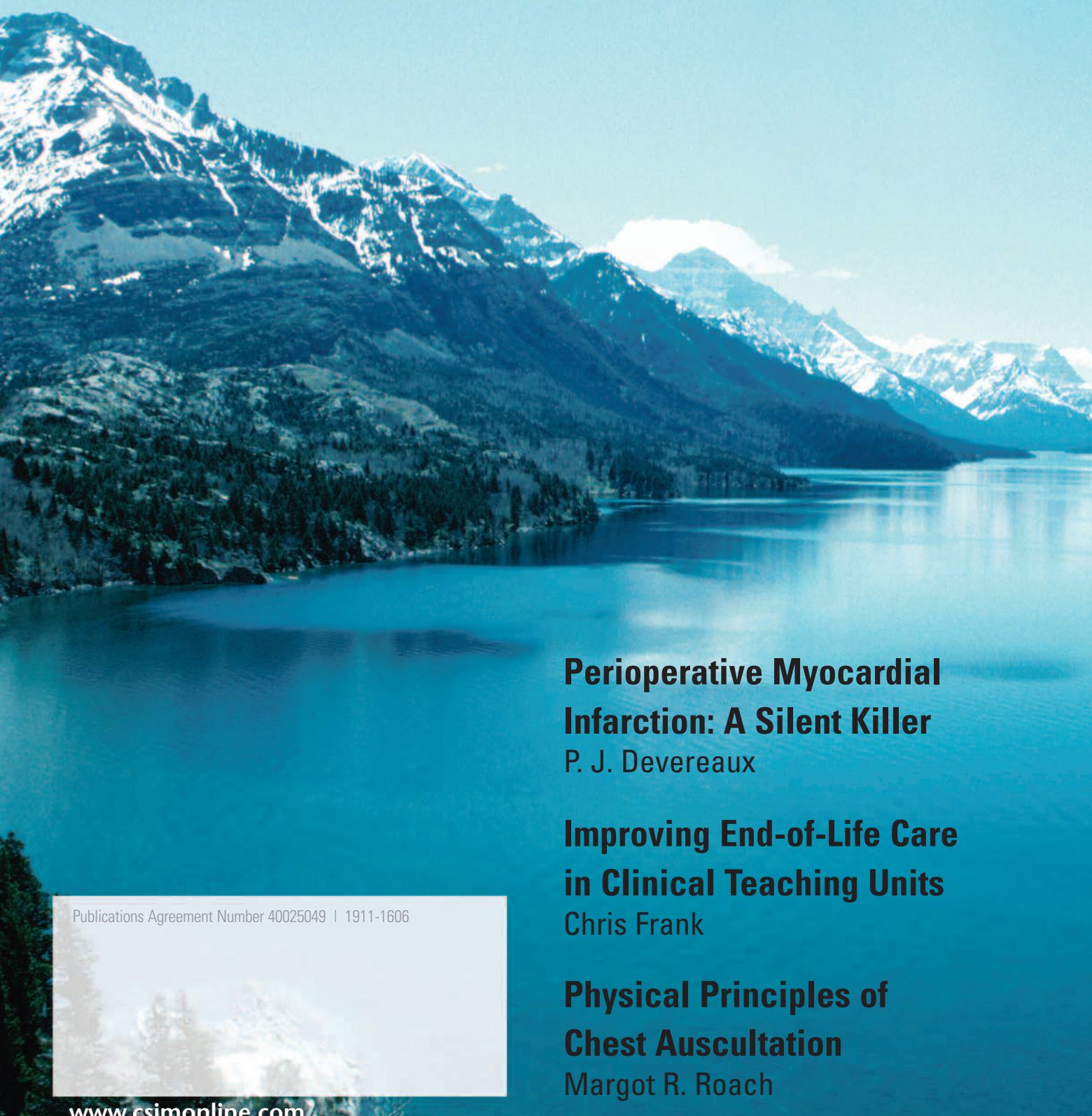
Volume 1, Issue 1
Premier Issue

# Canadian Journal of General Internal Medicine

## LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE



**Perioperative Myocardial Infarction: A Silent Killer**
P. J. Devereaux

**Improving End-of-Life Care in Clinical Teaching Units**
Chris Frank

**Physical Principles of Chest Auscultation**
Margot R. Roach

Publications Agreement Number 40025049 | 1911-1606

www.csimonline.com

# Treat your hypertensive patients with the power of MICARDIS®:

- Powerful 24-hour BP reductions shown, $p<0.0001$ including the early morning hours (6:00 AM-11:59 AM), $p<0.0001$[2†]
- Longest half-life of all $AT_1$ receptor blockers[3-8§]
- Simple, flexible, once-daily dosing[3¥]

## ONTARGET

- The ONTARGET clinical trial program investigates ARB and ACE therapy in more than 31,000 patients.
- ONTARGET investigates MICARDIS® (telmisartan) and ramipril, alone or in combination, in the prevention of cardiovascular morbidity and mortality in patients at high risk for cardiovascular complications.
- Boehringer Ingelheim is committed to cardiovascular protection research.

MICARDIS® is not indicated to reduce cardiovascular or cerebrovascular morbidity and mortality, or to improve renal outcomes.

Pr MICARDIS®

TELMISARTAN 80mg $AT_1$ RECEPTOR BLOCKER

GOOD MORNING. MICARDIS.

Boehringer Ingelheim

COMMITTED TO CARDIOVASCULAR PROTECTION RESEARCH

www.boehringer-ingelheim.ca

PAAB

Member R&D

# MICARDIS® Demonstrated Powerful BP Reductions Measured from MORNING to MORNING[1]


**Demonstrated significantly greater 24-hour ABPM reduction vs. placebo, $p<0.05$[1#]**

MICARDIS® (telmisartan) is indicated for the treatment of mild to moderate essential hypertension and may be used alone or in combination with thiazide diuretics.[3] The most common adverse events vs. placebo were headache (8.0% vs. 15.6%), upper respiratory tract infection (6.5% vs. 4.6%), dizziness (3.6% vs. 4.6%), pain (3.5% vs. 4.3%), fatigue (3.2% vs. 3.3%), back pain (2.7% vs. 0.9%), diarrhea (2.6% vs. 1.0%) and sinusitis (2.2% vs. 1.9%).[3] If pregnancy is detected, MICARDIS® should be discontinued as soon as possible.[3] In patients who are volume-depleted by diuretic therapy, dietary salt restrictions, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with MICARDIS®.[3]

# 6-week, multinational, multicentre, randomized, double-blind, double-dummy, parallel group study comparing MICARDIS® 80 mg and Losartan 50 mg with placebo arm. MICARDIS® 80 mg mean 24-hour SBP vs. placebo = -13.3 mmHg vs. -1.8 mmHg, DBP = -8.4 mmHg vs. -0.8 mmHg, $p<0.05$.

† 14-week, multicentre, prospective, randomized, open-label, blinded-endpoint, parallel group, forced-titration study of MICARDIS® and Altace® in patients with confirmed ambulatory hypertension. Mean 24-hour SBP = -14.8 mmHg vs. -10.7 mmHg, $p<0.0001$ and DBP = -9.9 mmHg vs. -6.7 mmHg, $p<0.0001$. Morning (06:00 AM-11:59 AM) SBP = -14.3 mmHg vs. -9.7 mmHg, $p<0.0001$.

§ Comparative clinical significance is unknown.

¥ Dosing available in MICARDIS® 40 mg, MICARDIS® 80 mg and MICARDIS® PLUS 80/12.5 mg HCTZ.

Canadian Journal of
General Internal Medicine
LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE
Volume 1, Issue 1



| Subscription Rates | 1 year |
|---|---|
| Libraries and hospitals | $60.00 |
| Individuals | $34.00 |
| Single copy | $13.00 |

Canadian subscribers add 6% GST
International and US subscribers remit in US dollars

AJP Andrew John Publishing Inc.

*Canadian Journal of General Internal Medicine* is published four times a year by Andrew John Publishing Inc., with offices located at 115 King Street West, Suite 220, Dundas, ON L9H 1V1.



# CONTENTS

OUR MESSAGE IS SIMPLE

# Adalat® XL®

## Demonstrated to get BP down.

PrAdalat® XL® is also indicated in the management of chronic stable angina†

Adalat® XL® (nifedipine) is indicated in the management of mild to moderate essential hypertension. Adalat® XL® should normally be used in those patients in whom treatment with diuretics or beta-blockers has been ineffective, or has been associated with unacceptable adverse effects.

Adalat® XL® is indicated in the management of chronic stable angina (effort-associated angina) without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or nitrates, or who cannot tolerate these agents. Some patients may benefit from initiation of therapy with Adalat® XL® at 20 mg once daily. Usual maintenance dose with Adalat® XL® is 30 to 60 mg once daily.

*In hypertension*: the most common adverse events reported with Adalat® XL® were edema, which was dose-related and ranged in frequency from approximately 10 to 30% in the 30 to 120 mg dose range, headache (16.6%), fatigue (6.2%), dizziness (4.4%), constipation (3.5%) and nausea (3.5%).

*In angina*: the most common adverse events reported were edema (10.1%), headache (3.1%), angina pectoris (3.1%).

Please refer to the Product Monograph for contraindications, warnings and precautions.

† Effort-associated angina without evidence of vasospasm in patients who remain symptomatic despite adequate doses of beta-blockers and/or nitrates, or who cannot tolerate these agents.

®Adalat is the original brand of nifedipine. Adalat, Bayer and Bayer Cross are registered trademarks of Bayer AG under license to Bayer Inc. XL is a registered trademark of Bayer Inc., denoting its once-daily nifedipine. Round Rose design is a trademark of Bayer Inc.

**Reference:** Product Monograph, Adalat® XL®, revised August 12, 2004.

Bayer HealthCare
Pharmaceuticals Division
Bayer Inc. 77 Belfield Road Toronto, Ontario M9W 1G6

Member R&D PAAB

XL1253-0306E

PrAdalat® XL®
(nifedipine extended release tablets)

BECAUSE IT WORKS

# Table des matières

# Message from the President

What a year! The CSIM has accomplished so much: the Care-Fully document, the application for GIM as a distinct discipline, Health Promotion, CPD, and the transformation of our journal into the *Canadian Journal of General Internal Medicine* (*CJGIM*), to name a few. We're moving so fast. Sometimes I feel breathless just trying to keep up.

We have expanded our journal's editorial board, and learned some of the ins and outs of medical publishing. At the same time, we have noted major upheavals on the Canadian journal landscape. It seems timely to review these events and learn from them.

In February of this year, the *Canadian Medical Association Journal* (*CMAJ*) surprised us all by dismissing their editor in chief, Dr. John Hoey, and his deputy, Anne Marie Todkill, both with over ten years' experience. At that time the *CMAJ*, with 70,000 subscribers, was ranked as the fifth-leading general medical journal in the world. Receiving more than 100 original research papers per month, it could afford to be highly selective in publishing the most important of these. The *CMAJ* became full-text and free online in 1999, and online readers have outnumbered print readers by more than six to one. Its impact extends well beyond the Canadian borders: only a third of its readership live in Canada.

Trouble had been brewing at the *CMAJ* for some time. In 2001 the journal published an editorial supporting the medical use of marijuana. This was followed by an editorial concerning doctors in Shawinigan, Quebec, whose ER department closed six minutes before the arrival of a patient with an acute MI. The patient died on the way to the nearest open ER. On re-reading the original editorial and ensuing correspondence, we learn that there may have been some misinterpretation of Dr. Hoey's meaning, amplified by a French translation in which the phrase "broken trust" ("confiance rompue") was translated as "betrayed trust" ("confiance trahie").

The straw that broke the camel's back was an article that appeared in December 2005, dealing with the newly approved emergency contraceptive pill. A dispute with the publishers led to the dismissal of the editors, citing "irreconcilable differences." The controversy provoked much discussion over important societal issues such as the role of pharmacists in the health care system; their duty to obtain sufficient patient information before dispensing certain OTC medications; patients' right to privacy and confidentiality; the difference between scientific research and investigative reporting; and the role of editorial independence.

Eight senior and intermediate editors along with sixteen of the nineteen members of the journal's editorial board subsequently resigned in protest. Some scientific editors agreed to stay on and help to stabilize and maintain the *CMAJ*. The CSIM has a particular interest in these events. Dr. Hoey is a respected internist, epidemiologist, and public health physician. In fact, he was one of my professors way back in the 1970s at the "Vic" in Montreal.

Much ink has been spilled on the fate of this journal, and several important issues have been debated in the *Lancet*, *New England Journal of Medicine*, and the *CMAJ* itself. "How can one determine if a dispute is about editorial independence? Is editorial independence limited to original research or should it include commentary, editorials and news coverage?"

Several months later, things are looking much brighter for the CMA. They have accepted all twenty-five recommendations of the Pound Report on governance. These recommendations include the transfer of *CMAJ* from CMA Holdings Inc (a for-profit subsidiary) back to the CMA; strengthening of the Journal Oversight Committee; and allowing the editor-in-chief full control of content, regardless of the topic.

What has this taught us? We have learned of the importance of editorial independence. We have learned of the importance of carefully selecting the correct phrase to avoid misunderstanding. And we have learned of the importance of precise translation.

Dr. Hoey is developing an online medical journal to appear in the next few months titled *Open Medicine* (www.openmedicine.ca). In addition, he has also graciously agreed to provide editorial advice for the *CJGIM*.

We aim to inform, and to provide a forum for, our own readership, which extends beyond our membership to many of the 2,400 medical specialists in Canada who practise GIM.

CSIM turns an exciting page with the first issue of *CJGIM*. Wish us luck!

*Donald Echenberg*

# Message du Président

Quelle année ! La Société canadienne de médecine interne a accompli tellement de choses : le document Care-Fully, la requête pour que la médecine interne générale soit reconnue comme une discipline distincte, la promotion de la santé, CPD, et la transformation de notre revue en *Canadian Journal of General Internal Medicine* (*CJGIM*), pour n'en nommer que quelques-unes. Tout va si vite que parfois je me sens essoufflé à vouloir garder la cadence.

Nous avons élargi notre comité de rédaction et avons également acquis des connaissances en édition médicale. En même temps, nous avons observé les bouleversements survenus dans l'édition au Canada. Il semble opportun de revoir ces événements et d'en tirer une leçon.

En février dernier, le *Canadian Medical Association Journal* (*CMAJ*) nous a causé une surprise en renvoyant son rédacteur en chef, le Dr John Hoey, et son adjointe Anne Marie Todkill, les deux ayant plus de dix ans d'expérience. À ce moment-là, le *CMAJ*, avec ses 70 000 abonnés, occupait le cinquième rang parmi les revues médicales à travers le monde. Le *CMAJ* pouvait se permettre d'être très sélectif et de publier les articles de recherche les plus importants car il en recevait plus de 100 par mois. Le *CMAJ* a été publié en texte intégral et offert en ligne en 1999, et les lecteurs en ligne avaient dépassé le nombre des lecteurs de la copie papier de plus de six contre un. Les répercussions ont été ressenties bien au-delà des frontières canadiennes; seulement un tiers des abonnés vit au Canada.

Les problèmes au *CMAJ* existaient depuis quelque temps. En 2001, la revue a publié un éditorial qui favorisait l'emploi médical de la marijuana. Puis il a été rapporté dans un éditorial que des médecins à Shawinigan, Québec, avaient fermé le service d'urgence six minutes avant l'arrivée d'un patient souffrant d'un infarctus du myocarde aigu. Le patient est décédé lors du transport à un autre service d'urgence. À la relecture de l'éditorial original et de la correspondance qui s'ensuivit, nous avons constaté qu'il y avait peut-être eu une fausse interprétation de la signification du message du Dr Hoey, interprétation amplifiée par une traduction en français de "broken trust" ("confiance rompue") par "betrayed trust" ("confiance trahie").

Un article paru en décembre 2005 a été la goutte qui fit déborder le vase. Il était question dans cet article de la nouvelle pilule contraceptive du lendemain qui venait d'être approuvée. Un différend avec les éditeurs a provoqué la démission des rédacteurs en raison d'incompatibilité. La controverse a provoqué beaucoup de discussion sur des sujets à caractère social tels que le rôle des pharmaciens dans le système des soins de santé; leur rôle dans l'obtention de renseignements suffisants sur le patient avant de vendre certains médicaments grand public; le droit des patients à la confidentialité et à la vie privée; la différence entre la recherche scientifique et le journalisme d'enquête; et le rôle de l'indépendance du journalisme.

Huit rédacteurs senior et intermédiaires, ainsi que seize des dix-neuf membres du comité de rédaction de la revue ont démissionné en guise de protestation. Certains rédacteurs scientifiques ont accepté de continuer avec la revue et d'aider à stabiliser et maintenir le *CMAJ*. La Société canadienne de médecine interne était tout particulièrement intéressée à ces événements. Le Dr Hoey est un interniste, épidémiologiste et médecin de santé publique respecté. En fait, il était un de mes professeurs en 1970 au "Vic" à Montréal. Beaucoup d'encre a coulé au sujet du devenir de cette revue et plusieurs questions ont été soulevées dans le *Lancet*, le *New England Journal of Medicine,* et le *CMAJ*. Comment déterminer si un conflit est au sujet de l'indépendance du journalisme? Est-ce que l'indépendance du journalisme est limitée à une recherche nouvelle ou doit-elle inclure un commentaire, un éditorial et la couverture de l'actualité?

Plusieurs mois plus tard, la situation semble s'être rétablie au CMA. Ils ont accepté les vingt-cinq recommandations du Pound Report sur la gouvernance. Ces recommandations consistent à transférer le *CMAJ* de CMA Holdings Inc. (une filiale à but lucratif) au CMA; à consolider le Comité de surveillance de la revue; à permettre au rédacteur en chef d'avoir le plein contrôle du contenu, quel que soit le sujet.

Qu'avons-nous appris? Nous avons appris l'importance de l'indépendance du journalisme. Nous avons appris l'importance de bien choisir la phrase exacte pour éviter une mauvaise interprétation et nous avons également appris l'importance d'une traduction fidèle.

Le Dr Hoey est en train de mettre au point une revue médicale en ligne qui paraîtra au cours des prochains mois et qui s'intitule *Open Medicine* (www.openmedicine.ca). De plus, il a accepté avec plaisir de donner des conseils à la rédaction du *CJGIM*.

Notre but est d'informer et de fournir un forum à notre propre lectorat qui va au-delà des 2400 spécialistes médicaux au Canada qui pratiquent la médecine interne générale. La Société canadienne de médecine interne tourne une page importante avec l'arrivée du premier numéro du *CJGIM*. Souhaitez-nous bonne chance!

*Donald Echenberg*

# What's in a Name?

Many of you will ask, "Do I need a new journal? I already get several, and another will not be read." I have good news for you—this is still *The General Internist*, but with a new name. Don't worry; no extra trees will be felled to produce it. We now have a publisher, to the relief of our secretariat. The serendipitous task of funding each issue is now more organized and less demanding. *Canadian Journal of General Internal Medicine* (*CJGIM*) will have the hallmarks of a professional journal and a distribution of thousands.

Its new name emphasizes the fact that this is a Canadian journal, for the Canadian internist, with a Canadian focus. It aims to address common issues, answer common questions, and provide a forum for discussion and a platform for debate. In other words, it seeks to give our readers what our profession desperately needs—better communication. Communication between internists in varied practices across the country; between residents and career opportunities; between health care planners and specialists in the field; between the Royal College and the CSIM.

It also has the potential to showcase GIM across Canada. Departments of Medicine and individuals in the trenches can tell us what they do, what works, and what doesn't. What's new in teaching methods? Fellows and residents and students can put pen to paper, and see their work in print. Whether it be case reports, journal reviews, original research, or commentary, now there is a place to read it.

GIM faces challenging times, as numbers falter and recruitment proves tough. We need to explain to students and residents what it is we do and why we love doing it. We need to define our role in Canadian medicine, as a premier specialty in our own right, and move forward with conviction. Community and university specialists will have to form new partnerships, in education and research. And you'll read about it in *CJGIM*.

Justification indeed for a new name.

We welcome your opinions, your ideas, and your involvement. Write to us. We are *your* journal.

*Hector M. Baillie*

# Le nom, est-ce important?

Plusieurs d'entre vous se demanderont «Avons-nous besoin d'une autre revue? J'en déjà reçois plusieurs et je n'aurai pas le temps d'en lire une autre.» J'ai de bonnes nouvelles pour vous – il s'agit toujours de la revue *The General Internist*, mais sous un nouveau nom. Ne vous faites pas trop de souci, on ne coupera pas plus d'arbres pour la produire. Nous avons maintenant un éditeur, au grand bonheur de notre secrétariat. L'agréable tâche du financement de chaque numéro est maintenant plus organisée et moins exigeante. Le *Canadian Journal of General Internal Medicine* (*CJGIM*) possèdera tous les attraits d'une revue professionnelle et sera distribuée à des milliers de personnes.

Son nouveau nom vient souligner qu'il s'agit d'une revue canadienne, pour les internistes au Canada. Elle traite des enjeux courants, permet de répondre aux questions et fournit un forum pour la discussion et une plateforme pour le débat. En d'autres mots, elle permet d'offrir aux lecteurs ce que la profession recherche avidement — une meilleure communication, c'est-à-dire la communication entre les internistes de diverses pratiques au Canada; entre les résidents et les empleurs; entre les planificateurs des soins de santé et les spécialistes du domaine; entre le Collège royal et la Société canadienne de médecine interne.

Elle a également la possibilité de présenter la médecine interne générale partout au Canada. Les départements de médecine et les membres actifs peuvent nous dire ce qu'ils font, ce qui fonctionne et ce qui ne fonctionne pas, nous parler des nouveautés en méthodes d'enseignement. Les résidents et ceux qui font de la recherche et les étudiants peuvent publier leur travail. Qu'il s'agisse de rapports de cas, d'analyse de revues, de recherche nouvelle ou de commentaires, il est possible de les lire.

La médecine interne générale fait face à une période particulièrement difficile, à mesure que le nombre décline et que le recrutement s'avère difficile. Nous devons expliquer aux étudiants et aux résidents ce que nous faisons et pourquoi nous aimons ce que nous faisons. Nous devons définir notre rôle en médecine au Canada, en tant que spécialité, et continuer notre cheminement avec conviction. Les spécialistes communautaires et universitaires devront former de nouveaux partenariats en éducation et en recherche. Vous pourrez lire à ce sujet dans le *CJGIM*.

Vraiment, c'est une raison d'adopter un nouveau nom.

Nous apprécions votre opinion, vos idées et votre engagement. Écrivez-nous. Nous sommes *votre* revue.

*Hector M. Baillie*

# Perioperative Myocardial Infarction: A Silent Killer

P. J. Devereaux, MD, PhD; Justin de Beer, MD; Juan Carlos Villar, MD, PhD; Denis Xavier, MD; Akbar Panju, MB; Otavio Berwanger, MD, PhD; Germán Málaga, MD; Luc Lanther, MD, MSc; Jørn Wetterslev, MD, PhD

ABSTRACT

In this article, we discuss perioperative myocardial infarction in patients undergoing noncardiac surgery. Despite the limitations of previous research, the evidence suggests that a substantial number of patients undergoing noncardiac surgery suffer a myocardial infarction. Frequently, perioperative myocardial infarctions are clinically silent but nonetheless important events altering patient prognosis for death and further major cardiac events. Interventions may improve both the short- and long-term prognoses of patients suffering a perioperative myocardial infarction. To avoid missing perioperative myocardial infarctions, physicians should consider surveillance measures. Although large high-quality studies are needed, in the interim, physicians should consider monitoring troponins daily during the first 3 days after noncardiac surgery in patients with or at high risk of atherosclerotic disease.

## What Is the Frequency of Myocardial Infarction in Patients Undergoing Noncardiac Surgery?

Approximately 100 million adults worldwide undergo major noncardiac surgery requiring hospital admission annually.[1] Despite the procedural benefits, observational studies evaluating noncardiac surgery patients with or at risk of coronary artery disease[2–7] suggest that 3% of these patients suffer a perioperative myocardial infarction (MI).[8] Research evaluating unselected patients (i.e., not limited to patients with or at risk of coronary artery disease) suggests that 1% of adults undergoing noncardiac surgery suffer an MI.[9] Therefore, many patients suffer a perioperative MI annually.

Further, the magnitude of this problem is likely even greater than these event rates suggest because (1) most of the studies that these estimates are based upon excluded urgent/emergent surgical cases, which have a higher risk for perioperative MI[7]; (2) the studies used creatine kinase MB (CK-MB) in their diagnostic criteria for MI, a criterion prone to false-negative values for perioperative MI[10,11]; and (3) the studies are based on data that are over one decade old, and during the past 10 years surgical practice has shifted toward more elderly patients with more advanced cardiac disease undergoing noncardiac surgery.[8]

## Is There a Risk of a Perioperative MI Going Undetected?

Physicians rarely recommend monitoring perioperative cardiac enzymes or biomarkers to detect MI in patients undergoing noncardiac surgery.[12] Given this, there is a risk that perioperative MIs may go undetected for several reasons.

First, research suggests that 85% of patients suffering a perioperative MI will not experience chest discomfort,[4–6] likely because the majority of perioperative MIs occur during the first few days after surgery, when most patients are receiving analgesic medications.[13] Second, studies suggest that about 50% of patients suffering a perioperative MI will not experience any signs (e.g., tachycardia, hypotension) or symptoms (e.g., chest discomfort, shortness of breath, nausea) of an MI.[13] Third, even when patients do experience potential signs or symptoms (other than chest discomfort) of perioperative MI, surgeons may not consider MI because there are a number of more probable diagnoses (e.g., hypovolemia, bleeding, medication side effect, atelectasis, pneumonia).

## Do Perioperative MIs Matter?

Although further research is needed, it is probable that a substantial proportion of perioperative MIs are missed because they are clinically silent or associated with nonspecific signs or symptoms. This is a problem to the extent that a perioperative MI negatively alters patient prognosis.

A recent systematic review identified six observational studies requiring patients to have at least one troponin measurement after noncardiac surgery,[13] and all studies demonstrated that an elevated

*P. J. Devereaux, MD, PhD*: Departments of Clinical Epidemiology and Biostatistics and Medicine, McMaster University, Hamilton, Ontario; *Justin de Beer, MD*: Department of Surgery, McMaster University, Hamilton, Ontario; *Juan Carlos Villar, MD, PhD*: Grupo de Cardiología Preventiva, Universidad Autonoma de Bucaramanga, Bucaramanga, Colombia; *Denis Xavier, MD*: Department of Pharmacology, St. John's Medical College, Bangalore, India, and the Population Health Research Institute, McMaster University, Hamilton, Ontario; *Akbar Panju, MB*: Department of Medicine, McMaster University, Hamilton, Ontario; *Otavio Berwanger, MD, PhD*: Department of Clinical Epidemiology, Federal University of Rio Grande do Sul, Porto Alegre-RS, Brazil; *Germán Málaga, MD*: Department of Medicine, Universidad Peruana Cayetano Heredia, Lima, Peru; *Luc Lanther, MD, MSc*: Department of Medicine, University of Sherbrooke, Sherbrooke, Québec; *Jørn Wetterslev, MD, PhD*: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhagen, Denmark

Address for correspondence: P. J. Devereaux, MD, PhD, 9 Hilton Street, Hamilton, ON L8P 3K3; E-mail: philipj@mcmaster.ca

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:9-11

troponin after noncardiac surgery was a statistically significant independent predictor of death and major cardiac events in the 6 to 48 months after surgery.[14–19] Further, this association was present in the two studies that excluded patients who had both an elevated troponin and clinical signs or symptoms of an MI.[18,19] These studies suggest that perioperative troponin elevation, even without clinical signs or symptoms of MI, negatively altered patient prognosis.

Although these studies have limitations (e.g., the studies were underpowered and demonstrated markedly varied associations) and a definitive large cohort study is needed, the evidence available suggests it is not prudent to assume that clinically silent perioperative MIs are benign events.

## If Clinically Silent Perioperative MIs Were Detected, Could Physicians Improve Patient Outcomes?

Although a plethora of large randomized controlled trials (RCTs) have established a multitude of acute and long-term beneficial therapies to treat nonoperative MIs, there are no RCTs evaluating interventions to manage patients suffering a perioperative MI. Therefore, it remains unproven that physicians detecting perioperative MIs can improve patient outcomes, but we strongly suspect they can.

Studies suggest that between 15 and 20% of patients suffering a perioperative MI die prior to hospital discharge,[3,6] and it is intuitive that early detection of an MI will afford physicians the greatest opportunity to prevent death. We believe a host of strategies for managing perioperative MIs are more likely to benefit than harm patients. These include (1) more frequent monitoring of vital signs to allow early detection and reversal of cardiovascular instability before it becomes irreversible; (2) management in an intermediate or cardiac care unit; (3) identifying and correcting potential contributing factors (e.g., hypoxia, anemia); (4) avoidance of heart failure through optimal intravascular volume management; and (5) a few therapies known to benefit patients suffering a nonoperative MI (i.e., β-blocker, angiotensin-converting enzyme [ACE] inhibitor).

We believe that even patients who would survive to hospital discharge, despite having suffered an undetected perioperative MI, can benefit from detection of their MI. Approximately 10% of patients who suffer a perioperative MI with or without signs or symptoms will suffer a major cardiac event within 1 year of hospital discharge after surgery.[6,18,20] Given that the majority of these patients have some degree of underlying coronary artery stenosis,[21–23] it would seem prudent to offer these patients long-term management with known beneficial secondary prophylaxis cardiac interventions (e.g., aspirin, ACE inhibitor, statin therapy) until definitive RCTs on perioperative MI are conducted.

## What Can Physicians Do to Avoid Missing Perioperative MIs?

A potential solution to avoid missing clinically silent MIs is for physicians to monitor perioperative troponin levels. The fact that the majority of perioperative MIs occur during the first few postoperative days suggests that monitoring troponins daily for the first 3 days after surgery will provide the greatest yield. Although there is uncertainty regarding whom to monitor, a reasonable approach is to monitor the patients at highest risk of a perioperative MI (i.e., patients with known atherosclerotic disease or risk factors).

## Summary

Despite the limitations of previous research, the evidence suggests that many patients undergoing noncardiac surgery suffer a perioperative MI, a substantial proportion of perioperative MIs are clinically silent, perioperative MIs are important events altering patient prognosis for death and further major cardiac events, and interventions may improve both the short- and long-term prognoses of patients suffering a perioperative MI. Firm recommendations await the results of large high-quality studies. Until such time, physicians should consider monitoring troponins daily during the first 3 days after noncardiac surgery.

## Acknowledgements

P. J. Devereaux is supported by a Canadian Institutes of Health Research New Investigator Award. Denis Xavier is supported by a Canadian Institutes of Health Research HOPE Scholarship Award.

## References

1. Mangano D. Peri-operative cardiovascular morbidity: new developments. Ballieres Clin Anaesthesiol 1999;13:335-48.
2. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1:211-9.
3. Shah KB, Kleinman BS, Rao TL, et al. Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. Anesth Analg 1990;70:240-7.
4. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990;323:1781-8.
5. Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 1993;118:504-10.
6. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. Anesthesiology 1998;88:572-8.
7. Kumar R, McKinney WP, Raj G, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med 2001;16:507-18.
8. Devereaux PJ, Goldman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005;173:627-34.
9. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.
10. Adams JE III, Sicard GA, Allen BT, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med 1994;330:670-4.
11. Haggart PC, Adam DJ, Ludman PF, Bradbury AW. Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery. Br J Surg 2001;88:1196-200.
12. Devereaux PJ, Ghali WA, Gibson NE, et al. Physicians' recommendations for patients who undergo noncardiac surgery. Clin Invest Med 2000;23:116-23.
13. Devereaux PJ, Goldman L, Yusuf S, et al. Surveillance and prevention

of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005;173:779-88.
14. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002;106:2366-71.
15. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547-54.
16. Filipovic M, Jeger R, Probst C, et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol 2003;42:1767-76.
17. Oscarsson A, Eintrei C, Anskar S, et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol Scand 2004;48:1071-9.
18. Lopez-Jimenez F, Goldman L, Sacks DB, et al. Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. J Am Coll Cardiol 1997;29:1241-5.
19. Kertai MD, Boersma E, Klein J, et al. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28(1):59-66.
20. Mangano DT, Browner WS, Hollenberg M, et al. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992;268:233-9.
21. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57(1):37-44.
22. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133-9.
23. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996;77:1126-8.

# Infarctus du myocarde péri-opératoire : un tueur silencieux

P. J. Devereaux, MD, PhD; Justin de Beer, MD; Juan Carlos Villar, MD, PhD; Denis Xavier, MD; Akbar Panju, MB; Otavio Berwanger, MD, PhD; Germán Málaga, MD; Luc Lanther, MD, MSc; Jørn Wetterslev, MD, PhD

SOMMAIRE

Dans cet article, nous discutons de l'infarctus du myocarde péri-opératoire chez les patients qui doivent subir une chirurgie non cardiaque. Même si la recherche antérieure est limitée, des preuves laissent supposer qu'un assez bon nombre de patients qui doivent subir une chirurgie non cardiaque font un infarctus du myocarde. Souvent, l'infarctus du myocarde péri-opératoire est asymptomatique d'un point de vue clinique, mais néanmoins, un événement important venant modifier le pronostic de survie et la possibilité d'autres événements cardiaques majeurs. Les interventions peuvent améliorer à la fois le pronostic à court et à long terme des patients qui font un infarctus du myocarde péri-opératoire. Les médecins devraient envisager des mesures pour surveiller les patients et déceler les infarctus du myocarde péri-opératoires. Bien qu'il soit nécessaire de mener des études d'envergure et d'excellente qualité, en attendant, les médecins devraient surveiller les taux de troponine chaque jour pendant les trois premiers jours après une chirurgie non cardiaque chez les patients qui sont atteints d'athérosclérose ou qui courent un risque élevé d'en être atteint.

## Quelle est la fréquence de l'infarctus du myocarde chez les patients devant subir une chirurgie non cardiaque?

Environ 100 millions d'adultes de par le monde subissent une chirurgie majeure non cardiaque nécessitant l'hospitalisation chaque année.[1] Malgré les avantages procéduraux, les études par observation évaluant les patients ayant subi une chirurgie non cardiaque ayant une coronaropathie ou susceptibles d'avoir une coronaropathie[2–7] ont révélé que 3 % de ces patients souffraient d'un infarctus du myocarde (IM) péri-opératoire.[8] Des recherches évaluant les patients non choisis (c'est-à-dire non limité aux patients ayant une coronaropathie ou susceptibles d'avoir une coronaropathie) indiquent que 1 % des adultes qui subissent une chirurgie non cardiaque ont un IM.[9] Par conséquent, plusieurs patients souffrent d'un IM péri-opératoire chaque année.

De plus, l'ampleur de ce problème est probablement plus importante que ces taux laissent entrevoir parce que (1) la plupart des études sur lesquelles ces estimations sont basées excluaient les cas d'opération urgente/nouvelle qui avaient un risque plus élevé d'IM péri-opératoire[7]; (2) les études ont utilisé la créatine-kinase-MB (CK-MB) dans leurs critères diagnostiques pour l'IM, un critère pouvant donner des résultats faux négatifs pour l'IM péri-opératoire[10,11]; et (3) les études sont basées sur des données vieilles de 10 ans, et au cours des 10 dernières années la pratique de la chirurgie s'est concentrée sur les patients plus âgés souffrant de cardiopathie plus avancée et subissant une chirurgie non cardiaque.[8]

## Existe-t-il un risque que l'IM péri-opératoire ne soit pas détecté?

Les médecins recommandent rarement de surveiller les enzymes ou biomarqueurs cardiaques péri-opératoires pour détecter un IM chez les patients qui doivent subir une chirurgie non cardiaque.[12] Compte tenu de ces faits, il existe un risque que l'IM péri-opératoire ne soit pas détecté pour plusieurs raisons.

Premièrement, la recherche révèle que 85 % des patients qui font un IM péri-opératoire ne ressentiront pas de malaises thoraciques,[4–6] probablement parce que la majorité des IM péri-opératoires surviennent au cours des premiers jours suivant la chirurgie lorsque la plupart des patients reçoivent des analgésiques.[13] Deuxièmement, des études indiquent qu'environ 50 % des patients qui font un IM péri-opératoire n'auront aucun signe (tachycardie, hypotension) ni aucun symptôme (malaises thoraciques, essoufflement, nausée) de l'IM.[13] Troisièmement, même lorsque les patients ont des signes ou des symptômes (autres que les malaises thoraciques) d'IM péri-opératoire, les chirurgiens peuvent ne pas envisager l'IM car il y a un certain nombre d'autres diagnostics possibles (p. ex., hypovolémie, hémorragie, effet secondaire médicamenteux, atélectasie, pneumonie).

*P. J. Devereaux, MD, PhD*: Départements d'épidémiologie clinique et de biostatistiques, McMaster University, Hamilton, Ontario; *Justin de Beer, MD*: Département de chirurgie, McMaster University, Hamilton, Ontario; *Juan Carlos Villar, MD, PhD*: Grupo de Cardiología Preventiva, Universidad Autonoma de Bucaramanga, Bucaramanga, Colombie; *Denis Xavier, MD*: Département de pharmacologie, St. John's Medical College, Bangalore, Indes, et le Population Health Research Institute, McMaster University, Hamilton, Ontario; *Akbar Panju, MB*: Département of médecine, McMaster University, Hamilton, Ontario; *Otavio Berwanger, MD, PhD*: Département d'épidémiologie clinique, Federal University of Rio Grande do Sul, Porto Alegre-RS, Brésil; *Germán Málaga, MD*: Département de médecine, Universidad Peruana Cayetano Heredia, Lima, Pérou; *Luc Lanther, MD, MSc*: Département de médecine, Université de Sherbrooke, Sherbrooke, Québec; *Jørn Wetterslev, MD, PhD*: Copenhagen Trial Unit, Centre for Clinical Intervention Research, Copenhagen University Hospital, Copenhague, Danemark

Adresse pour correspondance : P. J. Devereaux, MD, PhD, 9 Hilton Street, Hamilton, ON L8P 3K3; Courriel : philipj@mcmaster.ca

Conflit d'intérêt : Aucun déclaré

*Can J Gen Intern Med* 2006;1:12-14

## Est-ce que les IM péri-opératoires sont importants?

Bien qu'il soit nécessaire de pousser davantage la recherche, il est probable qu'une proportion substantielle d'IM péri-opératoires ne sont pas détectés parce qu'ils sont asymptomatiques ou associés à des signes et symptômes non spécifiques. C'est un problème dans la mesure qu'un IM péri-opératoire affecte négativement le pronostic du patient.

Une révision méthodique récente a identifié six études par observation nécessitant que les patients aient au moins une mesure de la troponine après une chirurgie non cardiaque,[13] et toutes les études ont démontré qu'un taux élevé de troponine après une chirurgie non cardiaque était un prédicteur indépendant statistiquement significatif de mortalité et d'événements cardiaques majeurs dans les 6 à 48 mois après la chirurgie.[14–19] De plus, cette association se retrouvait dans les deux études qui excluaient les patients qui avaient un taux élevé de troponine et des signes ou des symptômes cliniques d'un IM.[18,19] Ces études laissent supposer qu'un taux élevé de troponine peri-opératoire, même sans les signes ou symptômes cliniques d'IM, vient affecter négativement le pronostic.

Même si ces études comportent certaines limites (p. ex., les études n'étaient pas assez puissantes et ont démontré des associations très variées) et qu'une étude de grandes cohortes soit nécessaire, les preuves disponibles laissent envisager qu'il n'est pas prudent d'assumer que les IM péri-opératoires cliniquement asymptomatiques soient des événements bénins.

## Si les IM péri-opératoires cliniquement asymptomatiques étaient détectés, est-ce que les médecins pourraient améliorer le devenir du patient?

Bien qu'une abondance d'études cliniques d'envergure, contrôlées, à répartition aléatoire aient déterminé une multitude de traitements à court et à long terme pour les IM, il n'existe aucune étude permettant d'évaluer les interventions nécessaires pour la prise en charge des patients subissant un IM péri-opératoire. Par conséquent, il est impossible de prouver que les médecins qui détectent les IM péri-opératoires peuvent améliorer le devenir du patient, mais nous soupçonnons qu'ils le peuvent.

Des études révèlent qu'entre 15 et 20 % des patients subissant un IM peri-opératoire meurent avant le renvoi de l'hôpital[3,6] et la détection précoce d'un IM donnera la chance aux médecins de prévenir le décès. Nous croyons qu'un certain nombre de stratégies pour traiter les IM péri-opératoires seront plus avantageuses que le contraire. Ces stratégies sont les suivantes (1) prise des signes vitaux plus fréquente afin de permettre la détection et revirement d'une instabilité cardiovasculaire avant qu'elle ne devienne irréversible; (2) le traitement dans une unité de soins intermédiaires ou cardiaques; (3) l'identification et la rectification des facteurs contributifs (p. ex., hypoxie, anémie) ; (4) l'évitement de l'insuffisance cardiaque par la gestion optimale du volume intravasculaire; et (5) quelques traitements connus comme étant avantageux pour les patients subissant un IM non lié à la chirurgie (c.-à-d., β-bloquant, inhibiteur de l'enzyme de conversion de l'angiotensine).

Nous croyons que même les patients qui survivent un IM péri-opératoire qui n'a pas été détecté lors de l'hospitalisation peuvent bénéficier de la détection de leur IM. Environ 10 % des patients qui subissent un IM péri-opératoire manifestant ou non des signes ou des symptômes auront un événement cardiaque majeur en moins d'un an après le renvoi de l'hôpital après l'opération.[6,18,20] Étant donné que la majorité de ces patients ont un certain degré de sténose sous-jacente des artères coronariennes,[21–23] il semblerait prudent de traiter ces patients à long terme par l'entremise d'interventions cardiaques prophylactiques secondaires (p. ex., AAS, inhibiteur de l'ECA, statine) jusqu'à ce que des études contrôlées à répartition aléatoire sur l'IM péri-opératoire soient menées.

## Que peuvent faire les médecins pour ne pas manquer de diagnostiquer l'IM péri-opératoire?

Une solution possible pour ne pas manquer de diagnostiquer les IM cliniquement asymptomatiques est de surveiller les taux de troponine péri-opératoires. Le fait que la majorité des IM péri-opératoires surviennent au cours des quelques jours suivant l'opération laisse entrevoir que la surveillance des troponines chaque jour pendant les 3 premiers jours après la chirurgie donnera les meilleurs résultats. Bien qu'il existe une certaine incertitude quant au malade à surveiller, une approche raisonnable est de surveiller les patients les plus susceptibles de subir un IM peri-opératoire (c.-à-d. les patients ayant une maladie athéroscléreuse ou susceptible d'en avoir une).

## Résumé

Même si la recherche antérieure est limitée, des preuves laissent supposer que plusieurs patients qui doivent subir une chirurgie non cardiaque font un IM péri-opératoire, une assez bonne proportion des IM péri-opératoires sont asymptomatiques d'un point de vue clinique, les IM péri-opératoires sont des événements importants venant modifier le pronostic de survie et la possibilité d'autres événements cardiaques majeurs, et les interventions peuvent améliorer à la fois le pronostic à court et à long terme des patients qui font un IM péri-opératoire. Des recommandations bien définies attendent les résultats d'études d'envergure de grande qualité. En attendant, les médecins devraient surveiller les taux de troponine chaque jour pendant les trois premiers jours après une chirurgie non cardiaque.

## Remerciements

P. J. Devereaux a reçu la bourse du nouvel investigateur du Canadian Institutes of Health Research. Denis Xavier a reçu la bourse HOPE du Canadian Institutes of Health Research.

## Références

1. Mangano D. Peri-operative cardiovascular morbidity: new developments. Ballieres Clin Anaesthesiol 1999;13:335-48.
2. Detsky AS, Abrams HB, McLaughlin JR, et al. Predicting cardiac complications in patients undergoing non-cardiac surgery. J Gen Intern Med 1986;1:211-9.
3. Shah KB, Kleinman BS, Rao TL, et al. Angina and other risk factors in patients with cardiac diseases undergoing noncardiac operations. Anesth Analg 1990;70:240-7.
4. Mangano DT, Browner WS, Hollenberg M, et al. Association of perioperative myocardial ischemia with cardiac morbidity and mortality in men undergoing noncardiac surgery. The Study of Perioperative Ischemia Research Group. N Engl J Med 1990;323:1781-8.

5. Ashton CM, Petersen NJ, Wray NP, et al. The incidence of perioperative myocardial infarction in men undergoing noncardiac surgery. Ann Intern Med 1993;118:504-10.
6. Badner NH, Knill RL, Brown JE, et al. Myocardial infarction after noncardiac surgery. Anesthesiology 1998;88:572-8.
7. Kumar R, McKinney WP, Raj G, et al. Adverse cardiac events after surgery: assessing risk in a veteran population. J Gen Intern Med 2001;16:507-18.
8. Devereaux PJ, Goldman L, Cook DJ, et al. Perioperative cardiac events in patients undergoing noncardiac surgery: a review of the magnitude of the problem, the pathophysiology of the events and methods to estimate and communicate risk. CMAJ 2005;173:627-34.
9. Lee TH, Marcantonio ER, Mangione CM, et al. Derivation and prospective validation of a simple index for prediction of cardiac risk of major noncardiac surgery. Circulation 1999;100:1043-9.
10. Adams JE III, Sicard GA, Allen BT, et al. Diagnosis of perioperative myocardial infarction with measurement of cardiac troponin I. N Engl J Med 1994;330:670-4.
11. Haggart PC, Adam DJ, Ludman PF, Bradbury AW. Comparison of cardiac troponin I and creatine kinase ratios in the detection of myocardial injury after aortic surgery. Br J Surg 2001;88:1196-200.
12. Devereaux PJ, Ghali WA, Gibson NE, et al. Physicians' recommendations for patients who undergo noncardiac surgery. Clin Invest Med 2000;23:116-23.
13. Devereaux PJ, Goldman L, Yusuf S, et al. Surveillance and prevention of major perioperative ischemic cardiac events in patients undergoing noncardiac surgery: a review. CMAJ 2005;173:779-88.
14. Kim LJ, Martinez EA, Faraday N, et al. Cardiac troponin I predicts short-term mortality in vascular surgery patients. Circulation 2002;106:2366-71.
15. Landesberg G, Shatz V, Akopnik I, et al. Association of cardiac troponin, CK-MB, and postoperative myocardial ischemia with long-term survival after major vascular surgery. J Am Coll Cardiol 2003;42:1547-54.
16. Filipovic M, Jeger R, Probst C, et al. Heart rate variability and cardiac troponin I are incremental and independent predictors of one-year all-cause mortality after major noncardiac surgery in patients at risk of coronary artery disease. J Am Coll Cardiol 2003;42:1767-76.
17. Oscarsson A, Eintrei C, Anskar S, et al. Troponin T-values provide long-term prognosis in elderly patients undergoing non-cardiac surgery. Acta Anaesthesiol Scand 2004;48:1071-9.
18. Lopez-Jimenez F, Goldman L, Sacks DB, et al. Prognostic value of cardiac troponin T after noncardiac surgery: 6-month follow-up data. J Am Coll Cardiol 1997;29:1241-5.
19. Kertai MD, Boersma E, Klein J, et al. Long-term prognostic value of asymptomatic cardiac troponin T elevations in patients after major vascular surgery. Eur J Vasc Endovasc Surg 2004;28(1):59-66.
20. Mangano DT, Browner WS, Hollenberg M, et al. Long-term cardiac prognosis following noncardiac surgery. The Study of Perioperative Ischemia Research Group. JAMA 1992;268:233-9.
21. Dawood MM, Gutpa DK, Southern J, et al. Pathology of fatal perioperative myocardial infarction: implications regarding pathophysiology and prevention. Int J Cardiol 1996;57(1):37-44.
22. Cohen MC, Aretz TH. Histological analysis of coronary artery lesions in fatal postoperative myocardial infarction. Cardiovasc Pathol 1999;8:133-9.
23. Ellis SG, Hertzer NR, Young JR, Brener S. Angiographic correlates of cardiac death and myocardial infarction complicating major nonthoracic vascular surgery. Am J Cardiol 1996;77:1126-8.

# Evidence-Based Clinical Practice Guidelines for the Management of Obesity

David C. W. Lau, MD, PhD, FRCPC

ABSTRACT

The prevalence of childhood and adult obesity continues to increase in Canada. One in four adults have a BMI >30, and our children are becoming increasingly obese too. Associated co-morbidities, particularly diabetes, place a significant burden on personal well-being and health care costs. Obesity Canada, an organisation founded in 1999, plans to tackle the obesity epidemic with practical treatment and prevention guidelines.

SOMMAIRE

La prévalence de l'obésité chez l'enfant et l'adulte continue d'augmenter au Canada. Un adulte sur quatre a un IMC >30, et nos enfants sont de plus en obèses. Les co-morbidités associées, particulièrement le diabète, représentent un fardeau important pour le bien-être de la personne et les coûts des soins de santé. Obesity Canada, organisme fondé en 1999, a comme but d'aborder l'épidémie d'obésité et de proposer un traitement pratique et des lignes directrices de prévention.

The prevalences of overweight and obesity continue to increase in Canada in both children and adults, and in all areas of the country. Data from the 2004 Canadian Community Health Survey indicate that over half of the adult population is overweight (body mass index [BMI] ≥25 kg/m$^2$), while one in four adults is obese (BMI ≥30 kg/m$^2$).[1] These numbers highlight a pressing public health problem that shows no signs of improving in the near future. Obesity among Canadian children and adolescents is advancing at an even more rapid pace than that seen in adults. In 2004, one in four Canadian children and adolescents (ages 2 to 17) was overweight. In the past 15 years, the obese rate has dramatically increased from 2 to 10% in boys and from 2 to 9% in girls.[2,3] This is of particular concern, given the tendency for obese children to become obese adults. Moreover, obesity-related health problems, notably type 2 diabetes, now occur at a much earlier age and continue to progress into adulthood.[4]

We can no longer view obesity as a mere cosmetic or body image issue. There is compelling evidence that overweight individuals have an increased risk of developing a variety of health problems, including type 2 diabetes, hypertension, dyslipidemia, coronary heart disease, stroke, osteoarthritis, and certain forms of cancer.[4] It has recently been estimated that approximately 1 in 10 premature deaths among Canadian adults 20 to 64 years of age is directly attributable to overweight and obesity. The cost of obesity in Canada has been conservatively estimated to be $2 billion a year, or 2.4% of the total health care expenditures in 1997.[5] In addition to impacting personal health, these increased health risks translate into an increased burden on the health care system.

The etiology of obesity is complex and multifactorial. Within the context of environmental, social, and genetic factors, at the simplest level, obesity results from long-term positive energy balance, influenced by the imbalance of energy intake and energy expenditure. The rapid increase in the prevalence of obesity over the past 20 years has a basis in environmental and cultural factors, rather than genetic ones. Adipose tissue has been recognized as an important endocrine organ, one that releases a large number of adipokines and contributes to the development of the metabolic syndrome.[6] As standards of living in developed and developing countries improve, overnutrition and sedentary lifestyle supplant physical labour and regular physical activity; the result is a positive energy balance and weight gain.[7]

Considerable advances have been made in dietary, exercise, behavioural, pharmacological, and bariatric–surgical approaches to successful long-term management of obesity. A modest weight loss of 5 to 10% can significantly improve metabolic co-morbidities and health status.[7] While lifestyle intervention remains the cornerstone treatment of obesity, adherence rate is poor and long-term success is modest. This is a consequence of patient factors and physician attitudes to treatment. Pharmacotherapy and bariatric surgery are useful treatments, but for a variety of reasons they are not widely adopted.[7]

Despite our steady progress in successful obesity management, the prevalence of obesity continues to rise. Prevention and intervention strategies are required to slow, and hopefully reverse, this alarming trend. Population interventions to date have tended to focus on individual risk factors and have been largely ineffective. Simple and practical guidelines for the busy practitioner are desperately needed.

A number of clinical practice guidelines (CPGs) have been published, but these were largely developed on the basis of consensus statements by an expert panel. Most of these guidelines focused on individuals rather than on communities and populations. Recognizing these deficiencies, Obesity Canada, a not-for-profit organization, was founded in 1999 with a goal of tackling the obesity epidemic. CPGs for the treatment and prevention of childhood and adult obesity are being written. Members of the steering committee and expert panel have also identified major gaps in knowledge in this area, and the need for a considerable research effort. This will include enhanced surveillance and population-based data; new research on the biological, social,

*David C. W. Lau, MD, PhD, FRCPC*: Department of Medicine, Biochemistry and Molecular Biology, Julia McFarlane Diabetes Research Centre, University of Calgary, Calgary, Alberta

Address for correspondence: David C. W. Lau, MD, PhD, FRCPC, Room 2521, Julia McFarlane Diabetes Research Centre, Health Sciences Centre, 3330 Hospital Drive NW, Calgary, AB T2N 4N1; E-mail: dcwlau@ucalgary.ca

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:15-16

cultural, and environmental determinants of obesity; and research on effective treatment strategies, policies, and interventions.

As obesity is increasingly viewed as a societal issue, the steering committee and expert panel members unanimously agreed to include sections on the *prevention of obesity in children and adults at the population level*, as well as implications of the CPGs for health policy makers and other interested parties.

As knowledge flows from new research, the Canadian CPGs for the management and prevention of obesity will be strengthened. We hope that, as a consequence of their implementation, Canadians will enjoy a slimmer and healthier future.

## References


1. Shields M. Findings from the Canadian Community Health Survey: Statistics Canada. Nutrition 2005;1.
2. Shields M. Measured obesity: overweight Canadian children and adolescents. Ottawa: Statistics Canada; 2005.
3. Tremblay MS, Willms JD. Is the Canadian childhood obesity epidemic related to physical inactivity? Int J Obes Relat Metab Disord 2003;27:1100-5.
4. Lau DCW, Yan H, Dhillon B. Metabolic syndrome: a marker of patients at high cardiovascular risk. Can J Cardiol 2006;22(Suppl B):85-90B.
5. Birmingham CL, Muller JL, Palepu A, et al. The cost of obesity in Canada. CMAJ 1999;160:483-8.
6. Lau DC, Dhillon B, Yan H, et al. Adipokines: molecular links between obesity and atherosclerosis. Am J Physiol Heart Circ Physiol 2005;288(5):H2031-41. Epub.
7. Lau DCW. Obesity. In: Gray J, ed. Therapeutic Choices, 4th edition. Ottawa: Canadian Pharmacists Association; 2003:1096-101.

# Hypertriglycéridémie et grossesse : prévention de pancréatite par plasmaphérèses

Marie-Hélène Bastien, MD; Evelyne Rey, MD, MSc, FRCPC

SOMMAIRE

**L'hypertriglycéridémie due à une déficience complète en lipoprotéine lipase est une maladie rare. Cette condition est exacerbée par l'augmentation des oestrogènes pendant la grossesse. Voici le cas d'une femme ayant nécessité plusieurs plasmaphérèses durant sa grossesse dans le but de prévenir une pancréatite.**

L'hypertriglycéridémie due à une déficience complète en lipoprotéine lipase est une maladie rare (Québec prévalence de 200 / 1 000 000). Cette condition est exacerbée par l'augmentation des oestrogènes pendant la grossesse, augmentant ainsi les risques de pancréatite et de mortalité associée qui peut atteindre 20 %.[1] Bien que la plasmaphérèse ait été décrite comme traitement de la pancréatite aigue, son utilisation en prévention de cette complication de l'hypertriglycéridémie est rare.[2] Voici le cas d'une femme ayant nécessité plusieurs plasmaphérèses durant sa grossesse dans le but de prévenir une pancréatite.

## Cas

Il s'agit une femme de 24 ans d'origine canadienne-française Gravida 2, Avorta 1 dont la déficience en LPL (double mutation hétérozygote pour le gène de la LPL G188E et P207) a été diagnostiquée peu après sa naissance. Avant cette grossesse, la triglycéridémie de la patiente était bien contrôlée par une diète faible en gras. Dès le début de la grossesse, la patiente a été prise en charge par une équipe multidisciplinaire incluant une nutritionniste. Une diète contenant 12,5 g/jour de graisse à chaînes longues (diète normale : 75 g /jour) a permis de maintenir le niveau de triglycérides (TG) en dessous de 20 mmol/L jusqu'à la 17e semaine de grossesse. Par la suite, le niveau de TG s'est élevé jusqu'à 39 mmol/L et ce malgré une diminution de l'apport en graisse à chaînes longues jusqu'à 0,5g/jour, l'utilisation de fénofibrate jusqu'à 200 mg et de deux périodes de jeûne de 36 heures.

La première plasmaphérèse a eu lieu à 25 semaines de grossesse. La patiente refusant tout produit sanguin, les échanges plasmatiques ont donc été fait avec du salin physiologique et des colloïdes artificiels. La triglycéridémie a chuté en dessous de 20 mmol/L. Cet effet a été de courte durée et le niveau de TG a atteint 71 mmol/L. À la 28e semaine de grossesse, le taux de TG a été abaissé à 21 mmol/L par deux plasmaphérèses en trois jours et maintenus à ce niveau par quatre autres plasmaphérèses jusqu'à l'accouchement, à la 34ieme semaine de grossesse. Le nouveau-né, une fille pesant 2,5 Kg, était en bonne santé. Le lendemain de l'accouchement les TG étaient à 16 mmol/L.

En aucun temps la patiente n'a en aucun temps présenté des signes ou des symptômes de pancréatite, de problèmes de coagulation ou infectieux. Tout au long de la grossesse, l'examen physique de la patiente était normal. Elle a présenté des épisodes d'hypotension et d'hypocalcémie lors des plasmaphérèses, ceux-ci ont été corrigés rapidement. À quelques reprises, des thromboses du cathéter ont nécessité une thrombolyse locale.

## Discussion

Ce cas illustre à quel point le niveau de TG peut être difficile à contrôler chez ces patientes enceintes, malgré une diète très restreinte en gras. L'utilisation du fénofibrate est en théorie inefficace chez les personnes avec une déficience en LPL mais quelques cas ont été décrits en grossesse avec succès.[3] Nous avons opté pour des plasmaphérèses car, malgré le traitement conventionnel, le niveau de triglycérides demeurait dangereusement élevé. En effet, plusieurs cas de pancréatite aigue en grossesse ont été décrits avec des TG ≤35 mmol/L.[4] Selon nous, la morbidité et la mortalité associées aux pancréatites, tant pour le bébé que pour la mère, justifiaient les plasmaphérèses malgré le peu de littérature actuelle supportant notre décision.

## References

1. Montgomery WH, Miller FC. Pancreatitis and pregnancy. Obstet Gynecol 1970 ; 35 : 658–664.
2. Dittrich E, Schmaldiesnt S, et coll. Immunoadsorption and plasma exchange in pregnancy. Kidney Blood Press Res 2002 ; 25 : 232–239.
3. Tsai C E, Brown JA, et coll. Potential of essential fatty acid deficiency with extremely low fat diet in lipoprotein lipase deficiency during pregnancy : a case report. BMC Pregnancy Childbirth 2004 ; 4 (1) : 27.
4. Archard JM, Westell PF. Pancreatitis related to severe acute hypertriglyceridemia during pregnancy treatment with lipoprotein apheresis. *Intens Care Med* 1991 ; 17 : 236–237.

*Marie-Hélène Bastien, MD* : RV médecine interne Université Laval; *Evelyne Rey, MD, MSc, FRCPC* : Hôpital Sainte-Justine, Montréal

Adresse de correspondence : Marie-Hélène Bastien, MD, 3775 ave des compagnons app 244, Québec, QC G1X 5C3; courriel : mhbastien@hotmail.com

Conflict of interest : Aucun declare

*Can J Gen Intern Med* 2006;1:17

# Hypertriglyceridemia and Pregnancy: Preventing Pancreatitis by Using Plasmapheresis

Marie-Hélène Bastien, MD; Evelyne Rey, MD, MSc, FRCPC

ABSTRACT

Hypertriglyceridemia due to a complete lipoprotein lipase deficiency is a rare disease. The condition is exacerbated by the increased estrogen during pregnancy. This is the case of a woman who required several plasmaphereses during her pregnancy in order to prevent pancreatitis.

Hypertriglyceridemia due to a complete lipoprotein lipase deficiency is a rare disease (the prevalence in Quebec is 200 in 1,000,000). The condition is exacerbated by the increased estrogen during pregnancy, thus increasing the risks of pancreatitis and associated mortality, which may reach 20%.[1] Although plasmapheresis has been described as a treatment for acute pancreatitis, its use in preventing this complication of hypertriglyceridemia is rare.[2] This is the case of a woman who required several plasmaphereses during her pregnancy in order to prevent pancreatitis.

## Case

The patient was a 24-year-old woman of French-Canadian origin, gravida 2 abortus 1, who was diagnosed with an LPL deficiency (double heterozygous mutation for LPL gene G188E and P207) shortly after she was born. Prior to this pregnancy, the patient's hypertriglyceridemia was well controlled through a low-fat diet. From the start of the pregnancy, the patient was managed by a multidisciplinary team including a nutritionist. A diet containing 12.5 g/day of long-chain fats (normal diet 75 g/day) kept her triglyceride (TG) level below 20 mmol/L until the seventeenth week of pregnancy. Subsequently, her TG level rose to 39 mmol/L, despite a decrease in long-chain fat consumption to 0.5g/day, the use of fenofibrate up to 200 mg, and two 36-hour periods of fasting.

The first plasmapheresis took place at 25 weeks of pregnancy. Since the patient refused any blood products, the plasma exchanges were made with physiological saline and artificial colloids. Her triglyceride level fell to below 20 mmol/L. The effect did not last long, and her TG level reached 71 mmol/L. At the twenty-eighth week of pregnancy, her TG level dropped to 21 mmol/L after two plasmaphereses in three days, and was maintained at that level by four additional plasmaphereses until she gave birth, in the thirty-fourth week of pregnancy. The newborn, a girl weighing 2.5 kg, was healthy. The day after she gave birth, her TG was 16 mmol/L.

At no time did the patient show signs or symptoms of pancreatitis or coagulation or infection disorders. Throughout the pregnancy, the patient's physical examination was normal. She experienced episodes of hypotension and hypocalcemia during the plasmaphereses, which were quickly corrected. Several times, catheter thromboses required local thrombolysis.

## Discussion

This case illustrates how difficult it can be to control TG levels in pregnant patients, despite a very-low-fat diet. The use of fenofibrate is theoretically ineffective in people with LPL deficiency, but a few successful cases during pregnancy have been described.[3] We opted for plasmaphereses because, despite the conventional treatment, her triglyceride levels remained dangerously high. Indeed, several cases of acute pancreatitis in pregnancy have been described with TG ≤35 mmol/L.[4] In our opinion, the morbidity and mortality associated with pancreatitis, both for the baby and the mother, justified the plasmaphereses despite the small amount of current literature supporting our decision.

## References

1. Montgomery WH, Miller FC. Pancreatitis and pregnancy. Obstet Gynecol 1970;35:658–664.
2. Dittrich E, Schmaldiesnt S, et coll. Immunoadsorption and plasma exchange in pregnancy. Kidney Blood Press Res 2002;25:232–239.
3. Tsai C E, Brown JA, et coll. Potential of essential fatty acid deficiency with extremely low fat diet in lipoprotein lipase deficiency during pregnancy: a case report. BMC Pregnancy Childbirth 2004;4(1):27.
4. Archard JM, Westell PF. Pancreatitis related to severe acute hypertriglyceridemia during pregnancy treatment with lipoprotein apheresis. *Intens Care Med* 1991;17:236–237.

*Marie-Hélène Bastien, MD*: RV Internal Medicine Université Laval; *Evelyne Rey, MD, MSc, FRCPC*: Hôpital Sainte-Justine, Montréal

Address for correspondence:Marie-Hélène Bastien, MD, app 244, 2775 av des Compagnons, Sainte-Foy, QC G1X 5C3; E-mail: mhbastien@hotmail.com

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:18

# Physical Principles of Chest Auscultation

Margot R. Roach, MD

ABSTRACT

Respiratory sounds are generated mechanisms that obey basic physical principles. Understanding these principles can improve one's diagnostic acumen in auscultation of the chest.

SOMMAIRE

Les sonorités pulmonaires sont des mécanismes produits qui obéissent à des principes physiques de base. La compréhension de ces principes peut améliorer l'acuité diagnostique à l'auscultation du thorax.

Intelligent examination of the chest requires knowledge of how the sounds generated there are produced and transmitted in both health and disease. Sound is described by its frequency, amplitude, and quality. The way sound is transmitted and the amount of damping or attenuation and reflection it experiences depend on the impedance of the surrounding tissue.

The *airways*, with tidal flow, have 22 generations of tubes excluding the trachea and the alveoli. In the first 10 generations, inspiratory flow is turbulent; slightly less so on expiration. Turbulence produces sound with a broad frequency spectrum (200 to 2000 Hz), increasing with tube size and flow rate. A sound's overtones (compare middle C on a piano and a violin) depend on the fundamental frequency and the overtones produced by the thoracic cavity, and vary with the degree of inflation, as well as the size, shape, and structure of the chest wall. Tracheobronchial sounds come from the first three to four generations of airways, and *vesicular sounds* from generations four to ten. Beyond this, flow is non-turbulent, so no sounds are produced. Normal tracheobronchial sounds are heard over the neck, often the sternum, and occasionally the upper spine, whereas the vesicular sounds are heard over the mid-thorax laterally.

Maximum sound amplitude occurs at its origin and is damped or attenuated as a function of distance from the source. The amount of *damping* depends on *frequency* of the sound (high frequencies are damped more than low ones are) and the *impedance* of the tissue. This means that solids transmit sound faster than liquids, and gases transmit the slowest. Because consolidated lung has an impedance between that of liquid and metal, it will dampen the sounds very little. Hence, if a lobe is consolidated, the tracheobronchial sounds will be transmitted to the chest wall through that lobe, whereas they are effectively damped out in travelling through normal lung. Similarly, vesicular sounds may have an increased intensity over a segment that is consolidated if it is fed by medium-sized bronchi. An overinflated chest increases the distance the sound must travel through air, and hence the sounds are more attenuated.

At an *interface*, if the two impedances are comparable, most of the sound passes through; if they are different, most of the sound is reflected. At an air–water interface, only 0.1% of sound is transmitted, compared with 100% at a water–water interface. Thus, tracheobronchial sounds will be heard over an effusion over a region of consolidation, but there will be no audible sounds if the effusion is over normal lung.

*Wheezes* are high-pitched musical expiratory sounds with a single frequency that is velocity dependent. They are produced by eddy shedding rather than by turbulence, and are particularly apt to occur if a small tube opens into a much larger one. By way of example, eddies are easy to see in water if a log sticks out into a stream; the edge of the flow divider acts the same way in the lung.

Chests should be examined first with normal breathing and then with deep breathing. However, if the patient has irritable airways that are prone to collapse, often no expiratory sounds are heard. Wheezes can be heard in patients with minimal bronchospasm only with forced expiration, a manoeuvre that makes bronchioles collapse from the increased pressure in the thoracic cavity.

*Crackles* are produced by air moving through liquid. The viscosity of the fluid determines the character and frequency of the sound. Watery fluids, as occur in pulmonary edema, have a higher pitch than do thick viscous fluids that occur in pneumonia. Take a bottle with liquids of varying viscosity and try blowing bubbles with different sizes of straws and different flow rates. By changing the size of the bottle, and by including one with a small neck, you can make the overtones vary and change the quality of the sound. Crackles are usually heard best in inspiration. They are audible without a stethoscope if the fluid is in the first few generations of bronchi. If the sputum is very viscous, it will be hard to move and crackles may be absent. In these situations (e.g., in tuberculosis), you can increase the chance of hearing crackles if you ask the patient to take a deep inspiration and then to produce two short coughs during expiration to loosen the sputum, before inspiring once more.

The fine crackles observed occasionally with atelectasis do not come from the alveoli as the flow rate is too low. They likely originate in generations 12 to 14 of the bronchial tree; therefore, they are associated only with large areas of atelectasis. Since the adjacent lung may be overinflated, there may be more attenuation. Hence, these crackles may be harder to hear.

*Voice sounds* are produced in the larynx and more proximal parts of

Address for correspondence: Margot R. Roach, MD, 104 Sea Shore Drive, RR1, Tatamagouche, NS B0K 1V0; E-mail: mroach@pchg.net

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:19-20

the airway, and can be transmitted back into the open airways when the vocal cords are open. Loud sounds, or even whispered ones, may set the large bronchi vibrating and can then be heard over an area of consolidation. However, as voice sounds are carried primarily in the air, they are reflected at a pleural effusion regardless of whether it lies over a consolidated area. This difference in transmission of breath sounds and voice sounds allows one to determine whether there is an effusion over an area of consolidation.

*Pleural rubs* are due to the two layers of pleura partially sticking to each other and creating a sound like that produced by rubbing wet leather. Pleural rubs, and the pain associated with them, are diminished if fluid separates the pleura or if they are stuck together.

In summary, respiratory sounds are generated and propagated in accordance with basic physical principles. Understanding these principles can improve your diagnostic acumen in auscultation of the chest.

*Dr. Roach trained in mathematics/physics in New Brunswick, medicine at McGill, and biophysics at UWO. She obtained her FRCPC in 1965 and did postdoctoral studies in Oxford before taking appointments in medicine and biophysics at UWO. She has published research on the elastic properties of arteries and the consequent changes seen in arteriosclerosis and aneurysmal disease. A pioneer in medical biophysics, she has won many prestigious teaching and research awards, and is now happily retired in Tatamagouche, Nova Scotia.*

## Bibliography

Forgacs P. Lung Sounds. London: Bailiere Tindall; 1978:44-54.

Nath AR, Capel LH. Inspiratory crackles and mechanical events of breathing. Thorax 1974;29:695-8.

# "GIM" Goes Global: The First International Symposium in General Internal Medicine—Toronto, April 2007

William A. Ghali, MD, MPH; Jacques Cornuz, MD, MPH; Donald Echenberg, MD

ABSTRACT

GIM is yet to have a global identity, despite the similarity of what we do in different countries. Unlike other specialties, we have not invested in international conferences and trials, and as a result we have not developed the necessary networks. A conference in Toronto (April 2007) will address this issue.

SOMMAIRE

GIM doit avoir encore une identité globale, en dépit de la similitude de ce que nous faisons dans différents pays. À la différence d'autres spécialités, nous démuni investi dans des conférences internationales et les épreuves, et en conséquence nous n'avons pas développé les réseaux nécessaires. Une conférence à Toronto (avril 2007) abordera cette question.

*To realize the full possibilities of this economy, we must reach beyond our own borders, to shape the revolution that is tearing down barriers and building new networks among nations and individuals, and economies and cultures: globalization. It's the central reality of our time.*

—William J. Clinton

*It has been said that arguing against globalization is like arguing against the laws of gravity.*

—Kofi Annan

Mark your calendars. An important event is about to occur in Toronto next April—the staging of the First International Symposium in General Internal Medicine (GIM). The symposium arises from over 3 years of dialogue among international leaders in GIM, and will be held in conjunction with the 30th Annual Meeting of the Society of General Internal Medicine (SGIM) at the Sheraton Centre Toronto (April 25–28, 2007).

GIM has, for the most part, evolved in country-specific "silos" over the past several decades. This is in contrast to other subspecialties of internal medicine, which have developed a worldwide presence through the staging of large international meetings and the associated formation of collaborative networks designed to advance agendas in research, education, and clinical care. Supporting the call for a more global role for GIM is the recognition that the clinical work of general internists is quite similar in many countries (e.g., the United States, Canada, Switzerland, Japan, Argentina, Australia, and New Zealand).[1]

The differing emphasis on primary care roles for general internists may have led some to conclude that GIM differs too much between countries for interaction to be fruitful. However, this is a relatively minor issue when one considers our common areas of interest, such as the management of complex patients with multi-system disease, chronic disease management, prevention, and the management of patients with undifferentiated symptom presentations. GIM synergy is even greater when one considers the shared academic focus in areas such as medical education, clinical epidemiology, health services research, medical informatics, health economics, and the challenges of quality and safety.[1]

The International Symposium in Toronto will feature sessions on quality of care and patient safety, the role of the general internist in global health, and the burgeoning areas of e-Health innovation and chronic disease management. This will be followed by the SGIM's annual meeting, which has adopted the theme "The Puzzle of Quality: Clinical, Educational, and Research Solutions"—something we can all relate to. Further information can be found at www.sgim.org.

The rich mixture of plenary sessions, oral and poster research sessions, workshops, and clinical updates has routinely attracted over 2,000 attendees from the United States and abroad. In the past, relatively few Canadian general internists have attended, possibly because of a misperception that SGIM is focused exclusively on primary care. On the contrary, SGIM annual meetings have something to offer almost all clinical and academic profiles, including Canadian internists.

A wave of globalization is about to engulf GIM. Come to Toronto this spring, and help us take a first big step toward creating a vibrant and global discipline of general internal medicine!

## Reference

1. Ghali WA, Greenberg PB, Mejia R, et al. International perspectives on general internal medicine and the case for 'globalization' of a discipline. J Gen Intern Med 2006;21:197-200.

*William A. Ghali, MD, MPH*: Departments of Medicine and Community Health Sciences, and Centre for Health and Policy Studies, University of Calgary, Calgary, Alberta; *Jacques Cornuz, MD, MPH*: Policlinique Médicale Universitaire, and Institute for Social and Preventive Medicine, University of Lausanne, Lausanne, Switzerland; *Donald Echenberg, MD*: Department of Medicine, University of Sherbrooke, Sherbrooke, Quebec

E-mail address for correspondence: wghali@ucalgary.ca

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:21

# Improving End-of-Life Care in Clinical Teaching Units: The Associated Medical Services, Inc., Fellowship in End-of-Life Care

Chris Frank, MD, CCFP, FCFP; Deb Pichora, RN, MSc; Cori Schroder, MD, CCFP, FCFP; Phil Wattam, MD, FRCPC; Daren Heyland, MD, FRCPC, MSc

ABSTRACT

Associated Medical Services, Inc., is a charitable organization supporting innovations in academic medicine and health services in Ontario. In 2005, AMS awarded nine fellowships in end-of-life (EOL) care to address the clinical needs of hospitalized non-cancer patients in the terminal stage of their illness. The goals of the fellowship are to improve knowledge, skills, and attitudes of internal medicine residents; to develop interdisciplinary models of exemplary EOL care in internal medicine CTUs; and to improve the overall care of patients with end-stage illness.

SOMMAIRE

Associated Medical Services Inc. est une société de bienfaisance apportant son appui aux innovations en médecine universitaire et services de la santé en Ontario. En 2005, l'AMS a octroyé neuf bourses pour les soins de fin de vie dans le but d'aborder les besoins cliniques des patients hospitalisés qui ne souffrent pas du cancer mais qui se trouvent en phase terminale. Les buts de ces bourses consistent à améliorer les connaissances, les compétences et les attitudes des résidents en médecine interne; à mettre au point des modèles interdisciplinaires de soins exemplaires de fin de vie dans les unités d'enseignement clinique en médecine interne; et à améliorer les soins généraux des patients atteints d'une maladie terminale.

A recent Senate subcommittee report titled "Quality End of Life Care: the Right of Every Canadian"[1] advanced the notion that a "quality death" is the right of every citizen and endorsed the principles and practice of palliative care. Traditionally, palliative care has focused on terminal cancer patients enrolled in palliative care programs. Evidence suggests that dying from cancer is not the same as dying from end-stage medical conditions. Non-cancer patients have a less predictable decline, experience more frequent hospital admissions, have do-not-resuscitate orders written later in their hospital course, and are less likely to receive palliative care consultation.[2,3] Canadian patients with advanced medical diseases have been shown to be more dissatisfied with their care than are patients with cancer.[4]

Although the federal government has increased resources for palliative care support at home,[5] the majority of Canadians die from non-cancer causes in hospital while under the care of general internists and other medical specialists. Improving end-of-life (EOL) care in this population of patients is an important goal.

## Associated Medical Services, Inc., Fellowship in End-of-Life Care

Associated Medical Services, Inc. (AMS), is a charitable organization supporting innovations in academic medicine and health services in Ontario. In 2005, AMS awarded fellowships in EOL care to nine physicians working in six Ontario teaching hospitals to address the unmet clinical needs of hospitalized patients at high risk of dying. The goals of the fellowship are to improve knowledge, skills, and attitudes of internal medicine residents, to develop interdisciplinary models of exemplary EOL care in internal medicine clinical teaching units, and to improve the overall care of patients with end-stage illness. The AMS fellowships will be implemented in the fall of 2006 and will continue over 5 years.

Studies suggest that physicians' knowledge and skills related to EOL care is inadequate.[6–8] It is not known how much EOL training residents in internal medicine programs in Canada receive, even though residents are the physicians who spend the most time providing direct EOL care in hospitals.[9] Residency is a great opportunity to influence EOL care as "residents are in a unique stage of their training; while they have mastered many basic clinical skills they remain open to educational experiences that might alter their lifelong practice patterns."[10]

The development of educational initiatives will be a key component of the fellowship. Baseline measurements of residents' knowledge, attitudes, and self-assessment; staff attitudes; patient and family satisfaction; and organizational culture will be done in the fall of 2006. This information will be used to guide curriculum development. Fellows will attempt to influence the core internal medicine curriculum by introducing EOL content into "traditional" medicine teaching topics (e.g., management of congestive heart failure) and by developing new sessions on EOL care within existing education formats at their centres. These will include academic half-days, sign-over rounds, and mortality/morbidity reviews.

One focus of the fellowship will be to improve resident skills in EOL communication. Internal medicine residents usually play a primary role

*Chris Frank, MD, CCFP, FCFP, Deb Pichora, RN, MSc,* and *Phil Wattam, MD, FRCPC*: Department of Medicine, Queen's University, Kingston, Ontario; *Cori Schroder, MD, CCFP, FCFP*: Departments of Oncology and Family Medicine, Queen's University, Kingston, Ontario; *Daren Heyland, MD, FRCPC, MSc*: Departments of Medicine and of Community Health and Epidemiology, Queen's University, Kingston, Ontario

Address for correspondence: Daren Heyland, MD, FRCPC, MSc, Angada 4, 76 Stuart Street, Kingston General Hospital, Kingston, ON K7L 2V7; E-mail: dkh2@post.queensu.ca

Conflict of interest: None declared

*Can J Gen Intern Med* 2006;1:22-23

in communication with sick patients and their families, during regular ward work and in family conferences. It is hoped that fellows will have an impact on residents' knowledge and skills in communication using a variety of formats such as small group workshops, role playing, and importantly, role modelling. Role modelling has been shown to be an important factor in improving communication skills,[11] and increasing fellows' participation in family conferences and EOL communication will be an important part of improving care. A literature review of studies related to family conferences has been done, and from this review a framework has been developed and distributed to aid in clinical role modelling and formal teaching.

Although, initiatives designed to improve residents' knowledge of EOL care have been shown to be successful,[6,8,12] they may not always lead to a concomitant change in practice or behaviour.[13] The fellows will use strategies shown to be helpful in facilitating change in practice, including acting as key physician opinion leaders, small-group problem-solving sessions, practice audit, and feedback. In some sites, EOL objectives have been added to the core internal medicine rotation objectives to promote evaluation of residents in their care of dying patients. Importantly, fellows will try to focus on improving models of care in their sites as a strategy to promote practice change. This includes increasing links with clinical pharmacists, optimizing the process of family conferences, improving links with palliative care services, and developing checklists for complicated discharge planning with dying patients.

## Evaluation Strategy

The goal of the evaluation is to assess the impact of the AMS fellowship on resident and staff knowledge, skills, and attitudes; on patient and family satisfaction; and on organizational culture. Residents will be evaluated using a quasi-experimental before-and-after study design. As illustrated in Figure 1, these findings will be used to inform subsequent educational and quality-improvement initiatives.

Quantity of EOL teaching will be tracked, and changes in resident knowledge and attitudes related to EOL care will be measured using a self-assessment tool based on the Educating Future Physicians in Palliative and End-of-Life Care (EFPPEC) competencies (available at www.efppec.ca), a knowledge test, and the Block and Arnold Attitudes about EOL Care Scale.

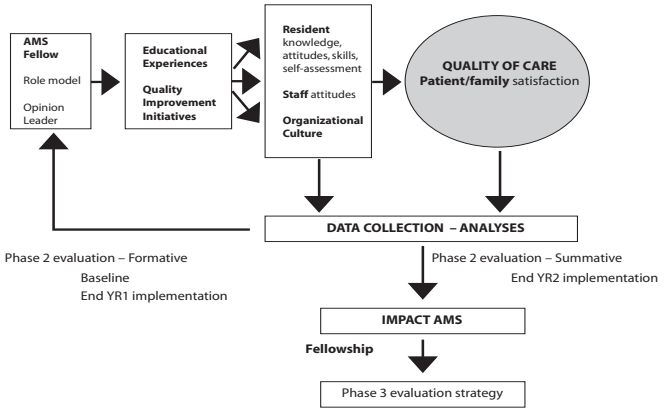



**Figure 1. Overview of the Associated Medical Services, Inc., fellowship evaluation.**

The AMS evaluation will be unique in its ability to link measures of residents' EOL knowledge and attitudes to patient and family feedback on care through the use of the CANHELP questionnaire, a validated Canadian tool to measure satisfaction with EOL care. This will be an important strategy to provide feedback for individual sites.

## Summary

Using change strategies known to make a difference in clinical outcomes,[14] the multifaceted interventions of the AMS Fellowship in EOL Care has a high probability of improving care for dying patients in clinical teaching units. The evaluation of the fellowship provides assessment of its impact (summative) while assisting in the refinement of the exemplary models of EOL care (formative). It is anticipated that the lessons learned from the fellowship will be applicable to other hospital settings across Canada.

*Dr. Frank is a family physician with certification in Care of the Elderly and works in Division of Geriatric Medicine and with palliative care at Queen's University.*

## References

1. Carstairs S, Beaudoin GA. Quality End of Life Care: The Right of Every Canadian. Ottawa: Government of Canada; 2000.
2. Tranmer JE, Heyland DK, Dudgeon D, et al. The symptom experience of seriously ill cancer and non-cancer hospitalized patients near the end of life. J Pain Symptom Manage 2003;25:420-9.
3. Tanvetyanon T, Leighton JC. Life-sustaining treatments in patients who died of chronic congestive heart failure compared with metastatic cancer. Crit Care Med 2003;31:60-4.
4. Heyland DK, Groll D, Rocker G, et al. End of life care in acute care hospitals in Canada. A quality finish? J Palliat Care 2005;21:142-50.
5. Department of Finance, Canada. Highlights of Budget 2003. Available at: http://www.fin.gc.ca/news03/03-010e.html#Highlights.
6. Field M, Cassel CK, eds. Approaching Death: Improving Care at the End of Life. Committee on Care at the End of Life, Division of Health Care Services, Institute of Medicine. Washington, DC. National Academy Press; 1997.
7. Oneschuk D, Fainsinger R, Janson H, Bruera E. Assessment and knowledge in palliative care in second year family medicine residents. J Pain Symptom Manage 1997;14:265-73.
8. Okon TR, Evans JM, Gomez CF, Blackhall LJ. Palliative educational outcome with implementation of PEACE tool integrated clinical pathway. J Palliat Care 2004;7:279-90.
9. Tulsky JA, Chesney MA, Lo B. How do medical residents discuss resuscitation with patients? J Gen Int Med 1995;10:436-42.
10. Fins JJ, Nilson EG. An approach to educating residents about palliative care and clinical ethics. Acad Med 2000;75:662-5.
11. Whiting N, Frank C. Get the code status: teaching housestaff about end-of-life communication with older patients. Geriatr Today 2004;7(1):6-9.
12. Liao S, Amin A, Rucker L. An innovative, longitudinal program to teach residents about end-of-life care. Acad Med 2004;79:752-7.
13. Sulmasy DP, Song KY, Marx ES, Mitchell JM. Strategies to promote the use of advance directives in a residency outpatient practice. J Gen Intern Med 1996;11:657-63.
14. Grimshaw J, Thomas RE, MacLennan G, et al. Effectiveness and efficiency of guideline dissemination and implementation strategies. Health Technol Assess 2004;8:1-72.

# Sodium Intake and Mortality in the NHANES II Follow-up Study

## Cohen HW, Hailpern SM, Fang J, Alderman M. Am J Med 2006;119:275. e7-14

Reviewed by Norm Campbell, MD, FRCPC; Bert Govig, MD, FRCPC

Canadians consume twice as much sodium as is recommended for health.[1] Meta-analyses demonstrate significant increases in blood pressure with increases in sodium intake,[2–4] and up to 17% of hypertension is caused by excess sodium ingestion.[5] Other health risks including osteoporosis, asthma, worsening of heart failure, and stomach cancers have been associated with high sodium consumption.[6] Almost 80% of the sodium in our diet is added by the food industry, and an extensive lobby led by the salt industry challenges the benefit of reducing sodium in our diet.[7,8] Its cause is aided by the lack of randomized controlled trials addressing the morbidity and mortality of patients consuming high- versus low-sodium diets. Observational trials are the next best level of evidence that can shed light on this issue, and this article reviews one attempt to answer the "salt question" using such data.

National Health and Nutrition Examination Survey II (NHANES II; 1976–1980) was a government-sponsored representative, cross-sectional survey of the dietary habits and health status of the US population. A recent article published in the *American Journal of Medicine* (*AJM*) used this data to compare the outcomes of those with high and low sodium intake—"Sodium Intake and Mortality in the NHANES II Follow-up Study."[9] According to the study analysis, low dietary sodium was associated with increased cardiovascular and all-cause mortality. However, a close examination of the *AJM* article raises serious concerns about the validity of the analysis and conclusions.

The first concern relates to the study analysis. The major mechanism by which diets high in sodium produce harm is through an increase in blood pressure. This analysis adjusted the data to control for blood pressure differences, thus mitigating much of the harmful effect of a high-sodium diet.

The next major issue is the presence of other variables that confound comparisons between the two groups. In the *AJM* study, those consuming a low-sodium diet were less educated, older, less physically active, and lighter (with a similar body mass index); had more diabetes; ate less; had higher cholesterol levels; and were more often Black. Some of these factors were crudely categorized, which reduces the accuracy of statistical adjustments. Lastly, many of these factors correlate with poverty, which is an independent risk factor for mortality; and although socioeconomic data were available, they were not used in the analysis or adjustment of the data.

Finally, several results in this study are puzzling:

1. Those with a low intake of dietary sodium were less healthy and educated, which is the contrary of what one expects to find in those who self-select for a low-sodium diet.
2. The findings in this analysis are discordant with analyses of previous NHANES-derived data with respect to the relationships between sodium consumption and blood pressure and cardiovascular events.[10,11]
3. The major method of achieving a low-sodium diet is eating unprocessed foods that are relatively high in potassium. In the *AJM* analysis, the low-sodium-diet group inexplicably had a low potassium intake.

Outcomes from observational trials are highly dependant on factors used to create the comparison groups. It is extremely difficult to control for all of the factors that influence people's behavioural choices, and these types of studies may lead us to erroneous conclusions. A recent example of this is the change in recommendations with respect to hormone replacement therapy, when prospective randomized controlled trials did not confirm the findings of observational studies.[12,13] Nutritional choices are arguably more complex than drug therapy choices, and we must be even more circumspect in the interpretation of observational trials in the field of nutrition. Given the methodological issues that this study raises and its unexpected and counterintuitive findings, its results should be duly noted and filed away for epidemiology teaching rounds. Instead, the results of this study have been highly promoted by the salt industry (www.saltinstitute.org). This sends a confusing and potentially harmful message to the public.

How safe is the addition of high quantities of sodium to our food? Based on the sum of the evidence, we believe that high dietary sodium is a serious health risk to our population. This same conclusion has been reached by the World Health Organization,[14] the Canadian and American governments,[1] and many other national governments and scientific organizations around the world. Recently the American Medical Association has recommended that the government revoke the "safe" status of sodium as food additive.[15] These highly conservative groups have no bias for or against sodium but have called for action to reduce dietary sodium.

Health care professionals need to be alert for "weak science" that generates an aura of controversy around health issues. This is a lesson that we have all learned from the saga of the tobacco industry (www.tobaccoscam.org), but other industries may also try to distort science for their benefit. The *AJM* article has substantial methodological concerns and does not contribute to the scientific literature on sodium and health.

*Norm Campbell, MD, FRCPC*: Professor of Medicine, Division of General Medicine, University of Calgary, Calgary, Alberta; *Bert Govig, MD, FRCPC*: Community General Internist—CSSSEA, Amos, Québec
E-mail address for correspondence: ncampbel@ucalgary.ca
Conflict of interest: None declared
*Can J Gen Intern Med* 2006;1:24-25

*Dr. Campbell was the 2005 winner of the Dr. David Sackett Senior Investigator Award. He is currently professor of medicine, Division of General Medicine, at the University of Calgary.*

## References


1. Panel on Dietary Reference Intakes for Electrolytes and Water, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: National Academies Press; 2004. Available at: www.nap.edu/catalog/10925.html.
2. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2004;1-64.
3. He FJ, MacGregor GA. How far should salt intake be reduced? Hypertension 2003;42:1093-9.
4. Geleijnse JM, Kok FJ, Grobbee D. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J Hum Hypertens 2003;17:471-80.
5. Geleijnse JM, Grobbee DE, Kok FJ. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. J Hum Hypertens 2005;19:S1-4.
6. de Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. J Hum Hypertens 2002;16:213-23.
7. MacGregor GA, Sever PS. Salt—overwhelming evidence but still no action: can a consensus be reached with the food industry? BMJ 1996;312:1287-9.
8. Godlee F. The food industry fights for salt. BMJ 1996;312:1239-40.
9. Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. Am J Med 2006;119:275.e7-14.
10. Hajjar IM, Grim CE, George V, Kotchen TA. Impact of diet on blood pressure and age-related changes in blood pressure in the US population. Arch Intern Med 2001;161:589-93.
11. He J, Ogden LG, Vupputuri S, et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 1999;282:2027-34.
12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
13. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1988;280:605-13.
14. World Health Organization. The World Health Report 2002. Geneva, Switzerland: World Health Organization; 2002.
15. Warner M. The war over salt. New York Times 2006 Sep 13;C1.

# Apport sodique et mortalité dans l'étude de suivi NHANES II

## Cohen HW, Hailpern SM, Fang J, Alderman M. Am J Med 2006;119:275. e7-14

Revu par Norm Campbell, MD, FRCPC; Bert Govig, MD, FRCPC

Les Canadiens et Canadiennes consomment deux fois plus de sodium qu'il n'est recommandé pour leur santé.[1] Des méta-analyses démontrent des élévations significatives de la tension artérielle avec l'augmentation de l'apport sodique,[2–4] et 17 % des cas d'hypertension sont causés par une ingestion excessive de sodium.[5] D'autres risques pour la santé incluent l'ostéoporose, l'asthme, l'aggravation de l'insuffisance cardiaque, et le cancer de l'estomac a été associé à la trop grande consommation de sel.[6] Presque 80 % du sodium de notre diète est ajouté par l'industrie alimentaire, et les pressions exercées par l'industrie du sel viennent remettre en question les bienfaits d'une diète réduite en sodium.[7,8] L'absence d'études cliniques, contrôlées, à répartition aléatoire abordant la morbidité et la mortalité des patients qui consomment beaucoup de sodium par rapport à ceux qui en consomment moins vient en aide à la cause. Des études par observation représentent ce qu'il y a de mieux pour élucider ce sujet, et cet article examine une tentative de répondre à la question du sel en utilisant de telles données.

Le *National Health and Nutrition Examination Survey II* (NHANES II; 1976–1980) était une enquête ponctuelle parrainée par le gouvernement sur les habitudes alimentaires et l'état de santé de la population américaine. Un article récent publié par l'*American Journal of Medicine* (*AJM*) a utilisé ces données pour comparer les résultats d'une consommation élévée et faible de sodium –« Apport sodique et mortalité dans l'étude de suivi NHANES II ».[9] Selon l'analyse, un faible apport en sodium a été associé à une augmentation de la mortalité cardiovasculaire et de la mortalité toutes causes. Toutefois, un examen minutieux de l'article de l'*AJM* a soulevé de sérieux problèmes au sujet de la validité de l'analyse et des conclusions.

La première préoccupation concerne l'analyse de l'étude. Les diètes riches en sodium peuvent nuire à la santé parce qu'il y a augmentation de la tension artérielle. Cette analyse a ajusté les données pour contrôler les différences de tension artérielle, et par conséquent, a atténué la grande partie de l'effet nuisible d'une diète à teneur élevée en sodium.

La deuxième préoccupation est la présence d'autres variables confusionnelles de comparaison entre les deux groupes. Dans l'étude de l'*AJM*, les personnes qui consommaient une diète hyposodique étaient moins éduquées, plus âgées, moins actives physiquement et plus minces (avec un indice de masse corporelle semblable); étaient atteintes de diabète; mangeaient moins; avaient des taux de cholestérol plus élevés; étaient plus souvent de race noire. Certains de ces facteurs ont été catégorisés sommairement, ce qui vient réduire la justesse des ajustements statistiques. Et finalement, plusieurs de ces facteurs correspondent à la pauvreté, ce qui est un facteur de risque indépendant pour la mortalité; et bien que des données socio-économiques soient disponibles, elles n'ont pas été utilisées dans l'analyse ni l'ajustement des données.

Finalement, plusieurs résultats de cette étude nous laissent perplexes :

1. Les personnes qui avaient une diète hyposodique étaient moins en santé et moins éduquées, ce qui est le contraire de ce qu'on peut s'attendre chez les personnes qui choisissent d'elles-mêmes d'adopter une diète à faible teneur en sodium.
2. Les résultats de cette analyse ne correspondent pas à ceux des analyses des données de l'étude NHANES pour ce qui est de la relation entre la consommation de sodium et la tension artérielle et les événements cardiovasculaires.[10,11]
3. Pour que la diète soit à faible teneur en sodium il suffit de manger des aliments qui ne sont pas transformés et dont la teneur en potassium est élevée. Dans l'analyse de l'*AJM*, la teneur en potassium du groupe qui consommait une diète hyposodique était inexplicablement faible.

Les résultats des études par observation reposent en grande partie sur des facteurs utilisés pour créer des groupes de comparaison. Il est extrêmement difficile de contrôler tous les facteurs qui influencent les choix comportementaux des gens et ces types d'études peuvent donner des conclusions erronées. Un exemple récent est le changement dans les recommandations en matière de traitement hormonal de substitution, lorsque des études cliniques prospectives, à répartition aléatoire et contrôlées n'ont pas confirmé les résultats des études par observation.[12,13] Les choix alimentaires sont, si on peut dire, plus complexes que les choix de traitements médicamenteux et nous devons être encore plus circonspects à l'égard de l'interprétation des études par observation dans le domaine de la nutrition. Étant donné les problèmes méthodologiques que cette étude soulève et ses résultats inattendus et contre-intuitifs, ses résultats devraient être notés en bonne et due forme et classés pour les leçons cliniques en épidémiologie. Au lieu de cela, l'industrie du sel a fait une vaste promotion des résultats de cette étude (www.saltinstitute.org). Ainsi, le message transmis au public est bouleversant et possiblement nuisible.

Est-ce sécuritaire d'ajouter de grandes quantités de sodium à notre nourriture? En se fondant sur toutes les preuves, nous croyons qu'une diète à teneur élevée en sodium représente un risque serieux pour la santé de la population. La même conclusion a été formulée par l'Organisation mondiale de la santé,[14] les gouvernements du Canada et des États-Unis,[1] et plusieurs autres organismes gouvernementaux à l'échelle nationale et sociétés scientifiques de par le monde. Tout dernièrement, *l'American Medical Association* a recommandé que le

*Norm Campbell, MD, FRCPC*: Professeur de médecine, Division de la médecine générale, Université de Calgary, Calgary, Alberta; *Bert Govig, MD, FRCPC*: Interniste général—CSSSEA, Amos, Québec
Adresse pour correspondance : ncampbel@ucalgary.ca
Conflit d'intérêt : Aucun déclaré
*Can J Gen Intern Med* 2006;1:26-27

gouvernement abolisse le statut sécuritaire du sodium comme additif alimentaire.[15] Ces groupes hautement conservateurs ne sont ni pour ni contre le sodium, mais ont fait appel à l'action pour réduire le sodium alimentaire.

Les professionnels des soins de santé doivent être prévenus au sujet de la «science imprécise» qui génère maintes controverses au sujet de questions de santé. C'est une leçon que nous avons tous retenue de l'industrie du tabac (www.tobaccoscam.org), mais d'autres industries peuvent également déformer la science à leur avantage. L'article de l'*AJM* comporte des problèmes méthodologiques appréciables et n'apporte rien à la documentation scientifique sur le sodium et la santé.

*Le Dr Campbell est le récipiendaire de la bourse en 2005 du Dr David Sackett Senior Investigator Award. Il est professeur de médecine à la Division de la médecine générale de l'Université de Calgary.*

## Références


1. Panel on Dietary Reference Intakes for Electrolytes and Water, Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary Reference Intakes for Water, Potassium, Sodium, Chloride, and Sulfate. Washington, DC: National Academies Press; 2004. Available at: www.nap.edu/catalog/10925.html.
2. He FJ, MacGregor GA. Effect of longer-term modest salt reduction on blood pressure. Cochrane Database Syst Rev 2004;1-64.
3. He FJ, MacGregor GA. How far should salt intake be reduced? Hypertension 2003;42:1093-9.
4. Geleijnse JM, Kok FJ, Grobbee D. Blood pressure response to changes in sodium and potassium intake: a metaregression analysis of randomised trials. J Hum Hypertens 2003;17:471-80.
5. Geleijnse JM, Grobbee DE, Kok FJ. Impact of dietary and lifestyle factors on the prevalence of hypertension in Western populations. J Hum Hypertens 2005;19:S1-4.
6. de Wardener HE, MacGregor GA. Harmful effects of dietary salt in addition to hypertension. J Hum Hypertens 2002;16:213-23.
7. MacGregor GA, Sever PS. Salt—overwhelming evidence but still no action: can a consensus be reached with the food industry? BMJ 1996;312:1287-9.
8. Godlee F. The food industry fights for salt. BMJ 1996;312:1239-40.
9. Cohen HW, Hailpern SM, Fang J, Alderman MH. Sodium intake and mortality in the NHANES II follow-up study. Am J Med 2006;119:275.e7-14.
10. Hajjar IM, Grim CE, George V, Kotchen TA. Impact of diet on blood pressure and age-related changes in blood pressure in the US population. Arch Intern Med 2001;161:589-93.
11. He J, Ogden LG, Vupputuri S, et al. Dietary sodium intake and subsequent risk of cardiovascular disease in overweight adults. JAMA 1999;282:2027-34.
12. Rossouw JE, Anderson GL, Prentice RL, et al. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA 2002;288:321-33.
13. Hulley S, Grady D, Bush T, et al. Randomized trial of estrogen plus progestin for secondary prevention of coronary heart disease in postmenopausal women. Heart and Estrogen/progestin Replacement Study (HERS) Research Group. JAMA 1988;280:605-13.
14. World Health Organization. The World Health Report 2002. Geneva, Switzerland: World Health Organization; 2002.
15. Warner M. The war over salt. New York Times 2006 Sep 13;C1.

# AWARD WINNERS

## Osler Award Winners 2006

The CSIM Osler Awards are presented annually to individuals demonstrating excellence in achievement in the field of general internal medicine (GIM) in clinical practice, research, medical education, or specialty development. The 2006 awards were sponsored by AstraZeneca and the recipients are Dr. Robert Dupuis, Dr. Gerald Karr, Dr. Henry de Souza, and Dr. Donald Steeves.

### Robert Dupuis

***(Nominated by Dr. D. Echenberg and Dr. B. Govig)***

Dr. Robert Dupuis trained at Laval and in Montreal, Quebec, before moving to Thetford Mines in 1986 to practise internal and cardiovascular medicine.

Dupuis has been very active in research, publishing extensively in major journals. He has been co-investigator in many national and international cardiology trials. He has been active in teaching internal medicine residents, and is an affiliated professor with Laval University. This is in addition to a busy clinical practice, including inpatient medicine, pacemaker clinic, and ICU work. Dupuis has been successful in recruiting colleagues on the basis of his model practice.

### Gerald Karr

***(Nominated by Dr. T. Ashton and Dr. C. Offer)***

Dr. Gerald Karr studied pharmacology, then medicine, in Winnipeg, graduating in 1969, and put both disciplines to use in an eight-year clinical association with the University of Calgary. For nearly thirty years, he has been an active member of staff of the Penticton Regional Hospital, BC.

Karr's career is distinguished by a lifelong contribution to leadership, specialty development, and health promotion. He has provided a lifetime of service to the provision of renal medicine in BC and locally, and he has been instrumental in developing clinical research and ethics programs, and in establishing preventive medicine strategies to his community. Karr has served on many committees in the BC College of Physicians and the CMA. He has been an active member, and president, of both the BC Medical Association and the Canadian Society of Internal Medicine. As a natural leader, he has been said "to have an excellent ability…in dealing with highly complex, controversial and sometimes emotional situations…an ability to get a meeting back on track, or bring order from chaos."

### Henry de Souza

***(Nominated by Dr. P. Fernandez and Dr. P. Bolli)***

Dr. Henry de Souza graduated from University College Dublin, practised in the UK training system for several years, and moved to Ontario in 1966. He is an assistant clinical professor at the University of Western Ontario and practises internal medicine at the Hotel Dieu, Niagara, and at St. Catherines General Hospital.

de Souza is well-known for his sharp clinical acumen, his depth of knowledge in internal medicine, and his longstanding advocacy of evidence-based medicine. He is a founding member of the Niagara Clinical Teaching and Research Centre, and has made an outstanding contribution to this group. He has held teaching appointments including Dalhousie, Toronto, Queen's, and UWO and is recognized as a gifted educator by peers and students alike. de Souza has been described as "very caring to patients, going out of his way to lend support to his patients, a real 'old guard' doctor with great dedication to his profession."

### Donald Steeves

***(Nominated by Dr. M. Raju and Dr. P. Bergin)***

Dr. Donald Steeves, a third-generation physician, graduated from Dalhousie Medical School in 1969. After four years of general practice in Liverpool, Nova Scotia, he returned to Dalhousie to complete internal medicine training. For the past twenty-six years, he has enjoyed a busy and diverse referral practice in Charlottetown, PEI. Depending on local availability of medical specialists, he has had to adapt his practice to reflect the needs of community and hospital.

Steeves has chaired P & T committees and a number of hospital and provincial medical committees dealing with intensive care, cardiovascular protocols and registries, and motor vehicle certification. Early on he was involved with the Dalhousie medical internship program, and in the past few years has been involved in cardiovascular trial research. Steeves has a special interest in difficult diagnostic and management problems in clinical medicine. "His hallmark is an incredible thoroughness and attention to detail, complemented by a superb knowledge base and clinical acumen."

## 2006 Dr. David Sackett Senior Investigator Award

The Canadian Society of Internal Medicine congratulates Dr. Deborah Cook of Hamilton for winning the 2006 Dr. David Sackett Senior Investigator Award.

### Deborah Cook

Dr. Deborah Cook completed undergraduate and postgraduate IM training at McMaster Medical School, going on to obtain a Critical Care Fellowship from Stanford University (1991). She returned to take an MSc (Design, Measurement and Evaluation Program), under the mentorship of Drs. David Sackett and Gordon Guyatt. Currently, Cook practices intensive care medicine at St. Joseph's Hospital in Hamilton, Ontario. She is professor of Medicine, Clinical Epidemiology and Biostatistics at McMaster University, and academic chair of Critical Care Medicine at St Joseph's Healthcare and McMaster University.

Cook is involved in multimethod multidisciplinary research, translating knowledge into practice to prevent morbidity and mortality, particularly in the critically ill. She is a Canada research chair with a range of interests including life-support technology, end-of-life choices, risk factors for critical illness, prevention of ICU-acquired illness, research ethics, and methodology. She has published over 500 articles in the medical literature.

In addition, Cook has trained and supervised numerous research trainees in Canada and elsewhere. Recently, she was awarded the President's Educational Leadership Award at McMaster University for her dedication to mentoring students and junior faculty, striving to make them successful independent clinician-scientists. The Royal College of Physicians of Ontario recently honoured her with the Council Award for outstanding achievement in eight roles as a medical expert, health advocate, communicator, collaborator, scientist, learner, manager, and humanist.

*The Senior Investigator Award was supported by an educational grant from Merck Frosst/Schering Pharmaceuticals.*

## 2006 New Investigator Award

The Canadian Society of Internal Medicine congratulates Dr. David Juurlink of Toronto for winning the 2006 CSIM New Investigator Award.

### David Juurlink

Dr. David Juurlink is a staff physician in the Division of General Internal Medicine and Head of the Division of Clinical Pharmacology and Toxicology at Sunnybrook Health Sciences Centre. He is also a medical toxicologist at the Ontario Regional Poison Information Centre at the Hospital for Sick Children.

Juurlink received degrees in pharmacy and medicine from Dalhousie University in Halifax, and completed postgraduate training in internal medicine, clinical pharmacology, and clinical toxicology, as well as a PhD in clinical epidemiology from the University of Toronto. His primary area of research is drug safety, with a particular interest in the clinical consequences of drug interactions.

*The New Investigator Award was supported by an educational grant from Merck Frosst/Schering Pharmaceuticals.*

# Welcome to New Members

CSIM welcomes the following new members of the society:

## Residents

Dr. Maher Naguib Mehany Abdel-Malak
Dr. Abdulgani Ab. M. Abonowara
Dr. Arlal Abu Sanad
Dr. Hussein Abdurrahman H. Abujrad
Dr. Ahmed Ahmed AlJohany
Dr. Shadi Akhtari
Dr. Majid Al Madi
Dr. Mohammed Al Mehthel
Dr. Abdullah Saeed M. Al Zahrani
Dr. Muhannad Dhia Judy Al-Jaber
Dr. Ali Almusawi
Dr. Turki Alwasaidi
Dr. Mark Bailey
Dr. Claire Barber
Dr. Karen Bensoussan
Dr. James Bin
Dr. Silvana Bolano del Vecchio
Dr. Christine Bourgault
Dr. Loree Lynn Boyle
Dr. Angèle Brabant
Dr. Melanie Brown
Dr. Savannah Cardew
Dr. Rajendra Carmona
Dr. Sean Carr
Dr. Jean-Christophe Carvalho
Dr. Lana Castellucci
Dr. Ronnie Chan
Dr. Vicky Chan
Dr. Ramandeep Kaur Chawla
Dr. Brian Jang Hwan Cho
Dr. Edward Clark
Dr. Vikram Ravindran Comondore
Dr. Stephen Congly
Dr. Joslyn Conley
Dr. Cecilia Costiniuk
Dr. Marie-Nöelle Côté
Dr. Beth-Ann Cummings
Dr. Konstadina Darsaklis
Dr. Sharmistha Das
Dr. Nathan John Degenhart
Dr. Gianni Ercole D'Egidio
Dr. Melanie Di Quinzio
Dr. Maya Doumit
Dr. Vera Dounaevskaia
Dr. Malak El-Rayes
Dr. Shane English
Dr. Leilawi Casilda Famorla
Dr. Tabassum Firoz
Dr. Andrew Grant
Dr. Alison Graver
Dr. Michelle Nora Grinman
Dr. Leena Hajra
Dr. Adnan Kazi Hameed
Dr. Douglas Hayami
Dr. Sari Michelle Herman
Dr. Jeremy Ho
Dr. Jenny Mei-Yeo Ho
Dr. Sarah Anne Ingber
Dr. Sahar Jameel Iqbal
Dr. Tariq Iqbal
Dr. Akshai Mohan Iyengar
Dr. David Jones
Dr. Nikola July
Dr. Jamil Kanji
Dr. Anmol S. Kapoor
Dr. Mary-Margaret Keating
Dr. Zahira Khalid
Dr. Omar H. Kify
Dr. Joseph Kim
Dr. Hin Hin Ko
Dr. Karen Kin-Yue Koo
Dr. Dayantha Kottachchi
Dr. Christian Kraeker
Dr. Darin S. Krygier
Dr. Puja Kumar
Dr. Kwadwo Kyeremanteng
Dr. Patrick Labbé
Dr. Christopher Labos
Dr. Martin Labuda
Dr. Marie-Josée Lacelle
Dr. Emily Lai
Dr. Marc-André Leclair
Dr. Linda May Lee
Dr. Christie Lee
Dr. Kar Cheong Lee
Dr. Edward Lee
Dr. Anson Li
Dr. Joy Jiah-yin Liao
Dr. Theresa Liu
Dr. Marie-Eve Lizotte
Dr. Khuê Ly
Dr. Ling Ling Ma
Dr. Jimmy Machaalany
Dr. Mark Anthony MacMillan
Dr. Nadia Malakieh
Dr. Samir Malhotra
Dr. Laura Susanne Marcotte
Dr. Heather McLeod
Dr. Sarah Margaret McMullen
Dr. Brandon Meyers
Dr. Nataliya Milman
Dr. Luc Moleski
Dr. Ibrahim Mohammad Momenkhan
Dr. Bahareh Motlagh
Dr. Sunita Sheila Mulpuru
Dr. Anthony Naassan
Dr. Jeya Nadarajah
Dr. Josiane Nawar
Dr. John Neary
Dr. Sarah Nelson
Dr. Carol Ott
Dr. Daniel Ovakim
Dr. Scott Owen
Dr. Tripti Papneja
Dr. Vishal Patel
Dr. Viktoria Pavlova
Dr. Lysanne Pelletier
Dr. Patricia Peticca
Dr. Aimee June Peuhkuri
Dr. Sanaz Piran
Dr. Sean Pritchett
Dr. Raffaela Profiti
Dr. Marco Puglia
Dr. Amira Rana
Dr. Daniel Renouf
Dr. Elizabeth Rhynold
Dr. Jennifer Ringrose
Dr. Irwindeep Sandhu
Dr. Yoko Saschin Schreiber
Dr. Christopher Sharpe
Dr. Dan Slabu
Dr. Daniel Smyth
Dr. Howard Song
Dr. Naomi Spitale
Dr. Srilata Kavita Sridhar
Dr. Jocelyn Srigley
Dr. Kristoffor Britton Stewart
Dr. Ganesh Subramanian
Dr. Ian Sutcliffe
Dr. Vincent Channing Tam
Dr. Penny Tam
Dr. Karthik Tennankore
Dr. Subarna Thirugnanam
Dr. Karen To
Dr. Vanessa Tremblay
Dr. Hariharan Vasan
Dr. Diane Villanyi
Dr. Revital Wanono
Dr. Thomas Warren
Dr. Lay Lay Win
Dr. Camilla Wong
Dr. Radhika Yelamanchili
Dr. Yong Dong You
Dr. Aaron Young
Dr. Oriana Hoi Yun Yu
Dr. Jane Yuan
Dr. Derek Yung

## Full Members

Dr. Paul Clavette
Dr. Avtar Singh Dhillon
Dr. Claudio Di Prizito
Dr. Kempe Gowda
Dr. Geneviève Grégoire
Dr. Jayna Holroyd-Leduc
Dr. Zafar Iqbal
Dr. Parul Khanna
Dr. Michelle Mohammed
Dr. Donald Moore
Dr. Jill Newstead-Angel
Dr. Greg Peters
Dr. Anna Purdy
Dr. Irina Sanatani
Dr. Walter F. Schlech III
Dr. Lawrence Schnurr
Dr. Ahmad Raed Tarakji
Dr. Shahzad Zia

## Associate Member

Dr. Manisha Khurana

## CSIM Membership

Membership as of September 14, 2006:

| | |
|---|---|
| Full members | 564 |
| Residents | 210 |
| Associate members | 2 |
| Seniors/retired members | 79 |
| Honorary members | 3 |
| Medical students | 2 |
| Corporate members | 4 |
| **TOTAL** | **864** |

# A Profile of the Canadian Society of Internal Medicine

By Domenica Utano

## What Is the CSIM?

The Canadian Society of Internal Medicine (CSIM) is the non-profit professional society that represents the interests of specialists in general internal medicine in Canada. Our mission is "to represent, promote and provide leadership for the discipline of general internal medicine across Canada, in terms of clinical practice, education and research."

### What Are CSIM'S Goals?

**Practice:**

1. To provide the best care by promoting an evidence-based approach to the practice of general internal medicine.
2. To encourage residents to pursue careers in general internal medicine.
3. To promote the use of information technology by general internists to enhance patient care.
4. To advocate fair compensation for services provided by general internists.

**Education:**

1. To develop a national definition of the roles and competencies of the general internist.
2. To plan the residency curriculum in conjunction with the RCPSC Specialty Committee in Internal Medicine.
3. To assist general internists in their professional development through effective, accessible, needs-based CME/CPD.

**Research:**

1. To facilitate a coordinated national approach to research in general internal medicine.
2. To support an endowment fund for research in general internal medicine.

### History of the CSIM

In 1983, a large group of internists discussed forming an organization that could act on their behalf. The CSIM was incorporated in 1984 with four hundred charter members. The creation of the society was spearheaded by the late Dr. J. Allan Gilbert, who became the CSIM's first president. A unique feature of the CSIM Council is that there is representation from all geographic regions across Canada. In addition, the CSIM represents general internists from university and community settings. The council is composed of 50 percent academic internists and 50 percent practising in a community setting. The society's current membership is at an all-time high of 864.

The CSIM's Annual Scientific Meeting (ASM) was previously held within the Royal College's annual conference. However, in 2001, the CSIM ventured on its own and held its first stand-alone meeting, which was a resounding success. Since then, the ASM has grown significantly both in size and in calibre. The meeting sessions present relevant and useful information, not only for the GIM specialist but also for sub-specialists in varying fields. Residents are encouraged to attend the ASM, and a special program is designed just for them.

### Recent Events

**GIM Working Group**

In May 2005, the CSIM was pleased to inform its members about the creation of the **Working Group in General Internal Medicine**, under the auspices of the Royal College of Physicians. The mandate of this group is to develop GIM training objectives and standards for training programs, as well as developing the concept of core competencies in GIM. The creation of this group marked the first time that general internal medicine had an official voice at the Royal College.

**GIM Document**

The society, under the leadership of Dr. Mahesh Raju, directed its attention on one of its most exciting initiatives–the production of its monograph ***Care-Fully: Defining a Plan for General Internal Medicine in Canada*** (published in October 2005). One of the goals of this document is to bring attention to the shortage of GIM specialists in Canada, as well as to highlight the crucial role general internists play in the Canadian health care system.

This document is in the process of being distributed to many stakeholders such as health ministers, hospital administrators, deans and chairs of medicine, and residency directors, to list but a few. An upcoming goal of the society is to collaborate with such stakeholders to improve the delivery of specialized medical care in Canada, thus ensuring that Canadians continue to receive high-quality care.

**CSIM Web site**

The CSIM Web site has been completely revamped over the course of the past two years. The new site, **www.csimonline.com**, links to hundreds of journals and other useful resources. It also hosts CSIM educational modules and polls that are used to foster a Canadian dialogue about issues pertinent to GIM in Canada.

**New GIM Journal**

The most recent event is the launch of this journal—the *Canadian Journal of General Internal Medicine*. Readers are invited to submit their clinical cases, their research projects, case reports, and commentaries. This is a new communication vehicle, and we encourage readers to use it and to forward submissions to csim@rcpsc.edu.

## Future Directions

The CSIM will continue its focus on the promotion of general internal medicine as a sub-specialty through the efforts of the Working Group in GIM. The *Care-Fully* document will be translated along with a second printing. Efforts will continue in advocating for increased resources to train more general internists and to increase the number of GIM residency training positions.

Other new initiatives for the society include creating a dialogue with internal medicine groups elsewhere in the world such as the IMSANZ (Internal Medicine Society of Australia and New Zealand), the SGIM (Society of General Internal Medicine), the ACP (American College of Physicians), and the ASMIQ (Association des spécialistes en medicine interne du Québec).

Another new initiative is in the field of health promotion. The CSIM would like to devote some of its energy into promoting health and preventing disease as well as promoting healthy living habits among our own members.

*After college, Domenica Utano pursued a career in banking. She switched careers ten years ago and has happily been with the Royal College ever since. Domenica is currently the association manager of the Canadian Society of Internal Medicine and of the Canadian Society for Clinical Investigation. She has been married for eight years, and her proudest accomplishment is being the mother of an active, beautiful little boy.*

## Bibliography

1. Associated Medical Services, *Medical Specialty Societies of Canada*. Toronto: The Boston Mills Press, 1991.
2. Canadian Society of Internal Medicine, *The General Internist*. 2005–2006.

# Société canadienne de médecine interne

## La société

La Société canadienne de médecine interne (SCMI) est l'association professionnelle à but non lucratif qui représente les intérêts des internistes généralistes au Canada. La société a pour mission « de représenter, promouvoir et diriger la spécialité de la médecine interne générale dans tout le Canada, sur les plans de la pratique clinique, de l'éducation et de la recherche. »

## Objectifs

### Pratique clinique :

1. Favoriser la prestation de soins conforme aux normes plus élevées par l'exercice de la médecine factuelle en médecine interne.
2. Encourager les diplômés en médecine à poursuivre une carrière en médecine générale interne.
3. Promouvoir l'utilisation des technologies de l'information par les internistes généralistes pour favoriser la prestation de soins.
4. Défendre la cause de la rétribution équitable des services fournis par les internistes généralistes.

### Éducation :

1. Élaborer une définition, applicable à l'échelle nationale, des rôles et compétences de l'interniste généraliste.
2. Concevoir le programme d'études de résidence de concert avec le Comité de la spécialité en médecine interne du CRMCC.
3. Favoriser le perfectionnement professionnel des internistes généralistes par un programme d'ÉMC / DPC judicieux, accessible et adapté aux besoins.

### Recherche :

1. Favoriser une approche nationale coordonnée pour la recherche en médecine interne générale.
2. Établir une fondation parrainée pour soutenir la recherche en médecine interne générale.

# Canadian Society of Internal Medicine Annual Scientific Meeting

**Hyatt Regency, Calgary, Alberta • November 1–4, 2006**

| | |
|---|---|
| **TUESDAY, OCTOBER 31** | |
| 1730–2030 | CSIM Executive Committee Meeting (closed) (over dinner) |
| **WEDNESDAY, NOVEMBER 1** | |
| 0800–1030 | CSIM Council Meeting (closed) (over breakfast) |
| 1030–1200 | CSIM Annual Meeting and Education Committees Meeting (closed) |
| 1130–1330 | Lunch for all CSIM Council and Committee Members (closed) |
| 1300–1430 | CSIM Membership and Education Committees Meeting (closed) |
| 1445–1500 | **WELCOME ADDRESS**<br>Dr. Donald Echenberg, CSIM President, Sherbrooke<br>Dr. Robert Herman, Chair 2006 Annual Meeting Committee, Calgary |
| 1500–1730 | **SHORT SNAPPERS**<br>1. Perioperative AMI–Dr. Akbar Panju, Hamilton<br>2. Optimal Asthma Management–Dr. Tony Bai, Vancouver<br>3. Incretins–TBA<br>4. New Insulins–TBA<br>5. New Method for Rapid HIV Testing–Dr. Donna Sweet, Wichita |
| 1730–1800 | **WELCOME RECEPTION** |
| 1800–1900 | **ACP SYMPOSIUM: The Top Clinical Trials from 2005/06**–Dr. Brendan MacDougall, Winnipeg<br>This symposium is sponsored by the American College of Physicians (Western Chapter) |
| 1900–2100 | **WELCOME DINNER (open to all)** |
| 1900–2100 | GIM Working Group and GIM Program Directors Meeting (closed) (over dinner) |
| **THURSDAY, NOVEMBER 2** | |
| 0630–0700 | **BREAKFAST** |
| 0700–0800 | **BREAKFAST SYMPOSIUM: Is Resistant Hypertension Really Resistant?**–Dr. Peter Hamilton, Edmonton<br>Including Highlights from the 2007 CHEP Recommendations—Dr. Nadia Khan, Vancouver<br>This symposium is sponsored by Bayer Canada |
| 0630–0745 | Research/Awards Committee Meeting (closed) (over breakfast) |
| 0800–0830 | **Keynote Address: New Investigator Award Winner 2006**<br>**Studying Drug Safety in the Real World** –Dr. David Juurlink, Toronto<br>The NIA is supported by an educational grant from Merck Frosst/Schering Pharmaceuticals |
| 0845–1130 | **CONCURRENT WORKSHOPS (select three)**<br>*(Repeating three times: 0845–0930, 0945–1030, 1045–1130)*<br>1. Acid Base Disorders–Dr. Irene Ma, Vancouver<br>2. Medical Simulation: Are you Up to Date as You Think?–Dr. Jean Setrakian, Montreal<br>3. ECGs (Challenging Tracings)–Dr. Dean Traboulsi, Calgary<br>4. CV Line Insertion–Dr. André Ferland, Calgary)<br>5. Endocrine Emergencies–Dr. John Dornan, Saint John<br>6. Dermatology for Internists–Dr. Richard Haber, Calgary<br>7. Medical Education: Bedside Teaching Settings Standards–Dr. Iain Mackie, Vancouver<br>8. Improving Presentation Skills–Dr. Louise Pilote, Montreal<br>9. Drugs in Pregnancy–Drs. Dave Sam, Toronto, and Paul Gibson, Calgary<br>10. Work up of Vasculitis–Dr. Elaine Yachyshyn, Edmonton |

| | |
|---|---|
| 1145–1300 | **LUNCHEON SYMPOSIUM:** Type 2 Diabetes in Canada–Where Are We Going?–Dr. Irene Hramiak, London<br>This symposium is sponsored by Merck Frosst Canada Ltd. |
| 1300–1330 | **Keynote Address: Dr. David Sackett Senior Investigator Award Winner 2006**<br>**Changing Clinician Behaviour to Implement Evidence in Practice** –Dr. Deborah Cook, Hamilton<br>The SIA is supported by an educational grant from Merck Frosst/Schering Pharmaceuticals |
| 1345–1500 | Oral Research Session<br>1. **Pneumococcal Vaccination and Risk of Myocardial Infarction**<br>–Dr. Jean-Christophe Carvalho, Sherbrooke<br>2. **A National Survey of Canadian Surgeons: Current use and Future Trial Evaluation of Perioperative Acetyl-Salicylic Acid (ASA)**<br>–Dr. Rajesh Hiralal, Hamilton<br>3. **Intensity of Warfarin Therapy and Use of Interacting Medications in a Long-Term Care**<br>–Dr. Bahareh Motlagh, Burlington<br>4. **Systematic Review of Screening Questionnaires for Type 2 Diabetes**<br>–Dr. Kara Nerenberg, Hamilton<br>5. **AntimicrobalsAntimicrobials for Right-Sided Endocarditis in Intravenous Drug Users: A Systematic Review**<br>–Dr. Derek Yung, Toronto |
| 1500–1600 | ACP Annual General Meeting |
| 1600–1700 | Free time |
| 1700–1800 | Wine and Cheese and Viewing of Research Posters |
| 1800–1900 | **CONCURRENT SYMPOSIA (Select one)**<br>1. **Pump Failure: Prevention, Prolongation and Perseverance**<br>–Drs. Malcolm Arnold, London, and Elizabeth Mann, Halifax<br>This symposium is sponsored by Sanofi-Aventis<br>2. **Stroke Prevention: Action for Global Protection of the Brain**<br>This symposium is sponsored by Pfizer Canada Inc. |
| 1900–2100 | DINNER (open to all) |
| 1900–2100 | Medical Education Research Interest Group (over dinner) |

## FRIDAY, NOVEMBER 3

| | |
|---|---|
| 0630–0700 | BREAKFAST |
| 0700–0800 | **BREAKFAST SYMPOSIUM: Peripheral Arterial Disease: Emerging Evidence, Establishing Risks and New Directions**<br>This symposium is sponsored by Sanofi-Aventis and Bristol Myers Squibb |
| 0800–0830 | **Edwards Lecture/ACP Lecture–Does It Matter How You Lower Blood Sugars in People with Type 2 Diabetes?**<br>–Dr. Jeff Johnson, Edmonton |
| 0845–1130 | **CONCURRENT WORKSHOPS (Select three)**<br>*(Repeating three times: 0845–0930, 0945–1030, 1045–1130)*<br>1. ECGs (Arrhythmias)—Dr. Sean Connors, St. John'sTBA<br>2. Chronic Kidney Disease: Management Issues for the General Internist—Dr. J.W. Barton, Saskatoon<br>3. Liver Disease in Pregnancy—Dr. Rshmi Khurana, Edmonton<br>4. Management of Valvular Heart Disease in the Perioperative Period—Dr. William Ghali, CalgaryTBA<br>5. Searching the Medical Literature—Dr. Sharon Straus, Calgary<br>6. Approach to Management of Skin Ulceration—Dr. Jack Toole, Winnipeg<br>7. Arthrocentesis/Joint Injection—Dr. Suzanne Morin, Montreal<br>8. Advances in the Diagnosis and Management of Substance Use Disorders—Dr. Mark Lysyshyn, Vancouver<br>9. Interpretation of X-ray and CT of the Chest—Dr. John H. MacGregor, CalgaryTBA<br>10. Emerging Pathogens in 2006—Donna Sweet, Wichita |
| 1145–1300 | **LUNCHEON SYMPOSIUM: Emerging Strategies for the Management of Renal Failure in the Diabetic Patient**<br>–Drs. Ellen Burgess, Calgary, and Joseph Zupnik, Toronto<br>This symposium is sponsored by Sanofi-Aventis and Bristol Myers Squibb |
| 1145–1300 | Peri-Operative Research Interest Group (over lunch) |

| | |
|---|---|
| 1315–1345 | **Keynote Address: CSIM/Royal College Osler Lecture and Discussion**<br>–Dr. John Hoey, Ottawa |
| 1345–1500 | Oral Research Session<br>1. **The Impact of Statins in the Perioperative Period: A Systematic Review of Controlled Studies**<br>–Dr. Anmol Kapoor, Edmonto<br>2. **Clinical Decision Support Tools for Disease Management in Osteoporosis: A Systematic Review of the Literature**<br>–Ms. Monika Kastner, Toronto<br>3. **Non-Invasive Cardiac Monitoring for Detecting New Atrial Fibrillation Following Acute Ischemic Stroke: A Systematic Review**<br>–Dr. Joy Liao, Hamilton<br>4. **Cardiorenal Syndrome in Patients with Complex Congenital Heart Disease**<br>–Dr. Sanaz Piran, Oakville<br>5. **Incidence, Clinical Patterns and Outcomes of Gastrointestinal Bleeding in Adult Patients Receiving Allogeneic Hematopoietic Stem Cell Transplantation for Acute Leukemia or Myelodysplastic Syndrome**<br>–Dr. Mark Puglia, Hamilton |
| 1500–1600 | CSIM Annual General Meeting (CSIM members only) |
| 1600–1700 | Free time |
| 1700–1800 | Wine and Cheese and Viewing of Research Posters |
| 1730–2130 | Working Group in GIM-Nucleus Group (closed) (over dinner) |
| 1800–1900 | CONCURRENT SYMPOSIA (Select one)<br>1. **Diabetes: A Cardiac Condition Manifesting as Hyperglycemia**<br>–Dr. David Bell, Birmingham<br>This symposium is sponsored by GlaxoSmithKline<br>2. **The Strongest Link: Hot Topics in Atrial Fibrillation–A Game That Explores the Evidence**<br>– Dr. Derek Exner, Calgary<br>This symposium is sponsored by Merck Frosst Canada Ltd. |
| 1900–2100 | DINNER (open to all) |

## SATURDAY, NOVEMBER 4

| | |
|---|---|
| 0630–0700 | BREAKFAST |
| 0700–0800 | **BREAKFAST SYMPOSIUM: From Diagnosis to Cirrhosis—Update on HCV**<br>– Dr. Alnoor Ramji, Vancouver<br>This symposium is sponsored by Hoffmann-La Roche Ltd. |
| 0630–0800 | Maternal Health Research Interest Group (over breakfast) |
| 0800–0900 | **ROUNDTABLE DISCUSSION**<br>**General Internal Medicine: Objectives of Training/Standards of Accreditation**<br>–Drs. Donna Sweet, Wichita, Sharon Card, Saskatoon, Barry Kassen, Vancouver, and Hector Baillie, Nanaimo |
| 0900–1000 | **SHORT SNAPPERS**<br>1. Dual Antiplatelet Blockage in CV Disease—Dr. Cathy Kells, Halifax<br>2. Dual RAAS Inhibition—Dr. Norman Campbell, Calgary<br>3. Four Drug Interactions Internists Should Fear—Dr. Dave Juurlink, Toronto<br>4. Optimal Investigation and Management of Urinary Tract Infections—Dr. Gary Victor, Ottawa |
| 1000–1145 | **CONCURRENT WORKSHOPS (Select two)**<br>*(Repeats twice: 1000–1045, 1100–1145)*<br>1. Electrolyte Abnormalities—Dr. Kevin McLaughlin, Calgary<br>2. Exercise Stress Testing—Dr. Mark Rabinovitch, Montreal<br>3. Haematologic Emergencies—Dr. Don Houston, Winnipeg<br>4. Pregnancy in Patients with Valvular and Other Hearth Disease—Dr. Cathy Kells, Halifax<br>5. Perioperative Management of Diabetes Mellitus—Drs. Anne PausJenssen and Sharon Card, Saskatoon |

| | |
|---|---|
| | 6. Some Common Diagnostic Tests: Is There More Than Just the Tea Leaves at the Bottom of the Cup?<br>–Dr. Jim Nishikawa, Ottawa<br>7. Mentoring Through Effective Lifestyle Change: The 3-Minute Clinical Intervention (2 hours)<br>–Dr. Jacques Bédard, Sherbrooke<br>8. Interpretation of PFTs<br>–Dr. Lisa PausJenssen, Saskatoon |
| 1000–1315 | **CAREERS IN GENERAL INTERNAL MEDICINE: A Program for Residents** (over lunch)<br>– Drs. Brian O'Brien, Edmonton, Hugo Bertozzi, Grand Prairie, and Brian Cummings, C.A., Kitchener |
| 1200–1315 | **LUNCHEON SYMPOSIUM: Clinical Implications of Guideline Changes in Lipid Management**<br>–Dr. Jacques Genest, Montreal<br>This symposium is sponsored by Merck Frosst/Schering Pharmaceuticals |
| 1330–1530 | **Ted Giles Clinical Vignettes 2006**<br>1. **Primary Cerebral Lymphoma in an Immunosuppressed Patient with Systemic Lupus Erythematosus**<br>–Dr. Linda Lee, Toronto<br>2. **Be Aware of Your Well**<br>–Dr. Marc-André Leclair, Sherbrooke<br>3. **Respiratory Distress, Pulmonary Infiltrates, and Eosinophilia**<br>–Dr. Christie Lee, Toronto<br>4. **Cryoglobulinemia Presenting as Pseudothrombocytosis**<br>–Dr. Adnan Hameed, Winnipeg<br>5. **Recurrent Acute Rheumatic Fever**<br>–Dr. Subarna Thirugnanam, Toronto<br>6. **Severe Hypokalemia in a Young Woman with Sjögren's Syndrome**<br>–Dr. Ted Clarke, Montreal<br>7. **A Gem of a Rash**<br>–Dr. Paul Bunce, Toronto<br>8. **An Unusual Pleural Effusion**<br>–Dr. Marie-Josée Lacelle, Sherbrooke<br>9. **A Case of Splitting Headache**<br>–Dr. Mark Kotowycz, Hamilton<br>10. **The Mystery Man with Jaundice–The Diagnosis Lies in the History**<br>–Dr. Leena Hajra, Toronto |
| 1530–1730 | Free time |
| 1730–1800 | Reception |
| 1800–1830 | **PHYSICIAN WELLNESS**–Drs. Jane Lemaire, Calgary, and Bert Govig, Amos |
| 1830–2300 | 5th Annual CSIM Dinner and Award Presentations |

## SUNDAY, NOVEMBER 5

| | |
|---|---|
| 0800–0930 | Annual Meeting Committee Meeting (closed) (over breakfast) |

***Our sincere thanks to the 2006 CSIM Annual Meeting Committee***

### See you at the next CSIM Annual Scientific Meetings

***October 10–13, 2007***
**at the Delta in St. John's, Newfoundland**

***October 15–18, 2008***
**at the Delta Centre-Ville, Montreal, Quebec**

### Notice of CSIM Annual Meeting of Members

Pursuant to Articles 3.01 and 3.03 of the bylaws, notice is hereby given that the Annual Meeting of Members of the Canadian Society of Internal Medicine will be held in Calgary, Alberta, during the 2006 Annual Scientific Meeting. The AGM is scheduled to take place Friday, November 3, at 1500 hours.

**Note:** Changes to the bylaws will be presented.

To review a copy of last year's AGM minutes, please visit the CSIM Web site at www.csimonline.com or contact the CSIM Office at csim@rcpsc.edu.

NEW AVALIDE 300/25 mg

# POWER TO THE PEOPLE


**These hypertensive patients are real. So is the power of *AVAPRO* and *AVALIDE*.†**

## POWER. PERFORMANCE. BP CONTROL.

*AVAPRO* is indicated for the treatment of essential hypertension. *AVAPRO* is also indicated for the treatment of hypertensive patients with Type 2 diabetes mellitus and renal disease to reduce the rate of progression of nephropathy as measured by the reduction of microalbuminuria, and the occurrence of doubling of serum creatinine. *AVAPRO* may be used alone or concomitantly with thiazide diuretics. The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors has not been established.

*AVALIDE* is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate. *AVALIDE* is not indicated for initial therapy. Irbesartan should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects.

*AVAPRO* and *AVALIDE* should not be used in pregnant women.

Refer to respective prescribing information for complete warnings, precautions, adverse events and patient selection criteria.

Appropriate monitoring is recommended for patients with renal impairment.

† The therapeutic effects on these actual patients may not be indicative of the effects of *AVAPRO*/*AVALIDE* on all patients.

Pr Avapro® (irbesartan) 150 mg 300 mg

Pr Avalide® (irbesartan+hydrochlorothiazide) 150/12.5 mg, 300/12.5 mg, 300/25 mg

Bristol-Myers Squibb Canada

sanofi aventis

Member R&D PMAB

An agreement between Bristol-Myers Squibb and sanofi-aventis for the codevelopment and marketing of irbesartan and clopidogrel, two compounds from sanofi-aventis research.

CDN.IRB.06.02.14E

## Speakers

J. Malcolm Arnold, London, Ontario
Tony Bai, Vancouver, British Columbia
Hector Baillie, Nanaimo, British Columbia
Jim Barton, Saskatoon, Saskatchewan
Jacques Bédard, Sherbrooke, Quebec
David S.H. Bell, Birmingham, Alabama
Hugo Bertozzi, Grand Prairie, Alberta
Paul Bunce, Toronto, Ontario
Ellen Burgess, Calgary, Alberta
Norman Campbell, Calgary, Alberta
Sharon E. Card, Saskatoon, Saskatchewan
Jean-Christophe Carvalho, Sherbrooke, Quebec
Ted Clarke, Montreal, Quebec
Deborah Cook, Hamilton, Ontario
Brian E. Cummings, Kitchener, Ontario
John Dorman, Saint John, New Brunswick
Derek Exner, Calgary, Alberta
André Ferland, Calgary, Alberta
Jacques Genest, Montreal, Quebec
William Ghali, Calgary, Alberta
Paul Gibson, Calgary, Alberta
Bert Govig, Amos, Quebec
Richard Haber, Calgary, Alberta
Leena Hajra, Toronto, Ontario
Adnan Hameed, Winnipeg, Manitoba
Peter Hamilton, Edmonton, Alberta
Rajesh Hiralal, Hamilton, Ontario
John Hoey, Perth, Ontario
Donald S. Houston, Winnipeg, Manitoba
Irene M. Hramiak, London, Ontario
Jeffrey A. Johnson, Edmonton, Alberta
David Juurlink, Toronto, Ontario
Nadia Kahn, Vancouver, British Columbia
Anmol Kapoor, Edmonton, Alberta
Barry Kassen, Vancouver, British Columbia
Monika Kastner, Toronto, Ontario
Catherine M. Kells, Halifax, Nova Scotia
Rshmi Khurana, Edmonton, Alberta
Mark Kotowycz, Hamilton, Ontario
Marie-Josée Lacelle, Sherbrooke, Quebec
Marc-André Leclair, Sherbrooke, Quebec
Christie Lee, Toronto, Ontario
Linda Lee, Toronto, Ontario
Jane Lemaire, Calgary, Alberta
Joy Liao, Hamilton, Ontario
Mark Lysyshyn, Vancouver, British Columbia
Irene Ma, Vancouver, British Columbia
Brendan MacDougall, Winnipeg, Manitoba
John MacGregor, Calgary, Alberta
Iain Mackie, Vancouver, British Columbia
Elizabeth Mann, Halifax, Nova Scotia
Kevin McLaughlin, Calgary, Alberta
Suzanne Morin, Montreal, Quebec
Bahareh Motlagh, Burlington, Ontario
Kara Nerenberg, Hamilton, Ontario
Jim Nishikawa, Ottawa, Ontario
Brian D. O'Brien, Edmonton, Alberta
Akbar Panju, Hamilton, ON
Anne PausJenssen, Saskatoon, SK
Lisa PausJenssen, Saskatoon, SK
Louise Pilote, Montreal, QC
Sanaz Piran, Oakville, Ontario
Mark Puglia, Hamilton, Ontario
Mark Rabinovitch, Côte Saint-Luc, Quebec
Alnoor Ramji, Vancouver, British Columbia
David Sam, Toronto, ON
Jean Setrakian, Montreal, QC
Sharon Straus, Calgary, AB
Donna Sweet, Wichita, KS
Subarna Thirugnanam, Toronto, Ontario
Jack W.P. Toole, Winnipeg, Manitoba
Dean Traboulsi, Calgary, Alberta
Gary Victor, Ottawa, Ontario
Elaine Yacyshyn, Edmonton, Alberta
Derek Yung, Toronto, Ontario
Joseph Zupnik, Toronto, Ontario

## Sponsors

The CSIM gratefully acknowledges support of our scientific program by educational grants from the following companies:

AstraZeneca
Bayer Healthcare
Boehringer Ingelheim
Bristol-Myers Squibb
GlaxoSmithKline
Hoffman-La Roche Ltd
Merck Frosst
Merck Frosst/Schering
Novartis
Pfizer Canada Inc.
Sanofi-Aventis

# Avapro®

*(irbesartan) 150 mg ■ 300 mg*

**Pr*AVAPRO*® (irbesartan)**

Tablets, 75, 150 and 300 mg

**THERAPEUTIC CLASSIFICATION** Angiotensin II AT$_1$ Receptor Blocker

**INDICATIONS AND CLINICAL USE** *AVAPRO* (irbesartan) is indicated for the treatment of essential hypertension. *AVAPRO* is also indicated for the treatment of hypertensive patients with Type 2 diabetes mellitus and renal disease to reduce the rate of progression of nephropathy as measured by the reduction of microalbuminuria, and the occurrence of doubling of serum creatinine. *AVAPRO* may be used alone or concomitantly with thiazide diuretics. The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors has not been established.

**CONTRAINDICATIONS** *AVAPRO* (irbesartan) is contraindicated in patients who are hypersensitive to any component of this product. **WARNINGS** **Pregnancy** Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, *AVAPRO* (irbesartan) should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of irbesartan as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, irbesartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as means of reversing hypotension and/or substituting for disordered renal function. Irbesartan is not removed by hemodialysis. **Hypotension - Volume Depleted Patients** Occasionally, symptomatic hypotension has occurred after administration of irbesartan, in some cases after the first dose. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision (see DOSAGE AND ADMINISTRATION). Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. **PRECAUTIONS** **Renal Impairment** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of irbesartan should include appropriate assessment of renal function. In hypertensive Type 2 diabetic patients with proteinuria (≥ 900 mg/day), a population which has a high risk of renal artery stenosis, no patient treated with *AVAPRO* in IDNT had an early acute rise in serum creatinine attributable to renal artery disease. **Valvular Stenosis** There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction. **Use in Nursing Mothers** It is not known whether *AVAPRO* (irbesartan) is excreted in human milk, but measurable levels of radioactivity were shown to be present in milk of lactating rats. Because many drugs are excreted in human milk, and because of their potential for affecting the nursing infant adversely, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. **Use in Children** Safety and effectiveness have not been established. **Use in the Elderly** Of the 4,140 hypertensive patients receiving irbesartan in clinical studies, 793 patients were 65 years of age and over. No overall age-related differences were seen in the adverse effect profile but greater sensitivity in some older individuals cannot be ruled out. **General** The effect of irbesartan on the ability to drive and the use of machinery has not been studied, but based on its pharmacodynamic properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machinery, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension. **Drug Interactions** Diuretics Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with *AVAPRO*. The possibility of symptomatic hypotension with the use of *AVAPRO* can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of irbesartan (see WARNINGS - Hypotension, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics. Agents Increasing Serum Potassium Since *AVAPRO* decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Lithium Salts As with other drugs which eliminate sodium, lithium clearance may be reduced. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered. Warfarin When irbesartan was administered as 300 mg once daily under steady-state conditions, no pharmacodynamic effect on PT (prothrombin time) was demonstrated in subjects stabilized on warfarin. Digoxin When irbesartan was administered as 150 mg once daily under steady-state conditions, no effect was seen on the pharmacokinetics of digoxin at steady-state. Simvastatin When irbesartan was administered in a small single-dose study with 12 young, healthy males aged 19 to 39, the single-dose pharmacokinetics of simvastatin were not affected by the concomitant administration of 300 mg irbesartan. Simvastatin values were highly variable whether simvastatin was administered alone or in combination with irbesartan. **ADVERSE REACTIONS** *AVAPRO* (irbesartan) has been evaluated for safety in more than 4,100 patients with essential hypertension including approximately 1,300 patients for over 6 months and 400 patients for 1 year or more. In placebo-controlled clinical trials, therapy was discontinued due to a clinical adverse event in 3.3 % of patients treated with irbesartan, versus 4.5 % of patients given placebo. The following potentially serious adverse reactions have been reported rarely with irbesartan in controlled clinical trials: syncope, hypotension. Adverse events occurring in ≥1% of the 2,606 hypertensive patients in placebo-controlled clinical trials include the following:

| Body System/Reaction | *AVAPRO* n = 1,965 Incidence (%) | Placebo n = 641 Incidence (%) |
|---|---|---|
| *General* | | |
| Abdominal Pain | 1.4 | 2.0 |
| Chest Pain | 1.0 | 1.7 |
| Edema | 1.5 | 2.3 |
| Fatigue | 4.3 | 3.7 |
| *Cardiovascular* | | |
| Tachycardia | 1.2 | 0.9 |
| *Dermatologic* | | |
| Rash | 1.3 | 2.0 |
| *Gastrointestinal* | | |
| Diarrhea | 3.1 | 2.2 |
| Dyspepsia / Heartburn | 1.7 | 1.1 |
| Nausea / Vomiting | 2.1 | 2.8 |
| *Musculoskeletal / Connective Tissue* | | |
| Musculoskeletal Pain | 6.6 | 6.6 |
| *Nervous System* | | |
| Anxiety / Nervousness | 1.1 | 0.9 |
| Headache | 12.3 | 16.7 |
| Dizziness | 4.9 | 5.0 |
| *Respiratory* | | |
| Cough | 2.8 | 2.7 |
| *Urogenital System* | | |
| Urinary Tract Infection | 1.1 | 1.4 |

The incidence of hypotension or orthostatic hypotension occurred in 0.4% of irbesartan treated patients, unrelated to dosage, and in 0.2% of patients receiving placebo. In addition, the following potentially important events occurred in <1% of patients receiving irbesartan, regardless of drug relationship: Body as a Whole: fever; Cardiovascular: flushing, hypertension, myocardial infarction, angina pectoris, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis; Dermatologic: pruritus, dermatitis, ecchymosis, erythema, urticaria, photosensitivity; Endocrine: sexual dysfunction, libido change, gout; Gastrointestinal: constipation, gastroenteritis, flatulence, distention abdomen, hepatitis; Musculoskeletal: muscle cramp, arthritis, myalgia, muscle weakness; Nervous System: sleep disturbance, numbness, somnolence, vertigo, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident; Renal/Genitourinary: abnormal urination; Respiratory: epistaxis, tracheobronchitis, pulmonary congestion, dyspnea, wheezing; Special Senses: visual disturbance, hearing abnormality, conjunctivitis, taste disturbance. **Post-marketing Experience** Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in post-marketing use. The following adverse reactions, regardless of drug relationship, have been reported very rarely in post-marketing use, syncope, asthenia, myalgia, jaundice, elevated liver function tests and impaired renal function including isolated cases of renal failure in patients at risk (see PRECAUTIONS - Renal Impairment). Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers. **Clinical Studies in Hypertension and Type 2 Diabetic Renal Disease** In clinical studies in patients with hypertension and Type 2 diabetic renal disease, the adverse drug experiences were similar to those in clinical trials of hypertensive patients with the exception of orthostatic symptoms (dizziness, orthostatic dizziness, and orthostatic hypotension) observed in IDNT (The Irbesartan Diabetic Nephropathy Trial) (proteinuria ≥ 900 mg/day, and serum creatinine from 1.0-3.0 mg/dL), in IDNT orthostatic symptoms occurred more frequently in the *AVAPRO* group (dizziness 10.2%, orthostatic dizziness 5.4%, orthostatic hypotension 5.4%) than in the placebo group (dizziness 6.0%, orthostatic dizziness 2.7%, orthostatic hypotension 3.2%). The rates (percents) of discontinuations due to orthostatic symptoms for *AVAPRO* versus placebo were: dizziness 0.3 vs 0.5; orthostatic dizziness 0.2 vs 0.0; and orthostatic hypotension, 0.0 vs 0.0. **Laboratory Test Findings** In controlled clinical trials of hypertension, clinically important differences in laboratory tests were rarely associated with *AVAPRO*. Liver Function Tests: In placebo-controlled trials, elevations of AST and ALT ≥3X upper limit of normal occurred in 0.1% and 0.2%, respectively, of irbesartan treated patients compared to 0.3% and 0.3%, respectively, of patients receiving placebo. The cumulative incidence of AST and/or ALT elevations ≥3X upper limit of normal was 0.4% in patients treated with irbesartan for a mean duration of over 1 year. Hyperkalemia: For hypertension with Type 2 diabetes and renal disease in clinical trials conducted in patients with diabetic renal disease, the laboratory test parameter profile was similar to that of hypertension, with the exception of hyperkalemia. In a placebo-controlled trial in 590 patients with hypertension, Type 2 diabetes, microalbuminuria, and normal renal function (IRMA 2), hyperkalemia ≥ 5.5 mEq/L occurred in 29.4% of the patients in the irbesartan 300 mg group and 22% of the patients in the placebo group. Discontinuation for hyperkalemia occurred in 0.5% of the patients in the irbesartan group. In another placebo-controlled trial in 1,715 patients with hypertension, Type 2 diabetes, proteinuria ≥ 900 mg/day, and serum creatinine ranging from 1.0 - 3.0 mg/dL (IDNT), hyperkalemia ≥ 5.5 mEq/L occurred in 46.3% of the patients in the irbesartan group and 26.3% of the patients in the placebo group. Discontinuation for hyperkalemia occurred in 2.1% and 0.4% of the patients in the irbesartan and placebo groups, respectively. Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with *AVAPRO* alone versus 0.9% on placebo. Hemoglobin: Mean decreases in hemoglobin of 0.16 g/dL were observed in patients receiving *AVAPRO*. No patients were discontinued due to anemia. Neutropenia: Neutropenia (<1000 cells/mm$^3$) was observed in 0.3% of irbesartan treated patients compared to 0.5% of patients receiving placebo. In clinical trials, the following were noted to occur with an incidence of < 1%, regardless of drug relationship: anemia, thrombocytopenia, lymphocytopenia, and increased CPK. **DOSAGE AND ADMINISTRATION** Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation, salt restriction, and other pertinent clinical factors. The dosage of other antihypertensive agents used with *AVAPRO* (irbesartan) may need to be adjusted. *AVAPRO* may be administered with or without food. **Essential Hypertension** The recommended initial dose of *AVAPRO* is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg. **Essential Hypertension with Type 2 Diabetic Renal Disease** The recommended initial dose of *AVAPRO* is 150 mg once daily. In patients whose blood pressure is not adequately controlled, the daily dose may be increased to 300 mg once daily, the preferred maintenance dose. No initial dosage adjustment is required in the elderly, or in patients with renal impairment (see PRECAUTIONS – Use in the Elderly). However, due to the apparent greater sensitivity of hemodialysis patients, an initial dose of 75 mg is recommended in this group of patients. No initial dosage adjustment is required in patients with mild-to-moderate hepatic impairment. **Concomitant Diuretic Therapy** In patients receiving diuretics, *AVAPRO* therapy should be initiated with caution, since these patients may be volume-depleted and thus more likely to experience hypotension following initiation of additional antihypertensive therapy. Whenever possible, all diuretics should be discontinued two to three days prior to the administration of *AVAPRO* to reduce the likelihood of hypotension (see WARNINGS - Hypotension, and PRECAUTIONS – Drug Interactions). If this is not possible because of the patient's condition, *AVAPRO* should be administered with caution and the blood pressure monitored closely. The recommended starting dose of *AVAPRO* is 75 mg once daily in hypovolemic patients (see WARNINGS – Hypotension). Thereafter, the dosage should be adjusted according to the individual response of the patient. **AVAILABILITY OF DOSAGE FORMS** *AVAPRO* (irbesartan) 75 mg tablets are white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2771 on the other. *AVAPRO* (irbesartan) 150 mg tablets are white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2772 on the other. *AVAPRO* (irbesartan) 300 mg tablets are white to off-white biconvex, oval tablets, with a heart shape debossed on one side and the digits 2773 on the other. *AVAPRO* 75, 150 and 300 mg tablets are available in bottles of 90 tablets.

Product monograph available upon request.

# Avalide

(irbesartan+hydrochlorothiazide) (150/12.5mg, 300/12.5mg, 300/25mg)

**Pr*AVALIDE*® (irbesartan/hydrochlorothiazide)** Tablets, 150/12.5 mg, 300/12.5 mg and 300/25 mg **PHARMACOLOGICAL CLASSIFICATION** Angiotensin II $AT_1$ Receptor Blocker / Diuretic **INDICATIONS AND CLINICAL USE** *AVALIDE* (irbesartan/hydrochlorothiazide) is indicated for the treatment of essential hypertension in patients for whom combination therapy is appropriate. *AVALIDE* is not indicated for initial therapy (see DOSAGE AND ADMINISTRATION). Irbesartan should normally be used in those patients in whom treatment with diuretic or beta-blocker was found ineffective or has been associated with unacceptable adverse effects. **Geriatrics (>65 years of age):** In clinical studies, no overall differences in safety or efficacy were observed between patients over 65 years of age and younger patients (See WARNINGS AND PRECAUTIONS - Special populations). **Pediatrics (<18 years of age):** The safety and efficacy of *AVALIDE* in patients <18 years of age have not been established (See WARNINGS AND PRECAUTIONS - Special populations). **CONTRAINDICATIONS** *AVALIDE* (irbesartan/hydrochlorothiazide) is contraindicated in patients who are hypersensitive to any component of this product. Because of the hydrochlorothiazide component, this product is contraindicated in patients with anuria, and in patients who are hypersensitive to other sulfonamide-derived drugs. **WARNINGS AND PRECAUTIONS**

**Serious Warnings and Precautions** When used in pregnancy during the second and third trimesters, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, AVALIDE should be discontinued as soon as possible. (see WARNINGS AND PRECAUTIONS-Special populations: Pregnant Women.).

**General** The effect of irbesartan on ability to drive and use machines has not been studied, but based on its pharmacodynamic properties, irbesartan is unlikely to affect this ability. When driving vehicles or operating machines, it should be taken into account that occasionally dizziness or weariness may occur during treatment of hypertension. **Carcinogenesis and Mutagenesis** See **TOXICOLOGY** for discussion of animal data. **Cardiovascular** Hypotension Occasionally, symptomatic hypotension has occurred after administration of irbesartan, in some cases after the first dose. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision (see DOSAGE AND ADMINISTRATION). Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident. Valvular Stenosis There is concern on theoretical grounds that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction. **Endocrine and Metabolism** Thiazides, including hydrochlorothiazide, can cause fluid or electrolyte imbalance (hypokalemia, hyponatremia and hypochloremic alkalosis). Calcium excretion is decreased by thiazides which may cause intermittent and slight elevation of serum calcium. If calcium or a calcium sparing drug (e.g., vitamin D therapy) is prescribed, serum calcium levels should be monitored and calcium dosage adjusted accordingly. Marked hypercalcemia suggests the possibility of hyperparathyroidism. Thiazides should be discontinued before carrying out tests for parathyroid function. Thiazides have been shown to increase the urinary excretion of magnesium, which may result in hypomagnesemia. Hyperuricemia may occur, and an acute attack of gout may be precipitated in certain patients receiving thiazide therapy. Insulin requirements in diabetic patients may be altered and latent diabetes mellitus may become manifest during thiazide diuretic therapy. Increases in cholesterol and triglyceride levels may be associated with thiazide diuretic therapy. Thiazides may decrease serum PBI levels without signs of thyroid disturbance. **Hepatic/Biliary/Pancreatic** Thiazides should be used with caution in patients with impaired hepatic function or progressive liver disease, since minor alterations in fluid and electrolyte balance may precipitate hepatic coma. **Immune** Hypersensitivity Reaction Sensitivity reactions to hydrochlorothiazide may occur in patients with or without a history of allergy or bronchial asthma. Systemic Lupus Erythematosus Thiazide diuretics have been reported to cause exacerbation or activation of systemic lupus erythematosus. **Renal** Azotemia Azotemia may be precipitated or increased by hydrochlorothiazide. Cumulative effects of the drug may develop in patients with impaired renal function. If increasing azotemia and oliguria occur during treatment of severe progressive renal disease, the diuretic should be discontinued. Renal Impairment As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of irbesartan should include appropriate assessment of renal function. Thiazides should be used with caution. Because of the hydrochlorothiazide component, *AVALIDE* (irbesartan/hydrochlorothiazide) is not recommended in patients with severe renal impairment (creatinine clearance ≤30 mL/min). **Special Populations** Pregnant Women Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women. When pregnancy is detected, irbesartan should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of irbesartan as soon as possible. Rarely (probably less often than once in every thousand pregnancies), no alternative to an angiotensin II receptor antagonist will be found. In these rare cases, the mothers should be apprised of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra-amniotic environment. If oligohydramnios is observed, irbesartan should be discontinued unless it is considered life-saving for the mother. Contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of *in utero* exposure to an angiotensin II receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as means of reversing hypotension and/or substituting for disordered renal function. Irbesartan is not removed by hemodialysis. Thiazides cross the placental barrier and appear in cord blood. The routine use of diuretics in otherwise healthy pregnant women is not recommended and exposes mother and fetus to unnecessary hazard, including fetal or neonatal jaundice, thrombocytopenia, and possibly other adverse reactions that have occurred in adults. Diuretics do not prevent development of toxemia of pregnancy and there is no satisfactory evidence that they are useful in the treatment of toxemia. Nursing Women It is not known whether irbesartan is excreted in human milk, but measurable levels of radioactivity was shown to be present in milk of lactating rats. Thiazides appear in human milk. A decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother. Pediatrics Safety and effectiveness have not been established. Geriatrics Of the 2,650 hypertensive patients receiving irbesartan/hydrochlorothiazide in clinical studies, 618 patients were 65 years of age and over. No overall age-related differences were seen in the adverse effect profile but greater sensitivity in some older individuals cannot be ruled out. **ADVERSE REACTIONS Adverse Drug Reaction Overview** *AVALIDE* (irbesartan/hydrochlorothiazide) has been evaluated for safety in 2,746 patients with essential hypertension including 968 patients for 1 year or more. The most commonly reported adverse events (occurring in ≥10% of patients treated with *AVALIDE*) was headache (11.0%), which occurred at a significantly higher incidence in the placebo group (16.1%). The adverse events most frequently resulting in clinical intervention (discontinuation of *AVALIDE*) were due to dizziness (0.7%) and headache (0.7%). The adverse event of hypotension is more likely to occur in volume depleted patients (See Warnings and Precautions related to Cardiovascular under Hypotension). The following potentially serious adverse reactions have been reported rarely with irbesartan in controlled clinical trials: syncope, hypotension. **Clinical Trial Adverse Drug Reactions** *Because clinical trials are conducted under very specific conditions the adverse reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates.* In placebo-controlled clinical trials, therapy was discontinued due to a clinical or laboratory adverse event in 3.6 percent of patients treated with irbesartan/hydrochlorothiazide, versus 6.8 percent of patients given placebo. Adverse events regardless of drug relationship, occurring in ≥1% of the irbesartan/ hydrochlorothiazide patients in placebo-controlled clinical trials include the following:

**Adverse events regardless of drug relationship, occurring in ≥1% of the irbesartan/hydrochlorothiazide patients in placebo-controlled clinical trials**

| | Irbesartan/HCTZ n = 898 (%) | Irbesartan n = 400 (%) | HCTZ n = 380 (%) | Placebo n = 236 (%) |
|---|---|---|---|---|
| *Cardiovascular* | | | | |
| Edema | 3.1 | 1.5 | 1.6 | 2.5 |
| Tachycardia | 1.2 | 0.5 | 0.5 | 0.4 |
| *Dermatologic* | | | | |
| Rash | 1.2 | 1.8 | 3.2 | 1.7 |
| *Gastrointestinal* | | | | |
| Nausea/Vomiting | 3.2 | 1.5 | 2.4 | 0.4 |
| Dyspepsia | 2.1 | 0.3 | 1.6 | 0.8 |
| Diarrhea | 2.1 | 2.8 | 1.1 | 3.4 |
| Abdominal Pain | 1.7 | 1.5 | 1.6 | 0.8 |
| *General* | | | | |
| Fatigue | 6.5 | 4.0 | 3.2 | 3.0 |
| Influenza | 2.8 | 2.0 | 1.8 | 1.3 |
| Chest Pain | 1.8 | 1.5 | 1.6 | 1.3 |
| *Immunology* | | | | |
| Allergy | 1.1 | 0.5 | 0.5 | 0 |
| *Musculoskeletal* | | | | |
| Musculoskeletal Pain | 6.5 | 6.0 | 9.7 | 4.7 |
| Muscle Cramp | 1.0 | 0.8 | 2.1 | 1.3 |
| *Nervous System* | | | | |
| Headache | 11.0 | 9.3 | 11.6 | 16.1 |
| Dizziness | 7.6 | 5.5 | 4.7 | 4.2 |
| Orthostatic Dizziness | 1.1 | 1.0 | 0.8 | 0.4 |
| Anxiety/Nervousness | 1.0 | 1.0 | 0.5 | 1.7 |
| *Renal/Genitourinary* | | | | |
| Urination Abnormal | 1.9 | 0.5 | 2.1 | 0.8 |
| Urinary Tract Infection | 1.6 | 1.5 | 2.4 | 2.5 |
| *Respiratory* | | | | |
| URTI | 5.6 | 8.3 | 7.1 | 5.5 |
| Sinus Disorder | 2.9 | 4.5 | 3.2 | 4.7 |
| Cough | 2.2 | 2.3 | 2.6 | 3.0 |
| Pharyngitis | 2.1 | 2.3 | 2.9 | 1.7 |
| Rhinitis | 1.9 | 2.0 | 1.6 | 2.5 |

**Irbesartan Alone** In addition, the following potentially important events occurred in less than 1% of patients receiving irbesartan, regardless of drug relationship: Body as a Whole: fever; Cardiovascular: flushing, hypertension, myocardial infarction, angina pectoris, arrhythmic/conduction disorder, cardio-respiratory arrest, heart failure, hypertensive crisis; Dermatologic: pruritus, dermatitis, ecchymosis, erythema, urticaria, photosensitivity; Endocrine: sexual dysfunction, libido disorder, gout; Gastrointestinal: constipation, gastroenteritis, flatulence, abdominal distention, hepatitis; Musculoskeletal: muscle cramp, arthritis, myalgia, muscular weakness; Nervous System: sleep disturbance, numbness, somnolence, vertigo, depression, paresthesia, tremor, transient ischemic attack, cerebrovascular accident. Renal/Genitourinary: abnormal urination; Respiratory: epistaxis, tracheobronchitis, pulmonary congestion, dyspnea, wheezing; Special Senses: visual disturbance, hearing impaired, conjunctivitis, taste disturbance. **Abnormal Hematologic and Clinical Chemistry Findings** *AVALIDE* Liver Function Tests: Occasional elevations of liver enzymes and/or serum bilirubin have occurred. In patients with essential hypertension treated with *AVALIDE* alone, one patient was discontinued due to elevated liver enzymes. Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in 2.3% of patients. No patient was discontinued due to increased BUN. One patient was discontinued due to a minor increase in serum creatinine. Irbesartan Liver Function Tests: In placebo-controlled trials, elevations of AST and ALT ≥3X upper limit of normal occured in 0.1% and 0.2%, respectively, of irbesartan treated patients compared to 0.3% and 0.3%, respectively, of patients receiving placebo. The cumulative incidence of AST and/or ALT elevations ≥ 3X upper limit of normal was 0.4% in patients treated with irbesartan for a mean duration of over 1 year. Hyperkalemia: In placebo-controlled trials, greater than a 10% increase in serum potassium was observed in 0.4% of irbesartan treated patients compared to 0.5% of patients receiving placebo. Creatinine, Blood Urea Nitrogen: Minor increases in blood urea nitrogen (BUN) or serum creatinine were observed in less than 0.7% of patients with essential hypertension treated with irbesartan alone versus 0.9% on placebo. Hemoglobin: Mean decreases in hemoglobin of 0.16g/dL were observed in patients receiving irbesartan. No patients were discontinued due to anemia. Neutropenia: Neutropenia (<1000 cells/mm$^3$) was observed in 0.3% of irbesartan treated patients compared to 0.5% of patients receiving placebo. In clinical trials, the following were noted to occur with an incidence of < 1%, regardless of drug relationship: anemia, thrombocytopenia, lymphocytopenia, and increased CPK. **Post-Market Adverse Drug Reactions** Angioedema (involving swelling of the face, lips, and/or tongue) has been reported rarely in post-marketing use. The following adverse reactions, regardless of drug relationship, were reported very rarely in post-marketing use: syncope, asthenia, jaundice, myalgia, elevated liver function tests, and impaired renal function including occasional cases of renal failure in patients at risk (see WARNINGS AND PRECAUTIONS – Renal - Renal Impairment). Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers. **DRUG INTERACTIONS Drug-Drug Interactions Diuretics** Patients on diuretics, and especially those in whom diuretic therapy was recently instituted, may occasionally experience an excessive reduction of blood pressure after initiation of therapy with irbesartan. The possibility of symptomatic hypotension with the use of irbesartan can be minimized by discontinuing the diuretic prior to initiation of treatment and/or lowering the initial dose of irbesartan (see WARNINGS AND PRECAUTIONS – Cardiovascular – Hypotension, and DOSAGE AND ADMINISTRATION). No drug interaction of clinical significance has been identified with thiazide diuretics. **Agents Increasing Serum Potassium** Since irbesartan decreases the production of aldosterone, potassium-sparing diuretics or potassium supplements should be given only for documented hypokalemia and with frequent monitoring of serum potassium. Potassium-containing salt substitutes should also be used with caution. Concomitant thiazide diuretic use may attenuate any effect that irbesartan may have on serum potassium. **Lithium Salts** As with other drugs which eliminate sodium, lithium clearance may be reduced in the presence of irbesartan. Therefore, serum lithium levels should be monitored carefully if lithium salts are to be administered with irbesartan. Lithium generally should not be given with diuretics. Diuretic agents reduce the renal clearance of lithium and increase risk of lithium toxicity. **Warfarin** When irbesartan was administered as 300 mg once daily under steady-state conditions, no pharmacodynamic effect on PT was demonstrated in subjects stabilized on warfarin. **Digoxin** When irbesartan was administered as 150 mg once daily under steady-state conditions, no effect was seen on the pharmacokinetics of digoxin at steady-state. Thiazide induced electrolyte disturbances may predispose to digitalis induced arrhythmias. **Simvastatin** When irbesartan was administered in a small single-dose study with 12 young, healthy males aged 19 to 39, the single-dose pharmacokinetics of simvastatin were not affected by the concomitant administration of 300 mg irbesartan. Simvastatin values were highly variable whether simvastatin was administered alone or in combination with irbesartan. **Nifedipine** The pharmacokinetics of irbesartan were not affected by coadministration of nifedipine. **Alcohol, Barbiturates, or Narcotics** Diuretic potentiation of orthostatic hypotension may

# Instructions to Authors

The *Canadian Journal of General Internal Medicine* publishes concise papers, which are subject to peer review. The *Journal* considers articles of original research, reviews, scholarly addresses, case reports, book reviews, historical interest, clinical tips, guidelines, letters to the editor, and so on. Requirements are in accordance with "Uniform requirements for manuscripts submitted to biomedical journals" (http://www.icmje.org). The editorial policies of the journal are in line with those of the Council of Science Editors (http://www.councilscience editors.org/services/draft_approved.cfm).

Authors must disclose any commercial interest in the subject of study and the source of any support. A covering letter should state that the work is original and should include the address for correspondence, as well as the phone and fax numbers and e-mail address to ensure rapid processing. After acceptance, the author(s) must sign a copyright transfer agreement.

The *Journal* reserves the right to edit manuscripts to ensure conformity with the *Journal*'s style. Such editing will not affect the scientific content.

## Manuscript Preparation

Manuscripts should be double-spaced and approximately four to six pages long (800 to 1,500 words). The manuscript must be sent by e-mail attachment (Word or Rich Text Format only). An abstract of up to 150 words should be provided, and a statement that the study was approved by the relevant research ethics board should be included, where relevant.

The lead author should also provide a brief bio sketch and high-resolution photo of himself or herself (see details regarding illustrations below).

### *References*

References should be numbered consecutively in the text by superscript numerals. Corresponding references should be listed at the end of the text. Exhaustive lists of references are not encouraged. Unpublished sources such as personal communications should be cited within the text and not included in the reference list.

The sequence for journal references should be as follows: author(s); title of paper; journal name abbreviated as in the Index Medicus; year of publication, volume number, first and last page numbers. When there are more than three authors, shorten to three and add "et al."

1. Col NF, Eckman MH, Karas RH, et al. Patient specific decisions about hormone replacement therapy in postmenopausal women. JAMA 1997;277:1140-7.

The sequence for chapters of a book should be as follows: author(s) of chapter, chapter title, author(s) of book, book title, edition, place of publication, publisher, year of publication, page numbers.

1. Galloway AC, Colvin SB, Grossi EA, et al. Acquired heart disease. In: Schwartz SI, Shires GT, Spencer FC, eds. Principles of Surgery, 6th edition. New York: McGraw-Hill; 1994:845-99.

### *Tables and illustrations*

Each table should be typed on a separate page, and should have a legend at the top indicating the information contained.

Illustrations may be sent electronically as a TIFF or JPEG file on a disk or CD. Do not embed images, etc., in text files. *Note: Figure reproduction cannot improve on the quality of the originals.*

### *Numbers, units, and abbreviations*

Measurements are to be metric. In scientific text, physical quantities and units of time should be expressed in numerals, for example, 2 kg, 6 mmol, 5 hours, 4°C.

Use only standard abbreviations, and avoid using abbreviations in the title. Define all abbreviations on their first mention.

### Permissions

Written permission must be obtained for material that has been published in copyrighted material; this includes tables, figures, and quoted text that exceeds 150 words. Signed patient release forms are required for photographs of identifiable persons. A copy of all permissions and patient release forms must accompany the manuscript.

### Proofs

Proofs for correction will be sent to authors by e-mail as a Word file. Authors are asked to fax or e-mail corrections back to the publisher within 72 hours. Unless otherwise indicated by the author, manuscripts will be published as sent.

### Please submit manuscripts to:

Dr. Hector Baillie
hbaillie@csimonline.com
*Only electronic submissions will be accepted.*

# EZETROL®

ezetimide

**10 mg**
**Once-daily tablet**

**10 mg Tablet**

**Cholesterol Absorption Inhibitor**

## SUMMARY PRODUCT INFORMATION

| Route of Administration | Dosage Form/ Strength | Clinically Relevant Nonmedicinal Ingredients |
|---|---|---|
| oral | tablet 10 mg | *For a complete listing see Dosage Forms, Composition and Packaging section.* |

## 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.

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

## WARNINGS AND PRECAUTIONS

**Serious Warnings and Precautions**

- hepatitis
- pancreatitis
- myopathy/rhabdomyolysis
- myalgia

**General**

When EZETROL® is to be administered with a statin, please refer also to the Product Monograph for that statin. Note that all statins are contraindicated in pregnant women (see the Product Monograph for the statin; see WARNINGS AND PRECAUTIONS; Special Populations; Pregnant Women).

**Hepatic/Pancreatic**

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

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

**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.

*The co-administration of EZETROL® and a statin is contraindicated in patients with active liver disease or unexplained and persistent elevations in serum transaminases.*

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.

**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. 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, 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). 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 are **contraindicated** in pregnant women (see the Product Monograph for the statin). 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. Note that all statins are **contraindicated** in nursing women (see the Product Monograph for the statin).

**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**

Plasma concentrations for total ezetimibe are about 2-fold higher in the elderly (≥ 65 years) than in the young (18 to 45 years). LDL-C reduction and safety profile are comparable between elderly and young subjects treated with EZETROL®. Therefore, no dosage adjustment is necessary in the elderly.

**Sex**

Plasma concentrations for total ezetimibe are slightly higher (<20%) in women than in men. LDL-C reduction and safety profile are comparable between men and women treated with ezetimibe. Therefore, no dosage adjustment is necessary on the basis of sex.

**Race**

Based on a meta-analysis of pharmacokinetic studies, there were no pharmacokinetic differences between Blacks and Caucasians.

## ADVERSE REACTIONS

**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.

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

**Clinical Trial Adverse Drug Reactions**

EZETROL® clinical trial experience involved 2486 patients in placebo-controlled monotherapy trials (1691 treated with EZETROL®) and 3922 patients in active controlled trials (262 of whom were treated with EZETROL® alone and 1708 treated with EZETROL® plus a statin). 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.

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/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.

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.

**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 angioedema, rash and urticaria
- nausea
- pancreatitis (see WARNINGS AND PRECAUTIONS)
- thrombocytopenia
- arthralgia
- cholelithiasis
- cholecystitis

## DRUG INTERACTIONS

**Serious Drug Interactions**

- cyclosporine

Drug-drug interactions are known or suspected with cholestyramine, cyclosporine and fibrates.

**Drug-Drug Interactions**

**Cytochrome P450 System:** No clinically significant pharmacokinetic interactions have been observed between ezetimibe and drugs known to be metabolized *via* CYP 1A2, 2D6, 2C8, 2C9, and 3A4 isoenzymes, or N-acetyltransferase such as caffeine, dextromethorphan, tolbutamide, and IV midazolam. It has been shown that ezetimibe neither induces, nor inhibits, these cytochrome P450 isoenzymes.

**Warfarin:** Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on bioavailability of warfarin and prothrombin time in a study of twelve healthy adult males. As with the initiation of any medication in patients treated with warfarin or another coumarin anticoagulant, additional International Normalised Ratio (INR) measurements are recommended for patients administered warfarin or another coumarin anticoagulant concomitantly with EZETROL®.

**Digoxin:** Concomitant administration of ezetimibe (10 mg once daily) had no significant effect on the bioavailability of digoxin and the ECG parameters (HR, PR, QT, and QTc intervals) in a study of twelve healthy adult males.

**Oral Contraceptives:** Co-administration of ezetimibe (10 mg once daily) with oral contraceptives had no significant effect on the bioavailability of ethinyl estradiol or levonorgestrel in a study of eighteen healthy adult females.

**Cimetidine:** Multiple doses of cimetidine (400 mg twice daily) had no significant effect on the oral bioavailability of ezetimibe and total ezetimibe in a study of twelve healthy adults.

**Antacids:** Concomitant antacid (aluminum and magnesium hydroxide) administration decreased the rate of absorption of ezetimibe but had no effect on the bioavailability of ezetimibe. This decreased rate of absorption is not considered clinically significant.

**Glipizide:** In a study of twelve healthy adult males, steady-state levels of ezetimibe (10 mg once daily) had no significant effect on the pharmacokinetics and pharmacodynamics of glipizide. A single dose of glipizide (10 mg) had no significant effect on the exposure to total ezetimibe or ezetimibe.

**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:** Concomitant fenofibrate or gemfibrozil administration increased total ezetimibe concentrations approximately 1.5- and 1.7-fold respectively, however these increases are not considered clinically significant. The safety and effectiveness of ezetimibe administered with fibrates have not been established. 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 is not recommended until use in patients is studied.

**Statins:** No clinically significant pharmacokinetic interactions were seen when ezetimibe was co-administered with atorvastatin, simvastatin, pravastatin, lovastatin, fluvastatin or rosuvastatin.

**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 m²) 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.

## 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) 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.

®Registered trademark used under license by Merck Frosst-Schering Pharma, G.P.

**TABLE 1***
**Clinical Adverse Events Occurring in ≥2% of Patients Treated with EZETROL® and at an Incidence Greater than Placebo, Regardless of Causality**

| Body System/Organ Class<br>Adverse Event | Placebo<br>(%) n=795 | EZETROL® 10 mg<br>(%) n=1691 |
|---|---|---|
| **Body as a whole - general disorders** | | |
| Fatigue | 1.8 | 2.2 |
| **Gastrointestinal system disorders** | | |
| Abdominal pain | 2.8 | 3.0 |
| Diarrhea | 3.0 | 3.7 |
| **Infection and infestations** | | |
| Infection viral | 1.8 | 2.2 |
| Pharyngitis | 2.1 | 2.3 |
| Sinusitis | 2.8 | 3.6 |
| **Musculoskeletal system disorders** | | |
| Arthralgia | 3.4 | 3.8 |
| Back pain | 3.9 | 4.1 |
| **Respiratory system disorders** | | |
| Coughing | 2.1 | 2.3 |

* Includes patients who received placebo or EZETROL® alone reported in Table 2.

**TABLE 2***
**Clinical Adverse Events Occurring in ≥2% of Patients and at an Incidence Greater than Placebo, Regardless of Causality, in EZETROL®/Statin Combination Studies**

| Body system/Organ Class<br>Adverse Event | Placebo<br>(%) n=259 | EZETROL® 10 mg<br>(%) n=262 | All Statins**<br>(%) n=936 | EZETROL® + All Statins**<br>(%) n=925 |
|---|---|---|---|---|
| **Body as a whole - general disorders** | | | | |
| Chest pain | 1.2 | 3.4 | 2.0 | 1.8 |
| Dizziness | 1.2 | 2.7 | 1.4 | 1.8 |
| Fatigue | 1.9 | 1.9 | 1.4 | 2.8 |
| Headache | 5.4 | 8.0 | 7.3 | 6.3 |
| **Gastrointestinal system disorders** | | | | |
| Abdominal pain | 2.3 | 2.7 | 3.1 | 3.5 |
| Diarrhea | 1.5 | 3.4 | 2.9 | 2.8 |
| **Infection and infestations** | | | | |
| Pharyngitis | 1.9 | 3.1 | 2.5 | 2.3 |
| Sinusitis | 1.9 | 4.6 | 3.6 | 3.5 |
| Upper respiratory tract infection | 10.8 | 13.0 | 13.6 | 11.8 |
| **Musculoskeletal system disorders** | | | | |
| Arthralgia | 2.3 | 3.8 | 4.3 | 3.4 |
| Back pain | 3.5 | 3.4 | 3.7 | 4.3 |
| Myalgia | 4.6 | 5.0 | 4.1 | 4.5 |

* Includes four placebo-controlled combination studies in which EZETROL® was initiated concurrently with a statin.
** All statins=all doses of all statins.

**Recommended Dose and Dosage Adjustment**

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

**Use in the Elderly:** No dosage adjustment is required for elderly patients (see WARNINGS AND PRECAUTIONS; Special Populations; Geriatrics).

**Use in Pediatric Patients:** Children and adolescents ≥ 10 years: No dosage adjustment is required (see WARNINGS AND PRECAUTIONS; Special Populations, Pediatrics).

**Use in Patients with Hepatic Impairment:** No dosage adjustment is required in patients with mild hepatic insufficiency (Child-Pugh score 5 to 6). 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; Hepatic/Pancreatic; Patients with Liver Impairment).

**Use in Patients with Renal Impairment:** No dosage adjustment is required for patients with renal impairment (see WARNINGS AND PRECAUTIONS; Renal; Renal Insufficiency).

**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; Drug-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.

## 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.

## ACTION AND CLINICAL PHARMACOLOGY

**Mechanism of Action**

EZETROL® is in a new class of lipid-lowering compounds that selectively inhibit the intestinal absorption of cholesterol and related plant sterols. EZETROL® is orally active, with a unique mechanism of action that differs from other classes of cholesterol-reducing compounds e.g., HMG-CoA reductase inhibitors (statins), bile acid sequestrants (resins), fibric acid derivatives, plant stanols.

Although ezetimibe is rapidly absorbed and is extensively metabolized to an active phenolic glucuronide which reaches the systemic circulation after oral administration (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacokinetics, Absorption), its action is localized at the brush border of the small intestine where it inhibits the absorption of cholesterol, leading to a decrease in the delivery of intestinal cholesterol to the liver. This results in a reduction of hepatic cholesterol stores and an increase in clearance of cholesterol from the blood. Ezetimibe does not increase bile acid excretion in contrast to bile acid sequestrants and does not inhibit cholesterol synthesis in the liver as do statins. EZETROL® and statins have distinct mechanisms of action that provide complementary cholesterol reduction.

Clinical studies have demonstrated that elevated levels of total-C, low density lipoprotein cholesterol (LDL-C) and apolipoprotein B (Apo B; the major protein constituent of LDL), promote atherosclerosis in humans. In addition, decreased levels of high density lipoprotein cholesterol (HDL-C) are associated with the development of atherosclerosis. Epidemiologic studies have established that cardiovascular morbidity and mortality vary directly with the level of total-C and LDL-C and inversely with the level of HDL-C. Like LDL, cholesterol-enriched triglyceride-rich lipoproteins, including very low density lipoproteins (VLDL), intermediate density lipoproteins (IDL), and remnants, can also promote atherosclerosis. **The effects of ezetimibe given either alone or in addition to a statin on cardiovascular morbidity and mortality have not been established.**

**Pharmacodynamics**

Preclinical studies in animals were performed to determine the selectivity of ezetimibe for inhibiting cholesterol absorption. Ezetimibe inhibited the absorption of [$^{14}$C]-cholesterol with no effect on the absorption of triglycerides, fatty acids, bile acids, progesterone, ethinyl estradiol, or the fat soluble vitamins A and D.

In a study of hypercholesterolemic patients, EZETROL® inhibited intestinal cholesterol absorption by 54%, compared with placebo. EZETROL® had no clinically meaningful effect on the plasma concentrations of the fat-soluble vitamins A, D, and E, and did not impair adrenocortical steroid hormone production.

**Pharmacokinetics**

**Absorption**

After oral administration, ezetimibe is rapidly absorbed and extensively conjugated to a phenolic glucuronide (ezetimibe-glucuronide) form which is at least as pharmacologically active as the parent drug. Mean ezetimibe peak plasma concentrations ($C_{max}$) of 3.4 to 5.5 ng/mL were attained within 4 to 12 hours ($T_{max}$). Ezetimibe-glucuronide mean $C_{max}$ values of 45 to 71 ng/mL were achieved between 1 and 2 hours ($T_{max}$). The extent of absorption and absolute bioavailability of ezetimibe cannot be determined as the compound is virtually insoluble in aqueous media suitable for injection.

Concomitant food administration (high fat or non-fat meals) had no effect on the extent of absorption of ezetimibe when administered as EZETROL® 10 mg tablets. $C_{max}$ of ezetimibe was increased by 38% when taken with high fat meals.

**Distribution**

Ezetimibe and ezetimibe-glucuronide are bound 99.7% and 88 to 92% to human plasma proteins, respectively.

**Metabolism**

Ezetimibe is metabolized primarily in the small intestine and liver via glucuronide conjugation (a phase II reaction) with subsequent biliary and renal excretion. Minimal oxidative metabolism (a phase I reaction) has been observed in all species evaluated. Ezetimibe and ezetimibe-glucuronide are the major compounds detected in plasma. The conjugated ezetimibe-glucuronide constitutes 80-90% of plasma drug levels with ezetimibe the remaining 10-20%. Both ezetimibe and ezetimibe-glucuronide are slowly eliminated from plasma with evidence of significant enterohepatic recycling. The half-life for ezetimibe and ezetimibe-glucuronide is approximately 22 hours.

**Excretion**

Following oral administration of $^{14}$C-ezetimibe (20 mg) to human subjects, total ezetimibe (ezetimibe + ezetimibe-glucuronide) accounted for approximately 93% of the total radioactivity in plasma. Approximately 78% and 11% of the administered radioactivity were recovered in the faeces and urine, respectively, over a 10-day collection period. After 48 hours, there were no detectable levels of radioactivity in the plasma. Ezetimibe was the major component in faeces (69% of the administered dose) while ezetimibe-glucuronide was the major component in urine and accounted for 9% of the administered dose.

## STORAGE AND STABILITY

Store between 15°C and 30°C. Protect from moisture.

## DOSAGE FORMS, COMPOSITION AND PACKAGING

EZETROL® is available as a 10 mg tablet for oral administration.

EZETROL® is formulated as white to off-white, capsule-shaped tablets debossed with "414" on one side. Each tablet contains 10 mg of active ingredient, ezetimibe.

Non-medicinal ingredients: croscarmellose sodium, lactose monohydrate, magnesium stearate, microcrystalline cellulose, povidone, and sodium lauryl sulphate.

EZETROL® tablets are packaged in blisters of 7 (as professional sample) and 30's.

EZETROL® tablets are also available in HDPE bottles of 100 tablets.

## PRODUCT MONOGRAPH AVAILABLE ON REQUEST

(986-a,10,05)

Member

R&D PAAB

MERCK FROSST / Schering Pharmaceuticals

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

# Internists Needed...

## In 4 Season Recreational Playground

Permanent and locum positions are available for general internists and respirologists in Kamloops, British Columbia.

General internists at Royal Inland Hospital provide a full range of inpatient and outpatient consultative services and cover a 9-bed intensive care unit. Internists with subspecialty training or interest in critical care, cardiology, geriatrics, endocrinology, infectious disease or nephrology would be welcome. Call is 1:5.

Kamloops is a popular and growing community 3.5 hours east of Vancouver. Royal Inland Hospital is a 228-bed tertiary referral and trauma centre, serving a catchment population of 240,000.

Specialists in Kamloops qualify for BC's highly competitive on-call payment program.

**Kamloops is situated in BC's Southern Interior where the choice to ski backcountry or powder, paddle pristine lakes, or hike and bike endless trails fits nicely into everyday work and family life. We have some of the highest levels of remuneration for health care professionals in Canada, our schools are first-rate, homes are affordable, and life here is simply ... easier.**

*Please contact us for further information:*

**Andrew Neuner**
Chief Operating Officer
Interior Health
519B Columbia Street
Kamloops, BC V2C 2T8
**andrew.neuner@interiorhealth.ca**

**Tel 250-851-7374**
**Cel 250-319-9934**
**Fax 250-851-7375**

Interior Health
www.interiorhealth.ca
www.healthmatchbc.org
health match bc

# MICARDIS® (telmisartan)

**40 mg and 80 mg Tablets**
**THERAPEUTIC CLASSIFICATION:**
**Angiotensin II $AT_1$ Receptor Blocker**

## INDICATIONS AND CLINICAL USE

MICARDIS® (telmisartan) is indicated for the treatment of mild to moderate essential hypertension.
MICARDIS® may be used alone or in combination with thiazide diuretics.
The safety and efficacy of concurrent use with angiotensin converting enzyme inhibitors have not been established. Information on the use of telmisartan in combination with beta blockers is not available.

## CONTRAINDICATIONS

MICARDIS® (telmisartan) is contraindicated in patients who are hypersensitive to any components of this product (see Composition).

## WARNINGS

**Pregnancy:**
Drugs that act directly on the renin-angiotensin system can cause fetal and neonatal morbidity and mortality when administered to pregnant women. If pregnancy is detected, MICARDIS® (telmisartan) should be discontinued as soon as possible. The use of drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy has been associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios has also been reported, presumably resulting from decreased fetal renal function; oligohydramnios in this setting has been associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus have also been reported, although it is not clear whether these occurrences were due to exposure to the drug. These adverse effects do not appear to have resulted from intrauterine drug exposure that has been limited to the first trimester. Mothers whose embryos and fetuses are exposed to an angiotensin II receptor antagonist only during the first trimester should be so informed. Nonetheless, when patients become pregnant, physicians should have the patient discontinue the use of MICARDIS® as soon as possible unless it is considered life-saving for the mother. Rarely, probably less often than once in every thousand pregnancies, no alternative to an angiotensin II $AT_1$ receptor antagonist will be found. In these rare cases, the physician should apprise mothers of the potential hazards to their fetuses, and serial ultrasound examinations should be performed to assess the intra amniotic environment. If oligohydramnios is observed, contraction stress testing (CST), a non-stress test (NST), or biophysical profiling (BPP) may be appropriate, depending upon the week of pregnancy. Patients and physicians should be aware, however, that oligohydramnios may not appear until after the fetus has sustained irreversible injury. Infants with histories of in utero exposure to an angiotensin II $AT_1$ receptor antagonist should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, attention should be directed toward support of blood pressure and renal perfusion. Exchange transfusion may be required as a means of reversing hypertension and/or substituting for disordered renal function. Telmisartan is not removed from plasma by hemodialysis. No teratogenic effects were observed when telmisartan was administered to pregnant rats at oral doses of up to 50 mg/kg/day and to pregnant rabbits at oral doses of up to 45 mg/kg/day with saline supplementation. In rabbits, fetotoxicity (total resorptions) associated with maternal toxicity (reduced body weight gain, mortality) was observed at the highest dose level (45 mg/kg/day). In rats, maternally toxic (reduction in body weight gain and food consumption) telmisartan doses of 50 mg/kg/day in late gestation and during lactation were observed to produce adverse effects in rat fetuses and neonates, including reduced viability, low birth weight, delayed maturation, and decreased weight gain. Significant levels of telmisartan were present in rat milk and rat fetuses' blood during late gestation.

**Hypotension:**
In patients who are volume-depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea or vomiting, symptomatic hypotension may occur after initiation of therapy with MICARDIS®. These conditions should be corrected prior to administration of MICARDIS®. In these patients, because of the potential fall in blood pressure, therapy should be started under close medical supervision. Similar considerations apply to patients with ischemic heart or cerebrovascular disease, in whom an excessive fall in blood pressure could result in myocardial infarction or cerebrovascular accident.

## PRECAUTIONS

**General:**
**Hepatic Impairment:** As the majority of telmisartan is eliminated by biliary excretion, patients with biliary obstructive disorders or hepatic insufficiency have reduced clearance of telmisartan. Three-to four-fold increases in $C_{max}$ and AUC were observed in patients with liver impairment as compared to healthy subjects. MICARDIS® (telmisartan) should be used with caution in these patients (see DOSAGE AND ADMINISTRATION).
**Renal Impairment:** As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely acute renal failure and/or death. There is no experience with long-term use of MICARDIS® (telmisartan) in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated. In susceptible patients, concomitant diuretic use may further increase the risk. Use of telmisartan should include appropriate assessment of renal function in these types of patients.
**Valvular Stenosis:** There is concern on theoretical grounds that patients with aortic stenosis might be at a particular risk of decreased coronary perfusion, because they do not develop as much afterload reduction.
**Hyperkalemia:** Drugs such as MICARDIS® that affect the renin-angiotensin-aldosterone system can cause hyperkalemia. Monitoring of serum potassium in patients at risk is recommended. Based on experience with the use of other drugs that affect the renin-angiotensin system, concomitant use with potassium-sparing diuretics, potassium supplements, salt substitutes containing potassium or other medicinal products that may increase the potassium level (heparin, etc.) may lead to a greater risk of an increase in serum potassium.
**Use in Nursing Mothers:** It is not known whether telmisartan is excreted in human milk, but telmisartan was shown to be present in the milk of lactating rats. Because of the potential for adverse effects on the nursing infant, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.
**Use in Children:** Safety and effectiveness in pediatric patients have not been established.
**Use in the Elderly:** Of the total number of patients receiving MICARDIS® (telmisartan) in clinical studies, 551 (18.6%) were 65 to 74 years of age and 130 (4.4%) were 75 years or older. No overall age-related differences were seen in the adverse effect profile, but greater sensitivity in some older patients cannot be ruled out.
**Effects on Ability to Drive and Use Machines:** No studies on the effect on the ability to drive and use machines have been performed. However, when driving vehicles or operating machinery, it must be borne in mind that dizziness or drowsiness may occasionally occur when taking antihypertensive therapy.

**Drug Interactions:**
*Warfarin:* MICARDIS® (telmisartan) administered for 10 days slightly decreased the mean warfarin trough plasma concentration; this decrease did not result in a change in international Normalized Ratio (INR). Coadministration of MICARDIS® also did not result in a clinically significant interaction with acetaminophen, amlodipine, glyburide, hydrochlorothiazide or ibuprofen. For digoxin, median increases in digoxin peak plasma concentration (49%) and in trough concentration (20%) were observed. It is recommended that digoxin plasma levels be monitored when initiating, adjusting or discontinuing MICARDIS®.
*Lithium:* Reversible increases in serum lithium concentrations and toxicity have been reported during concomitant administration of lithium with angiotensin converting enzyme inhibitors. Very rare cases have also been reported with angiotensin II receptor antagonists. Therefore, serum lithium level monitoring is advisable during concomitant use.

## ADVERSE EVENTS

MICARDIS® (telmisartan) has been evaluated for safety in 27 clinical trials involving 7,968 patients. Of these 7,968 patients, 5,788 patients were treated with MICARDIS® monotherapy including 1,058 patients treated for ≥1 year and 1,395 patients treated in placebo controlled trials. In 3,400 patients, discontinuation of therapy due to adverse events was required in 2.8% of MICARDIS® patients and 6.1% placebo patients. The following potentially serious adverse reactions have been reported rarely with telmisartan in controlled clinical trials: syncope and hypotension. In placebo-controlled trials, no serious adverse event was reported with a frequency of greater that 0.1% in MICARDIS®-treated patients.

## ALL CLINICAL TRIALS

The adverse drug events listed below have been accumulated from 27 clinical trials including 5,788 hypertensive patients treated with telmisartan. Adverse events have been ranked under headings of frequency using the following convention: very common (≥1/10); common (≥1/100, >1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000).
**Body as a Whole, General:** Common: Back pain (e.g. sciatica), chest pain, influenza-like symptoms, symptoms of infection (e.g. urinary tract infections including cystitis), fatigue, conjunctivitis. Uncommon: Abnormal vision, sweating increased.
**Cardiovascular System:** Common: Edema, palpitation.
**Central and Peripheral Nervous System:** Very common: Headache. Common: Dizziness, insomnia. Uncommon: Vertigo.
**Gastro-Intestinal System:** Common: Abdominal pain, diarrhea, dyspepsia, nausea, constipation, gastritis. Uncommon: Dry mouth, flatulence.
**Musculo-Skeletal System:** Common: Arthralgia, cramps in legs or leg pain, myalgia, arthritis, arthrosis. Uncommon: Tendinitis like symptoms.
**Psychiatric System:** Common: Anxiety, depression, nervousness.
**Respiratory System:** Common: Upper respiratory tract infections including pharyngitis and sinusitis, bronchitis, coughing, dyspnea, rhinitis.
**Skin and Appendages Systems:** Common: Skin disorders like eczema, rash.

## CLINICAL LABORATORY FINDINGS

**Hemoglobin:** Infrequently, a decrease in hemoglobin has been observed which occurs more often during treatment with telmisartan than with placebo.

## PLACEBO-CONTROLLED TRIALS

The overall incidence of adverse events reported with MICARDIS® (41.4%) was usually comparable to placebo (43.9%) in placebo-controlled trials. Adverse events occurring in 1% or more of 1,395 hypertensive patients treated with MICARDIS® monotherapy in placebo-controlled clinical trials, regardless of drug relationship, include the following:

| Adverse Event, by System | MICARDIS® Total n=1,395 % | Placebo n=583 % |
|---|---|---|
| **Body as a Whole** | | |
| Back pain | 2.7 | 0.9 |
| Chest pain | 1.3 | 1.2 |
| Fatigue | 3.2 | 3.3 |
| Influenza-like symptoms | 1.7 | 1.5 |
| Pain | 3.5 | 4.3 |
| **Central & Peripheral Nervous System** | | |
| Dizziness | 3.6 | 4.6 |
| Headache | 6.0 | 15.6 |
| Somnolence | 0.4 | 1.0 |
| **Gastrointestinal System** | | |
| Diarrhea | 2.6 | 1.0 |
| Dyspepsia | 1.6 | 1.2 |
| Nausea | 1.1 | 1.4 |
| Vomiting | 0.4 | 1.0 |
| **Musculoskeletal System** | | |
| Myalgia | 1.1 | 0.7 |
| **Respiratory System** | | |
| Coughing | 1.6 | 1.7 |
| Pharyngitis | 1.1 | 0.3 |
| Sinusitis | 2.2 | 1.9 |
| Upper respiratory tract infection | 6.5 | 4.6 |
| **Heart Rate and Rhythm Disorders** | | |
| ECG abnormal specific | 0.2 | 1.0 |
| Palpitation | 0.6 | 1.0 |
| **Cardiovascular Disorders, General** | | |
| Hypertension | 1.0 | 1.7 |
| Oedema peripheral | 1.0 | 1.2 |

The incidence of adverse events was not dose-related and did not correlate with the gender, age, or race of patients.
In addition, the following adverse events, with no established causality, were reported at an incidence of <1% in placebo-controlled clinical trials.
**Autonomic Nervous Systems Disorders:** sweating increased.
**Body as a Whole:** abdomen enlarged, allergy, cyst nos, fall, fever, leg pain, rigors, syncope.
**Cardiovascular Disorders, General:** hypotension, hypotension-postural, leg edema.
**Central & Peripheral Nervous System Disorders:** hypertonia, migraine-aggravated, muscle contraction-involuntary.
**Gastrointestinal System Disorders:** anorexia, appetite increased, flatulence, gastrointestinal disorder nos, gastroenteritis, gastroesophageal reflux, melena, mouth dry, abdominal pain.
**Heart Rate & Rhythm Disorders:** arrhythmia, tachycardia.
**Metabolic & Nutritional Disorders:** diabetes mellitus, hypokalemia.
**Musculoskeletal System Disorders:** arthritis, arthritis aggravated, arthrosis, bursitis, fasciitis plantar, tendinitis.
**Myo Endo Pericardial & Valve Disorders:** myocardial infarction.
**Psychiatric Disorders:** nervousness.
**Red Blood Cell Disorders:** anemia.
**Reproductive Disorders, Female:** vaginitis.
**Resistance Mechanism Disorders:** abscess, infection, bacterial, moniliasis genital, otitis media.
**Respiratory System Disorders:** bronchospasm, epistaxis, pneumonia, bronchitis.
**Skin & Appendage Disorders:** rash, skin dry.
**Urinary System Disorders:** dysuria, hematuria, micturition disorder, urinary tract infection.
**Vascular (Extracardiac) Disorders:** cerebrovascular disorder, purpura.
**Vision Disorders:** vision abnormal.
**Clinical Laboratory Findings:**
In placebo-controlled clinical trials involving 1,041 patients treated with MICARDIS® monotherapy, clinically relevant changes in standard laboratory test parameters were rarely associated with administration of MICARDIS®.
**Creatinine, Blood Urea Nitrogen:** Increases in BUN (≥11.2 mg/dL) and creatinine (≥0.5 mg/dL) were observed in 1.5% and 0.6% of MICARDIS®-treated patients; the corresponding incidence was 0.3% each for placebo-treated patients. These increases occurred primarily with MICARDIS® in combination with hydrochlorothiazide. One telmisartan-treated patient discontinued therapy due to increases in creatinine and blood urea nitrogen.
**Hemoglobin, Hematocrit:** Clinically significant changes in hemoglobin and hematocrit (<10 mg/dL and <30% respectively) were rarely observed with MICARDIS® treatment and did not differ from rates in placebo-treated patients. No patients discontinued therapy due to anemia.
**Serum Uric Acid:** An increase in serum uric acid (≥2.7 mg/dL) was reported in 1.7% of patients treated with MICARDIS® and in 0.0% of patients treated with placebo. Clinically significant hyperuricemia (≥10 mEq/L) was observed in 2.3% of patients with MICARDIS® with 0.4% reported in patients at baseline. Increases in serum acid were primarily observed in patients who received MICARDIS® in combination with hydrochlorothiazide. No patient was discontinued from treatment due to hyperuricemia.
**Liver Function Tests:** Clinically significant elevations in AST and ALT (>3 times the upper limit of normal) occurred in 0.1% and 0.5% respectively of patients treated with MICARDIS® compared to 0.8% and 1.7% of patients receiving placebo. No telmisartan-treated patients discontinued therapy due to abnormal hepatic function.
**Serum Potassium:** Marked laboratory changes in serum potassium (≥+/-1.4 mEq/L) occurred rarely and with a lower frequency in MICARDIS®-treated patients (0.3%, 0.1%, respectively) than in placebo patients (0.6%, 0.3%, respectively). Clinically significant changes in potassium (that exceed 3 mEq/L were found in 0.8% of MICARDIS®-treated patients, with 0.5% of these reported at baseline. The corresponding rates for placebo-treated patients were 0.6% and 0.8%.
**Cholesterol:** In placebo-controlled trials, marked increases in serum cholesterol were reported in a total of 6 telmisartan-treated patients (0.4%) and no placebo patients. Two of these patients were followed over time; in both cases cholesterol values reverted to baseline levels. Serum elevations in cholesterol were reported as adverse events in 11 of 3,445 patients (0.3%) in all clinical trials. There were no reported cases of hypercholesterolemia in telmisartan-treated patients in placebo-controlled trials.

## POST-MARKETING EXPERIENCE

Since the introduction of telmisartan in the market, cases of erythema, pruritus, faintness, insomnia, depression, stomach upset, vomiting, hypotension, bradycardia, tachycardia, dyspnoea, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported rarely. As with other angiotensin II antagonists rare cases of angio-oedema, pruritis, rash and urticaria have been reported.
Cases of muscle pain, muscle weakness, myositis and rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

## SYMPTOMS AND TREATMENT OF OVERDOSAGE

Limited data are available with regard to overdosage in humans. The most likely manifestation of overdosage would be hypotension and/or tachycardia. If symptomatic hypotension should occur, supportive treatment should be instituted. Telmisartan is not removed by hemodialysis.

## DOSAGE AND ADMINISTRATION

The recommended dose of MICARDIS® (telmisartan) is 80 mg once daily.
The antihypertensive effect is present within 2 weeks and maximal reduction is generally attained after four weeks. If additional blood pressure reduction is required, a thiazide diuretic may be added.
No initial dosing adjustment is necessary for elderly patients or for patients with renal impairment, but greater sensitivity in some older individuals cannot be ruled out. Markedly reduced telmisartan plasma levels were observed in patients on hemodialysis.
For patients with hepatic impairment, a starting dose of 40 mg is recommended (see PRECAUTIONS, Hepatic Impairment). MICARDIS® should be taken consistently with or without food.

**Composition:**
MICARDIS® Tablets contain the following inactive ingredients: sodium hydroxide, meglumine, povidone, sorbitol, and magnesium stearate.

**Stability and Storage Recommendations:**
MICARDIS® Tablets are hygroscopic and require protection from moisture. Tablets are packaged in blisters and should be stored at room temperature, 15 to 30°C (59-86°F).
Tablets should not be removed from blisters until immediately prior to administration.

## AVAILABILITY OF DOSAGE FORMS

MICARDIS® is available as white, oblong-shaped, uncoated tablets containing telmisartan 40 mg or 80 mg. Tablets are marked with the Boehringer Ingelheim logo on one side, and on the other side, with a decorative score and either 51H or 52H for the 40 mg and 80 mg strengths, respectively.
MICARDIS® Tablets 40 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.
MICARDIS® Tablets 80 mg are individually blister sealed in cartons of 28 tablets as 4 cards containing 7 tablets each.

Product Monograph available upon request.


**References:**
**1.** Mallion JM *et al.* ABPM Comparison of the Antihypertensive Profiles of the Selective Angiotensin II Receptor Antagonists Telmisartan and Losartan in Patients With Mild-to-Moderate Hypertension. *Journal of Human Hypertension* 1999;13(10):657-664. **2.** Lacourcière Y, *et al.* A Multicenter, 14-Week Study of Telmisartan and Ramipril in Patients With Mild-to-Moderate Hypertension Using Ambulatory Blood Pressure Monitoring. *American Journal of Hypertension* 2006;19:104-112. **3.** MICARDIS® Product Monograph, Boehringer Ingelheim (Canada) Ltd. October 2005. **4.** Cozaar® Product Monograph, E.I. du Pont de Nemours and Company. **5.** Diovan® Product Monograph, Novartis. **6.** Avapro™ Product Monograph (Canada), Sanofi-Synthelabo. **7.** Atacand® Product Monograph, AstraZeneca Pharma Inc. **8.** Teveten® Product Monograph, Solvay Pharma Inc.


MICARDIS®
TELMISARTAN 80mg AT1 RECEPTOR BLOCKER
GOOD MORNING. MICARDIS.


Boehringer Ingelheim
www.boehringer-ingelheim.ca
Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.,
Burlington, Ontario L7L 5H4


PRAB
R&D

## Employment

To inquire about rates or to submit material to advertise in *CJGIM* please contact

Brenda Robinson at Andrew John Publishing: 905.628.4309 or brobinson@andrewjohnpublishing.com.

Subject to availability. Book early!

## GENERAL INTERNIST

**Stanton Territorial Health Authority** has an opening for a **General Internist** to practice in **Yellowknife,** the capital of the NWT with almost 20,000 residents offering a unique blend of **adventure** in a modern environment. The work entails a catchment population of 50,000 with travel clinics throughout the Northwest Territories and in the Kitikmeot Region of Nunavut.

**THE BENEFITS:**
Working within a very strong collaborative network of dynamic and highly skilled Family Practitioners and Nurses, the Physician Specialists are employed on an alternative payment contract basis that is comparative to any Canadian region with no overhead costs. These contracts provide a variety of employment benefits and retention incentives as well as a very competitive salary, removal package, recruitment and retention bonuses, at least 10 days of paid CME, excellent leave entitlements and northern allowances. Practice includes referral clinical practice, along with travel to the Arctic and sub-Arctic communities. The call requirement for this position is one in four.

**For more information, please contact:**
Angela Tucker,
Physician Services Officer
Telephone: (867) 669-3149
Toll Free: (867) 389-3149
Cell: (867) 445-8714
Website:
www.yellowknife-physicians.ca
Email:
angela_tucker@gov.nt.ca

## HEALTH COMMUNITIES, HEALTHY ISLAND PEOPLE, SEAMLESS SERVICE

### GENERAL INTERNIST

The Department of internal medicine at Campbell River & District General Hospital in Campbell River, BC, Canada is seeking an Internist to join our group. We have excellent specialist backup and strong working relationships amongst our consultants, our GP colleagues, and ourselves. Opportunities exist to teach in the UBC post grad and undergraduate programs as well as collaborative research. Additionally involvement with the VIHA Department of Medicine as a whole including rounds is available.

Remuneration is fee-for-service (approximately $250,000 annually). May be eligible for additional remuneration including retention premium (7.14%), retention flat fee sum ($6242 paid quarterly), recruitment incentive ($10,000), and relocation costs. Candidates must be certified by the Royal College of Physicians & Surgeons Canada and be eligible for licensure in British Columbia. For a community profile go to www.campbellrivertourism.com.

If interested please contact Renee Shimla, Medical Administration VIHA, via Email at renee.shimla@viha.ca or telephone at 250-334-5451 or facsimile at 250-334-5468.

DALHOUSIE UNIVERSITY *Inspiring Minds* — Capital Health

## GENERAL INTERNAL MEDICINE

### Dalhousie University/ Capital District Health Authority Halifax, Nova Scotia

The Division of General Internal Medicine, Department of Medicine, Dalhousie University/ Capital District Health Authority has immediate openings for full-time general internists at the QEII Health Sciences Centre in Halifax. The successful applicants will participate in the provision of patient care in the setting of medical teaching units and ambulatory care with medical students and residents in internal medicine and other programs. Full-time members are expected to develop and/or participate in clinical or educational research. The Department offers strong research support personnel and mentorship. The Department has an attractive alternate funding plan.

The Division members are a collegial, cooperative group. We have strong outpatient resources, especially in hypertension, and work closely with advanced practice nurses. Halifax is a vibrant city with diverse cultural, artistic and sports activities. We value quality of life.

Requirements include a Canadian fellowship in Internal Medicine or equivalent and eligibility for a license in Nova Scotia. All qualified candidates are encouraged to apply; however, Canadians and permanent residents will be given priority. Dalhousie University is an Employment Equity/Affirmative Action Employer. The University encourages applications from qualified Aboriginal Peoples, persons with disabilities, racially visible persons and women.

*Please send curriculum vitae and the names and addresses of three referees to:*

Dr. Elizabeth Mann, Head, Division of General Internal Medicine
Dalhousie University/Capital Health
Rm. 405 Bethune Bldg., VG Site-QEII HSC
1278 Tower Road, Halifax, NS, B3H 2Y9
Tel: (902) 473-2156 • Fax: (902) 473-8430
genmed@dal.ca

Applications close 30 days from date of this advertisement.

# General Internal Medicine

Photo courtesy Marikay Falby

## The Opportunity

The GIM (General Internal Medicine) division is a partnership between the University of Saskatchewan and the Saskatoon Health Region with both community- and university-based clinicians, educators and researchers. Collective responsibilities include clinical care of inpatients and outpatients, education of undergraduate and postgraduate trainees (including a flexible one- or two-year GIM post-core fellowship training program), and research.

At present we are seeking general internal medicine clinicians whose primary role is clinical care in the inpatient and outpatient setting. There is opportunity for those who desire to participate in both undergraduate and postgraduate education.

## The Candidate

The successful candidate will be licensed in Internal Medicine, preferably trained through a general internal medicine training program, and hold or be eligible for a Saskatchewan medical licence.

## Canadian Light Source (CLS) Synchrotron

The $173.5 M Canadian Light Source synchrotron, a national facility owned by the University of Saskatchewan, is the largest science project in Canada in more than 30 years. This facility is a unique national resource that will light the way to a new era of science and innovation for academic, industrial, and governmental researchers. The "BMIT" (Biomedical Imaging and Therapy) beamline should be functioning by late 2006. This will allow imaging of the body, to a resolution several-fold greater than ever before. Furthermore, precisely targeted radiation therapy will be possible. An active CLS Users Group headed by Drs. Bill Tomlinson and Dean Chapman (Anatomy and Cell Biology) is available for consultations with clinical faculty.

## The University

A publicly funded institution established in 1907, the University of Saskatchewan offers a full range of curricula, both academic and professional, with students registered in 13 colleges, including health sciences (medicine, nursing, dentistry, physiotherapy, pharmacy and nutrition, and kinesiology) and veterinary sciences.

## The Region

Saskatoon Health Region is one of the most integrated and complex health delivery agencies in Canada. We are the largest health region in Saskatchewan serving more than 300,000 residents in over 100 cities, towns, and rural municipalities. Saskatoon Health Region is the largest single employer in the province with over 11,000 staff and 750 physicians across the Region providing a complete range of health services to residents of central and northern Saskatchewan. The city's three acute care hospitals – St. Paul's, City, and Royal University – comprise the tertiary teaching centre for the province.

## The City

Saskatoon Shines – with more hours of sunshine than any other major Canadian city. With a population of 230,000, Saskatoon is the largest city in Saskatchewan, boasting small town spirit and big city amenities. World class events, festivals and attractions … strong arts and music focus … a short drive to the northern lake country … a variety of indoor and outdoor sporting facilities … and more golf courses per capita than anywhere in North America. The city is noted for its affordable housing, outstanding walking and biking trails along the riverbank, and excellent educational facilities, including the University of Saskatchewan. What's more – everything is within 15 minutes of home.

## To Apply:

If you are seeking a challenging career opportunity, please apply in confidence to:


Sharon E. Card, M.D., M.Sc., F.R.C.P.C.
GIM Division Head
Division of General Internal Medicine
Department of Medicine
Royal University Hospital
103 Hospital Drive
Saskatoon, Sask.
S7N 0W8
Phone: (306) 966-7961
Fax: (306) 966-1943
sharon.card@saskatoonhealthregion.ca


*The University and Saskatoon Health Region are committed to employment equity. Members of designated groups are encouraged to self-identify (Aboriginal, persons with disabilities and visible minorities).*

# EZETROL® AND YOUR STATIN: DEMONSTRATED SUPERIOR EFFICACY THROUGH DUAL INHIBITION[1]


## *YOU CAN DOUBLE THE STATIN DOSE OR CONSIDER ADDING EZETROL®*

EZETROL®, a cholesterol absorption inhibitor, administered alone or in combination with an hydroxymethylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor (statin), is indicated as adjunctive therapy to diet 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 when diet and other non-pharmacological measures are not enough.

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.

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

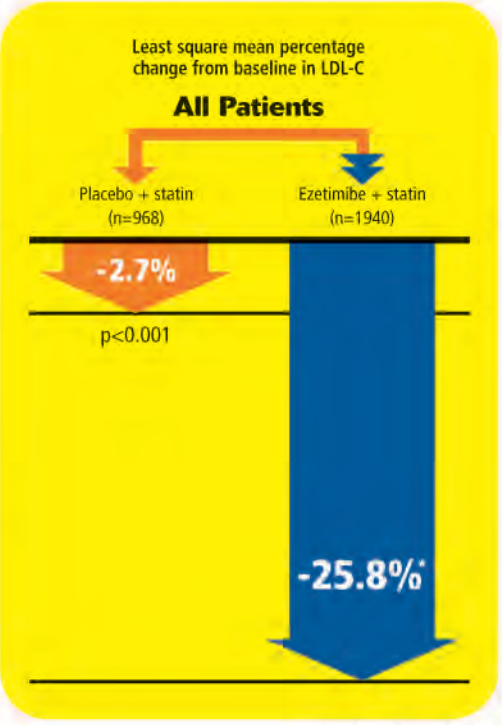
Due to the unknown effects of EZETROL® in patients with moderate or severe hepatic insufficiency, EZETROL® is not recommended in these patients. For patients developing signs or symptoms of hepatitis, liver functions should be evaluated. Acute pancreatitis should be considered in patients taking EZETROL® 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, pancreatitis and myopathy/rhabdomyolysis.

The safety and effectiveness of EZETROL® with fibrates have not been established; therefore, co-administration with fibrates is not recommended until use in patients is studied.

## ADDING EZETROL® TO A STATIN PROVIDED AN ADDITIONAL 25.8% MEAN REDUCTION IN LDL-C

**VERSUS 2.7% WITH A STATIN ALONE ($p<0.001$).[2,*]**




Adapted from Pearson TA et al[2]

*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.

**EZETROL® 10 MG ONCE DAILY FAVORABLE SAFETY AND TOLERABILITY PROFILE**

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

**FOR EFFICACY**
**EZETROL®**
*ezetimibe*
***and a Statin***
***BETTER TOGETHER!***

MERCK FROSST / Schering Pharmaceuticals
Merck Frosst-Schering Pharma, G.P., Kirkland, Quebec

PAAB

EZT-05-CDN-44200412-JA

®Registered trademark used under license by Merck Frosst-Schering Pharma, G.P.