics: The pharmacokinetics of EZETROL® in adolescents (10 to 18 years) have been shown to be similar to that in adults. Treatment experience with EZETROL® in the pediatric population is limited to 4 patients (9 to 17 years) in the sitosterolemia study and 5 patients (11 to 17 years) in the HoFH study. Treatment with EZETROL® in children (<10 years) is not recommended.

Geriatrics/Sex/Race: No dosage adjustment is necessary in the elderly or on the basis of sex or race (see WARNINGS AND PRECAUTIONS, Special Populations in the product monograph).

ADVERSE REACTION

(see full listing in the Supplemental Product Information)

Adverse Drug Reaction Overview

The most commonly reported adverse events in clinical studies were upper respiratory tract infection, headache, myalgia and back pain. In post-marketing use, serious adverse events reported rarely or very rarely, regardless of causality, included hepatitis, hypersensitivity reactions, pancreatitis and myopathy/rhabdomyolysis.

To report a suspected adverse reaction, please contact Merck Frosst-Schering Pharma, G.P. by:

Toll-free telephone: 1-800-567-2594

Toll-free fax: 1-877-428-8675

By regular mail:

Merck Frosst-Schering Pharma, G.P.
P.O. Box 1005
Pointe-Claire - Dorval, QC H9R 4P8

DRUG INTERACTIONS

Serious Drug Interactions

- cyclosporine

Drug-drug interactions are known or suspected with cholestyramine, cyclosporine and fibrates. For the full listing of drug-drug interactions, see DRUG INTERACTIONS in the product monograph.

Cholestyramine: Concomitant cholestyramine administration decreased the mean AUC of total ezetimibe (ezetimibe + ezetimibe-glucuronide) approximately 55%. The incremental LDL-C reduction due to adding ezetimibe to cholestyramine may be lessened by this interaction.

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see WARNINGS AND PRECAUTIONS,

ADVERSE REACTIONS in the Supplemental Product Information section). Co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of EZETROL® with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Cyclosporine: Caution should be exercised when initiating ezetimibe in the setting of cyclosporine. Cyclosporine concentrations should be monitored in patients receiving EZETROL® and cyclosporine.

In a study of eight post-renal transplant patients with creatinine clearance of >50 mL/min on a stable dose of cyclosporine, a single 10 mg dose of ezetimibe resulted in a 3.4-fold (range 2.3- to 7.9-fold) increase in the mean AUC for total ezetimibe compared to a healthy control population from another study (n=17). In a different study, a renal transplant patient with severe renal insufficiency (creatinine clearance of 13.2 mL/min/1.73 m^2) who was receiving multiple medications, including cyclosporine, demonstrated a 12-fold greater exposure to total ezetimibe compared to concurrent controls.

In contrast, in a two-period crossover study in twelve healthy subjects, daily administration of 20 mg ezetimibe for 8 days with a single 100-mg dose of cyclosporine on Day 7 resulted in a mean 15% increase in cyclosporine AUC (range 10% decrease to 51% increase) compared to a single 100-mg dose of cyclosporine alone.

Administration

DOSAGE AND ADMINISTRATION

Dosing Considerations

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

Recommended Dose and Dosage Adjustment

The recommended dose of EZETROL® is 10 mg once daily orally, alone, with a statin, or with fenofibrate. EZETROL® can be taken with or without food at any time of the day but preferably at the same time each day.

No dosage adjustment is required for elderly patients, children and adolescents ≥10 years, patients with mild hepatic insufficiency (Child-Pugh score 5 to 6), and patients with renal impairment.

Treatment with EZETROL® is not recommended in patients with moderate (Child-Pugh score 7 to 9) or severe (Child-Pugh score >9) liver dysfunction (see WARNINGS AND PRECAUTIONS).

Co-administration with Bile Acid Sequestrants: EZETROL® should be administered either 2 hours or longer before or 4 hours or longer after administration of a bile acid sequestrant (see DRUG INTERACTIONS, Cholestyramine).

Missed Dose

The recommended dosing regimen is one tablet, once daily. If a dose is missed, the patient should be counselled to resume the usual schedule of one tablet daily.

Study References

1. Product Monograph EZETROL® (ezetimibe) tablets, Merck Frosst-Schering Pharma, G.P., 2008

Supplemental Product Information

ADVERSE REACTIONS

Clinical Trial Adverse Drug Reactions

EZETROL® clinical trial experience involved 2486 patients in placebo-controlled monotherapy trials (1691 treated with EZETROL®) and 4547 patients in active controlled trials (449 of whom were treated with EZETROL® alone and 1708 treated with EZETROL® plus a statin and 185 patients treated with EZETROL® and fenofibrate). The studies were of 8 to 14 weeks duration. The overall incidence of adverse events reported with EZETROL® was similar to that reported with placebo and the discontinuation rates due to treatment related adverse events was similar between EZETROL® (2.3%) and placebo (2.1%).

Monotherapy: Adverse experiences reported in ≥2% of patients treated with EZETROL® and at an incidence greater than placebo in placebo-controlled studies of EZETROL®, regardless of causality assessment, are shown in Table 1 of the product monograph.

The frequency of less common adverse events was comparable between EZETROL® and placebo.

Only two patients out of the 1691 patients treated with EZETROL® alone reported serious adverse reactions-one with abdominal pain plus panniculitis, and one with arm pain and palpitation.

In monotherapy placebo-controlled clinical trials, 4% of patients treated with EZETROL® and 3.8% of patients treated with placebo were withdrawn from therapy due to adverse events.

Combination with a Statin: EZETROL® has been evaluated for safety in combination studies in more than 2000 patients. In general, adverse experiences were similar between EZETROL® administered with a statin and a statin alone. However, the frequency of increased transaminases was slightly higher in patients receiving EZETROL® administered with a statin than in patients treated with a statin alone (see WARNINGS AND PRECAUTIONS; Hepatic/Biliary/Pancreatic; Patients with Liver Impairment).

Clinical adverse experiences reported in ≥2% of patients and at an incidence greater than placebo in four placebo-controlled trials where EZETROL® was administered alone or initiated concurrently with various statins, regardless of causality assessment, are shown in Table 2 of the product monograph.

In co-administration placebo-controlled clinical trials, 5.7% of patients treated with EZETROL® co-administered with a statin, 4.3% of patients treated with statin alone, 5.0% of patients treated with EZETROL® alone, and 6.2% of patients treated with placebo were withdrawn from therapy due to adverse events.

Combination with Fenofibrate: In a clinical study involving 625 patients treated for up to 12 weeks and 576 patients treated for up to 1 year, co-administration of EZETROL® and fenofibrate was well tolerated. This study was not designed to compare treatment groups for infrequent events. Incidence rates (95% CI) for clinically important elevations (> 3 X ULN, consecutive) in serum transaminases were 4.5% (1.9, 8.8) and 2.7% (1.2, 5.4) for fenofibrate monotherapy and EZETROL® co-administered with fenofibrate, respectively, adjusted for treatment exposure. Corresponding incidence rates for cholecystectomy were 0.6% (0.0, 3.1) and 1.7% (0.6, 4.0) for fenofibrate monotherapy and EZETROL® co-administered with fenofibrate, respectively (see WARNINGS AND PRECAUTIONS, Fenofibrate and DRUG INTERACTIONS). There were no CPK elevations > 10 X ULN in either treatment group in this study.

Abnormal Hematologic and Clinical Chemistry Findings

In controlled clinical monotherapy trials, the incidence of clinically important consecutive elevations in serum transaminases (ALT and/or AST ≥3 X ULN) was similar between EZETROL® (0.5%) and placebo (0.3%). In co-administration trials, the incidence was 1.3% for patients treated with EZETROL® co-administered with a statin and 0.4% for patients treated with a statin alone. These elevations were generally asymptomatic, not associated with cholestasis, and returned to baseline levels after discontinuation of therapy or with continued treatment.

In clinical trials there was no excess of myopathy or rhabdomyolysis associated with EZETROL® compared with the relevant control arm (placebo or statin alone). However, myopathy and rhabdomyolysis are known adverse reactions to statins and other lipid-lowering drugs. In clinical trials, the incidence of CK >10 X ULN was 0.2% for EZETROL® vs 0.1% for placebo, and 0.1% for EZETROL® co-administered with a statin vs 0.4% for statin alone.

Post-Market Adverse Drug Reactions

The following adverse events have been reported rarely or very rarely, regardless of causality:

- increased CK (creatine phosphokinase)
- myalgia (see WARNINGS AND PRECAUTIONS)
- myopathy/rhabdomyolysis (see WARNINGS AND PRECAUTIONS)
- elevations of liver transaminases
- hepatitis (see WARNINGS AND PRECAUTIONS)
- hypersensitivity reactions, including anaphylaxis, angioedema, rash and urticaria
- nausea
- pancreatitis (see WARNINGS AND PRECAUTIONS)
- thrombocytopenia
- arthralgia
- dizziness
- cholelithiasis
- cholecystitis
- depression
- paresthesia

OVERDOSAGE

In clinical studies, administration of ezetimibe, 50 mg/day to 15 healthy subjects for up to 14 days, or 40 mg/day to 18 patients with primary hypercholesterolemia for up to 56 days, was generally well tolerated. A few cases of overdosage with EZETROL® have been reported; most have not been associated with adverse experiences. Reported adverse experiences have not been serious. In the event of an overdose, symptomatic and supportive measures should be employed.

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

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HOW CAN EZETROL® HELP YOUR PATIENTS GET TO GOAL?

ADDING EZETROL® TO A STATIN PROVIDED

AN ADDITIONAL

25.8%

MEAN REDUCTION IN LDL-C

VS 2.7% WITH A STATIN ALONE FROM MEAN BASELINE LDL-C LEVELS OF 3.3 MMOL/L FOR BOTH TREATMENT GROUPS ($p<0.001$).[1,*]

EZETROL® 10 MG ONCE DAILY FAVORABLE SAFETY AND TOLERABILITY PROFILE

EZETROL®, a cholesterol absorption inhibitor, is indicated as adjunctive therapy to diet, when the response to diet and other non-pharmacological measures has been inadequate.

EZETROL®, administered alone or with an HMG-CoA reductase inhibitor (statin), is indicated for the reduction of elevated total cholesterol (total-C), low-density lipoprotein cholesterol (LDL-C), apolipoprotein B (Apo B) and triglycerides (TG) and to increase high density lipoprotein cholesterol (HDL-C) in patients with primary (heterozygous familial and non-familial) hypercholesterolemia. EZETROL®, administered in combination with fenofibrate, is indicated for the reduction of elevated total-C, LDL-C, Apo B, and non-HDL-C in patients with mixed hyperlipidemia.

EZETROL® is contraindicated in patients with hypersensitivity to any component of this medication. The co-administration of EZETROL® and a statin is contraindicated in patients with active liver disease or unexplained persistent elevations of serum transaminases. All statins and fenofibrate are contraindicated in pregnant and nursing women. When EZETROL® is administered with a statin or with fenofibrate in a woman of childbearing potential, refer to the product labeling for that medication.

When EZETROL® is used with a statin or fenofibrate, liver function tests should be performed at initiation of therapy and according to the recommendations of that medication. When using EZETROL® with or without a statin or fenofibrate, myopathy/rhabdomyolysis should be considered in patients presenting muscle pain and discontinuation of the drugs should be considered.

Due to the unknown effects of EZETROL® in patients with moderate or severe hepatic insufficiency, EZETROL® is not recommended in these patients. For patients developing signs or symptoms of hepatitis, liver functions should be evaluated. If cholelithiasis is suspected in a patient receiving EZETROL® and fenofibrate, gallbladder studies are indicated and alternative lipid-lowering therapy should be considered. Acute pancreatitis should be considered in patients taking EZETROL® who develop sudden acute abdominal pain.

The most commonly reported adverse events in clinical studies were upper respiratory tract infection (13.0%), headache (8.0%), myalgia (5.0%) and back pain (3.4%). In post-marketing use, serious adverse events reported rarely or very rarely, regardless of causality, included hepatitis, hypersensitivity reactions, including anaphylaxis, pancreatitis and myopathy/rhabdomyolysis.

The safety and effectiveness of EZETROL® co-administered with fenofibrate have been evaluated in a clinical study; co-administration of EZETROL® with other fibrates has not been studied. Co-administration with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

BEFORE PRESCRIBING **EZETROL®**, PLEASE CONSULT THE ENCLOSED PRESCRIBING INFORMATION. WHEN **EZETROL®** IS TO BE ADMINISTERED WITH A STATIN OR FENOFIBRATE, PLEASE ALSO CONSULT THE PRODUCT MONOGRAPH FOR THAT MEDICATION.

Reference:

1. Pearson TA et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: The ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clinic Proc 2005;80(5):587-95.

*EASE= Ezetimibe Add-on to Statin for Effectiveness trial. A multicenter, randomized, double-blind, placebo-controlled, 6-week study of community-based hypercholesterolemic patients (n=3030) already on a statin but not at National Cholesterol Education Program Adult Treatment Panel (NCEP ATP) III LDL-C goal. Patients were randomized to receive either ezetimibe 10 mg or placebo in addition to their ongoing statin therapy.

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Merck Frosst-Schering Pharma, G.P., Kirkland, Quebec

FOR EFFICACY EZETROL® ezetimibe and a Statin BETTER TOGETHER!

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See prescribing summary on page 50.