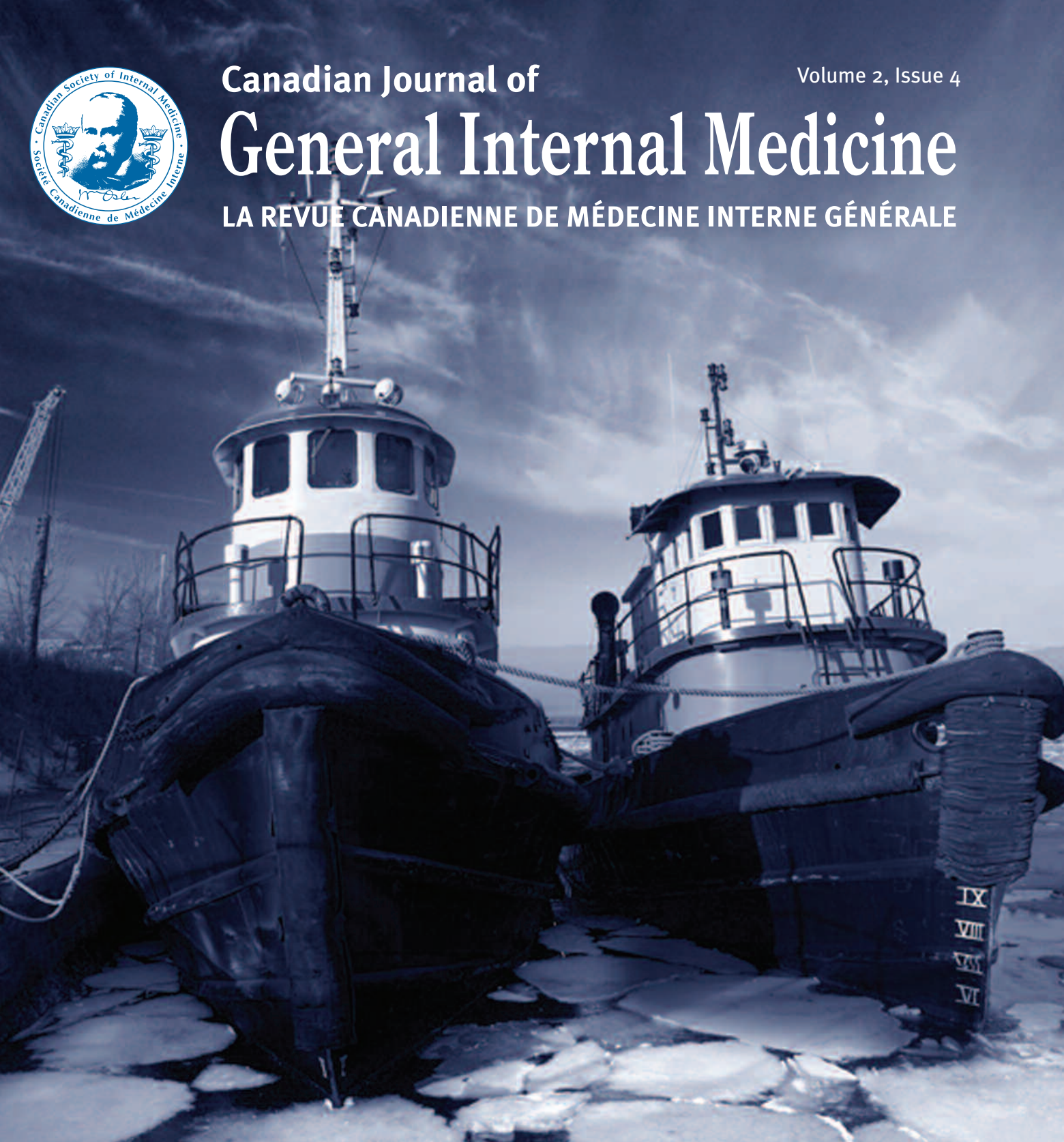
Volume 2, Issue 4

Canadian Journal of General Internal Medicine

LA REVUE CANADIENNE DE MÉDECINE INTERNE GÉNÉRALE



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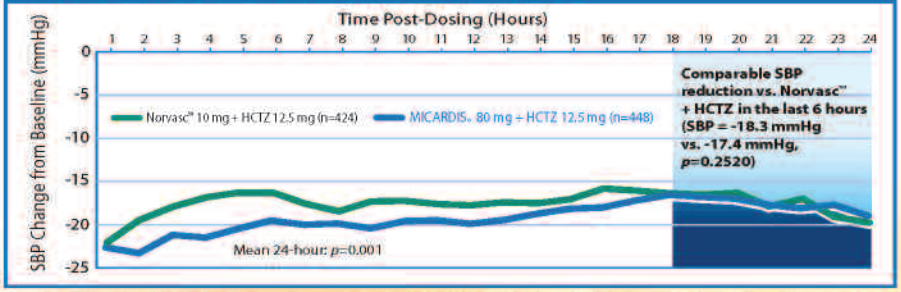
MICARDIS® + HCTZ vs. Norvasc™ + HCTZ



Adapted from Neldam S, *et al.*[2] A 14-week, multinational, prospective, randomized, open-label, blinded-endpoint, forced-titration study with a 2- to 4-week placebo run-in period comparing MICARDIS® + HCTZ (40 mg to 80 mg + 12.5 mg HCTZ) and Norvasc™ + HCTZ (5 mg to 10 mg to 10 mg + 12.5 mg HCTZ) on early morning SBP in 1,000 older patients with systolic hypertension (≥60 years) with cuff SBP of 141-179 mmHg, DBP ≤95 mmHg, and 24-hour APBM of SBP >125 mmHg at the end of the 2- to 4-week placebo run-in.

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.[6] 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%).[6] If pregnancy is detected, MICARDIS® should be discontinued as soon as possible. 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®.[6]

6-week, multinational, multicentre, randomized, double-blind, double-dummy, parallel-group study comparing MICARDIS® 40 mg and 80 mg and Cozaar® 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.[1]

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Bert Govig, MD

Internal medicine in Canada is thriving, as our annual meeting, in St. Johns, Newfoundland, clearly demonstrated. Over 400 attendees from Canada, the United States, and Australia joined a world-class panel of speakers to learn and socialize. Don Echenberg completed his presidency at this meeting with a flourish. Showing up with 18 internal medicine students, residents, and fellows, his university dominated the clinical, research, and poster presentations. The challenge to the rest of Canada is on, and we look forward to a heated competition next year.

Under Don's leadership, the CSIM has blossomed. Our annual scientific meeting is hugely successful, membership is at an all-time high, we have a new journal, *Canadian Journal of General Internal Medicine*, and we are increasingly taking a leading role in the national dialogue for medical education and health initiatives. The CSIM has benefited from the resurgence of globalism and holism in society at large. Young physicians see the value of generalism, and programs across the country are on the upswing. Sherbrooke University leads the pack, as it continues to populate hospitals across Quebec with a steady output of five general internists per year.

As we bid farewell to Don in his role as president, I would like to stress the extraordinary contributions that he has made to the CSIM over the past 20 years. He has promoted our causes with patience, passion, vision, and above all a "joie de vivre" that blurs the lines between work and play. Being a generalist, he has many hats and shifts comfortably between the roles of teacher, scientist, caregiver, health promoter, provocateur, and conciliator. I feel fortunate to know him as a colleague and a friend.

Beau travail !

Bert Govig, MD

La médecine interne est en plein essor au Canada, comme l'a si bien illustré notre dernière assemblée générale annuelle à St. John's (Terre-Neuve-et-Labrador). Plus de 400 personnes, en provenance du Canada, des États-Unis et de l'Australie, y étaient pour entendre des conférenciers de renommée mondiale et rencontrer des collègues. C'est à cette assemblée que Don Echenberg a terminé, avec un panache indéniable, son terme à la présidence. Accompagné de 18 étudiants, résidents et spécialistes de la médecine interne, il a présenté une délégation universitaire qui s'est démarquée dans les exposés cliniques, les exposés de recherche et les communications affichées. La barre a monté de plusieurs crans, et le reste du Canada aura tout un défi à relever. La concurrence sera vive l'an prochain, c'est le moins que l'on puisse dire.

Sous l'habile direction de Don, la SCMI s'est épanouie. Notre congrès scientifique annuel connaît un immense succès, les membres n'ont jamais été aussi nombreux, nous publions une nouvelle revue, *La Revue canadienne de médecine interne générale*, et la Société agit de plus en plus en tant que chef de file dans le dialogue canadien sur l'éducation médicale et les initiatives dans le domaine de la santé. En fait, la SCMI sort grande gagnante du mouvement social général vers la perspective globale et l'holisme. Les jeunes médecins sont conscients du bien-fondé du généralisme, et les programmes de formation partout au pays sont en pleine expansion. L'Université de Sherbrooke mène le bal, elle qui propose bon an mal an cinq internistes généralistes aux hôpitaux du Québec.

Alors que nous rendons hommage à Don à titre de président sortant, je ne saurais trop insister sur sa contribution exceptionnelle à la SCMI dans les 20 dernières années. C'est avec détermination, passion et vision qu'il a défendu notre cause, sans compter sa joie de vivre avec laquelle il nous a enseigné à concilier le travail et le plaisir. Étant un généraliste, il cumule bien des fonctions, qu'il exerce avec la même aisance, que ce soit comme enseignant, scientifique, prestataire de soins, promoteur de la santé, agent de changement ou médiateur. J'ai la chance de pouvoir le compter du nombre de mes amis et collègues.

About the Author

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

Au sujet de l'auteur

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

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ABOUT THE COVER

This issue's cover shows a couple of tugboats waiting for work in Toronto Harbour during spring breakup. The cover photo was taken by Peter Bowers, an amateur photographer who lives and works in Toronto. He gets a lot of photo opportunities while canoeing, kayaking, and skiing at his cottage in Haliburton. You can view other photos by Peter at http://www.flickr.com/photos/mr_fabulous/.

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

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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%).

If pregnancy is detected, MICARDIS® should be discontinued as soon as possible. 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®.

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

1. The ONTARGET/TRANSCEND Investigators. Rationale, design, and baseline characteristics of 2 large, simple, randomized trials evaluating telmisartan, ramipril, and their combination in high-risk patients: The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial/Telmisartan Randomized Assessment Study in ACE Intolerant Subjects with Cardiovascular Disease (ONTARGET/TRANSCEND) trials. *American Heart Journal* 2004;148 vol.1:52-61. 2. Data on file, Boehringer Ingelheim (Canada) Ltd.

Current Ongoing International Cardio and Vascular Trials:

	ONTARGET	TRANSCEND	PRoFESS®
Number of Patients Internationally	25,622[2]	5,926[2]	20,333[2]
Number of Canadian Patients	2,519[2]	426[2]	1,549[2]
Number of International Centres	730[1,2]	730[1,2]	674[2]

ONTARGET Cardiovascular Mortality and Morbidity Trial

- ONTARGET investigates MICARDIS® (telmisartan) and Altace® (ramipril), alone or in combination, in the prevention of cardiovascular morbidity and mortality in patients at high risk for cardiovascular complications.[1]
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    - Cerebrovascular event
    - Diabetes mellitus with evidence of end-organ disease

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- TRANSCEND investigates MICARDIS® vs. placebo for the prevention of cardiovascular morbidity and mortality in patients at high risk for cardiovascular complications and who are intolerant to angiotensin-converting enzyme inhibitors.[1]

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- PRoFESS® investigates patients with known prior ischemic strokes. Patients will receive at random either MICARDIS® or placebo. Both groups will also receive at random either Aggrenox® (ASA/extended-release dipyridamole) or Plavix® (clopidogrel).[2]

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AU SUJET DE LA PAGE COUVERTURE

La photographie de la page couverture a été prise par Peter Bowers, photographe amateur qui vit et travaille à Toronto. Il profite de toutes les occasions de prendre de magnifiques photos lorsqu'il fait du canoë-kayak ou du ski à son chalet situé à Haliburton. Vous pouvez voir d'autres photos prises par Peter à l'adresse suivante. http://www.flickr.com/photos/mr_fabulous/.

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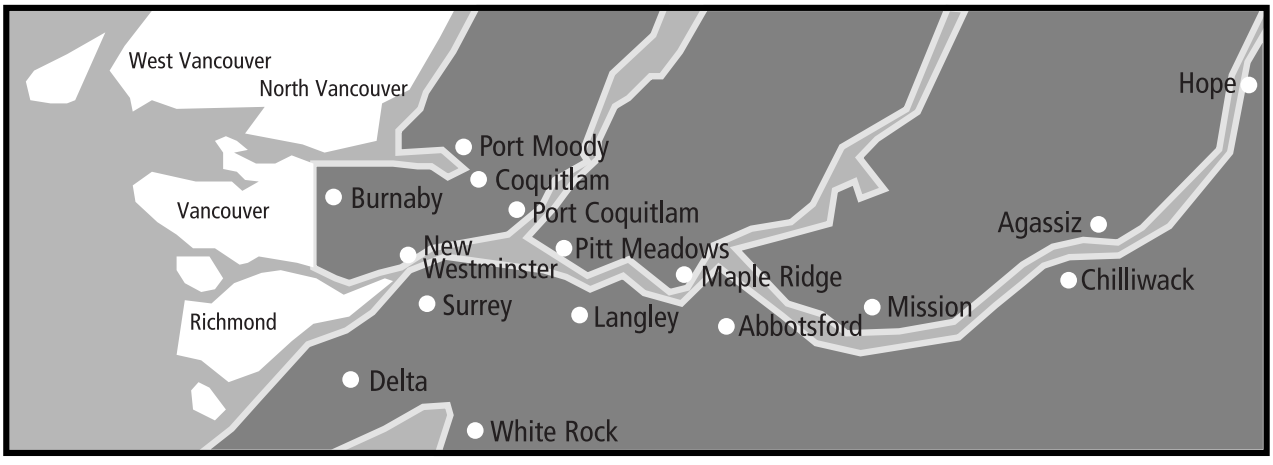
- Peace Arch Hospital – White Rock, BC
- Ridge Meadows Hospital – Maple Ridge, BC
- Surrey Memorial Hospital – Surrey, BC



We also have upcoming exciting opportunities at our new state-of-the-art facility, Abbotsford Regional Hospital and Cancer Centre, which opens in 2008.

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Medical Humanities: A New Section for CJGIM

Donald Farquhar, MD, Jock Murray, MD

The late American statesman Adlai Stevenson once observed that "the difference between what we know at twenty and what we know at fifty is incommunicable." One of the things that internists come to know, especially after some years in practice, is the importance of reaching a fuller understanding of the human experience of illness and health. To do so requires us to balance our knowledge of medical and biological sciences with an appreciation for the humanities.

For centuries, physicians have made efforts to reconcile body and spirit, competence and caring, and science and humanism. In recent decades, however, unprecedented advances in medical science and technology have led to growing concerns about our ability to maintain a human face on the practice of medicine. As a result, the public has become increasingly vocal in its complaints about the profession. Patients want their physicians to deliver scientifically sound medical care, but to do so with a high level of both technical proficiency and human compassion. Implicit in this is an emphasis on knowing the person with the disease and understanding the meaning of that experience.

For a long time, it was thought that the humanities could be taken for granted in the education of a physician. As a result of the post-Flexnerian emphasis on science, medical schools abandoned the humanities as an integral part of their curricula, relying instead on exposure in premedical studies or the experiential learning that was anticipated to occur through applying scientific knowledge and clinical skill to the ills of patients. There are now reassuring signs to be found in medical schools, residency programs, provincial regulatory bodies, medical publications, and reports on health care delivery that efforts are being made to re-emphasize the humanities in the education of our future physicians.

Medicine is a caring profession that strives to foster health, prevent or cure illness, and relieve suffering. Fundamentally, it is a humanistic undertaking that uses science to inform and advance that effort. As such, the medical humanities are an integral part of the process, as they have been for thousands of years, long before modern biomedical science came to the fore.

Recognizing and applauding this understanding of medicine as a balance between science and humanism, the *Canadian Journal of General Internal Medicine* is introducing a new regular section on the medical humanities. We invite you, our colleagues, to express some of what Adlai Stevenson referred to as the "incommunicable" things we come to know as physicians, by submitting topics in medical history, literature, philosophy, art, poetry, and music or personal reflections on your own discovery of the human experience through the diverse practice of internal medicine.

The CSIM Osler Awards 2007

Presented annually to individuals demonstrating excellence in GENERAL INTERNAL MEDICINE in clinical practice, research, medical education, or specialty development. These awards were supported by an unrestricted educational grant from AstraZeneca Canada Inc.

Steven Shumak, MD
Professor of Medicine, University of Toronto
Head, Division of General Internal Medicine, Sunnybrook
Nominated by Steven Shadowitz
Seconded by Wendy Levinson

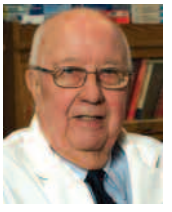
Dr. Shumak has gained a reputation of a first-class medical educator, having gained numerous teaching awards (in Alberta and Ontario). His academic career has been devoted to teaching individuals and groups, and "he has been a role model of what a General Internist should be." He has also provided strong and valued leadership in the Division of Medicine in Sunnybrook and at U of T.

To quote Osler, "*The best that is known and taught in the world – nothing less can satisfy a teacher worthy of a name.*"

Ameen Patel, MD
Clinical Educator, Associate Clinical Professor
McMaster University Medical Centre, Hamilton
Nominated by Akbar Panju
Seconded by Parveen Wasi

Dr. Patel is both an educator and an expert clinician (a "doctor's doctor"), with interests in perioperative medicine, thrombo-embolism, and osteoporosis. He has been recognized for his teaching excellence and is a leader in developing educational tools in GIM. He is known to go the extra mile to ensure his patients get the best care possible.

"*He is a role model who inspires residents to pursue a career in GIM.*"



David Wallace Ingram, MD
Professor of General Medicine and Therapeutics
Memorial University, St John's, Newfoundland
Nominated by Ann Colbourne
Seconded by Mahesh Raju

An avid reader and lifelong learner, Dr. Ingram maintains an active clinical practice and continues to challenge his peers with his consummate medical knowledge. He has received numerous awards in recognition of his service, passion, vision, and contribution to GIM. Over a practice spanning almost 60 years, "this living icon has influenced service evolution and health professional education in an understated and profound manner."

"*He is our contemporary William Osler.*"

Thank You to Sponsors

The CSIM gratefully acknowledges support of its 2007 Annual Scientific Meeting by unrestricted educational grants from:

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The Canadian Society of Internal Medicine is thankful to sponsors of the 2007 awards/lectures:

The *CSIM Awards for Excellence in Research* are supported by an unrestricted educational grant from **Biovail Pharmaceuticals.**

Congratulations to …

Oral Research Session

First Prize – "Characteristics and Outcomes of Patients not Receiving Reperfusion for STEMI in Current Practice," **Dr. Mark Kotowycz, McMaster University**

Second Prize – "Evaluation of Compliance with the Guidelines for Baseline and Follow-Up Testing When Amiodarone Is Introduced as a New Medication at the CHUS," **Dr. Isabelle Boulais, University of Sherbrooke**

Third Prize – "Impact of Antihypertensive Medication on Perioperative Period," **Dr. Catherine St. George, University of Sherbrooke**

Poster Research Session

"Characteristics of Hypertensive Emergencies and Urgencies at the Centre Hospitalier Universitaire de Sherbrooke between 1998 and 2006," **Dr. Marie-Josée Lacelle, University of Sherbrooke**

The *CSIM/Royal College Osler Lecture* was supported by an unrestricted educational grant from Pfizer Canada. This year's lecturer was **Dr. John Ruedy, Halifax**, "Performance Assessment – The Touch Stone of Learning."

The recipient of the *2007 Dr. David Sackett Senior Investigator Award* was **Dr. Murray Krahn, Toronto,** whose presentation was titled "Three Scientific Paradigms in Health Technology Assessment."

The recipient of the *2007 New Investigator Award* was **Dr. Chaim Bell, Toronto,** who spoke on "Gaps in Continuity of Care from the Hospital."

The above two awards were supported by an unrestricted educational grant from **Merck Frosst/Schering Pharmaceuticals.**

The *2007 Ted Giles Clinical Vignettes* winners are:

First Prize – "Unravelling the Gordonian Knot," **Dr. Vanessa Tremblay, University of Sherbrooke**

Second Prize – "Reason to Bleed: Severe Acquired Hemophilia in a Patient with Sickle Cell Disease," **Dr. Alina Gerrie, University of Toronto.**

CSIM Has Recently Endorsed Blood Pressure Canada's Policy Statement

The CSIM has recently endorsed Blood Pressure Canada's policy statement recommending that the Canadian government achieve a reduction in adult dietary sodium intake to less than 2,300 mg/d.* The policy called on government to establish a monitoring system and to set graduated targets and timelines to achieve this goal by 2020. To implement the policy, both the public and health care professionals need to be engaged and educated, and a working group of interested parties needs to be created. On the surface, this is a bland policy that asks our government to implement its own nutrition guidelines. Nevertheless, the endorsement is important for several reasons.

Over 90% of Canadians are estimated to develop hypertension if they live an average lifespan. Reducing high dietary sodium intakes in Canada will decrease the prevalence of hypertension by approximately one third and save over $400 million per year in the cost of physician visits and drug therapy.

Health issues of dietary sodium are substantive and require action. This policy statement is supported by 16 major national organizations representing cardiovascular scientists, physicians, nurses, pharmacists, dietitians, community and public health specialists, and heart patients (through the Heart and Stroke Foundation of Canada). Faced with such a strong front, the food industry cannot challenge the science behind a strategy that reduces salt additives.

This policy was announced on Parliament Hill on October 25, 2007. An educated public can help us in applying pressure regarding the importance of this issue. CSIM has created a Health Promotion Committee to review other initiatives and to promote collaboration and dialogue in the areas of preventive medicine, chronic disease, and wellness. In so doing, we can make an impact on the health of all Canadians.

*Canadian Dietary Reference Intakes.

Why Isn't Medical Genetics a Subspecialty in Internal Medicine?

A historical perspective on the development of medical genetics as a specialty in North America

Dawna M. Gilchrist, MD

One of the major expectations of the 21st century is the complete deciphering of the genetic code. The Human Genome Project holds the perceived promise of both comprehensive diagnosis and treatment of genetically based disease, and the anticipation of the so-called genetic revolution extends to any population with access to popular media. In a scant 40 years, genetics has gone from a position of esoterica to the central pathophysiology of virtually all human disease.

The Early Years

In 1952, there were only six medical genetics clinics in North America, including the Department of Genetics of the Hospital for Sick Children in Toronto under N. Ford Walker and the Department of Medical Genetics in the Children's Memorial Hospital of Montreal under F. C. Fraser. Two seminal clinics in medical genetics were formed in 1957. Both were in Divisions of Medical Genetics in Departments of Medicine – one at Johns Hopkins under leadership of Dr. Victor McKusick (a cardiologist) and the other in Seattle led by Dr. Arno Motulsky (a hematologist).

By the early 1960s, Johns Hopkins and Seattle were major training centres for medical geneticists in North America. Yet, despite the clinics' origins in Departments of Medicine, it was not adults that formed the main body of patients. Adult medicine in the 1950s and 1960s saw little use of the medical genetics knowledge of the time. However, advances in cytogenetics, biochemistry, and dysmorphology made genetics increasingly relevant to pediatrics.

Advances in Cytogenetics

Following the confirmation of the human diploid chromosome count of 46 in 1956, an explosion of cytogenetic evaluation followed – Down syndrome (trisomy 21), trisomies 13 and 18, and Klinefelter's and Turner's syndromes. It was soon recognized that definable syndromes of abnormal physical features, coupled with intellectual handicap, could be caused by chromosomal abnormalities. To this day, germline cytogenetic abnormalities are important in reproductive medicine and in the study of pediatric clinical syndromes, but rarely in hereditary disorders of adult onset.

Advances in Biochemistry

Technical advances such as chromatography for screening urine for abnormal metabolites, as well as paper and starch gel electrophoresis, enabled the search for structural abnormalities in proteins. It became obvious to pediatricians that inborn errors of metabolism could be diagnosed and, potentially, treated.

Dysmorphology as a Clinical Skill

If physicians are to benefit from laboratory diagnostics, they must first select those patients most likely to have a detectable abnormality. And so, to the long-standing tool of pedigree analysis was added the specific skill of searching for and recognizing syndromes of structural abnormalities – dysmorphology. David W. Smith, author of *Recognizable Patterns of Human Malformation*, trained or influenced several generations of medical geneticists. Smith did major service to the field by differentiating genetic dysmorphology from acquired structural anomalies.

Pediatrics Is Where It's At

Medical genetics was a very exciting place to be in the 1960s. Dysmorphologists were describing new syndromes. Cytogenetics and the biochemical laboratories were adding objective diagnoses to some. Treatment of inborn errors of metabolism was a potential reality. But it was almost entirely in children.

Of course, those physicians already trained in pediatrics and inclined to medical genetics were happily placed in the thick of things. Even those who started out in internal medicine – Judith Hall, David Rimoin and Charles Epstein, to mention but a few – took the obvious and permanent detour into pediatrics to pursue their interests in medical genetics.

Whither Will Genetics Go in Adult Medicine?

In retrospect, it is not surprising that genetics did not also find an early home in internal medicine, despite the involvement of such luminary internists as McKusick and Motulsky. While individuals with chromosomal abnormalities certainly can live to adult years, it is seldom that they escape diagnosis until that time. And the major clinical tool of dysmorphology is of little use in the diagnosis of genetic disorders of adult onset that have functional, rather than structural, pathology. With respect to the classically defined inborn errors of metabolism, internists tend not to see these individuals as many do not survive until adult years or, if they do, continue to be followed by metabolic geneticists.

That is not to say that adult patients with genetic disorders are not seen in medical genetics clinics, or that it is impossible for an internist to train in medical genetics. However, it is, undeniably, a general (mis)perception of the public and the medical community, as well as many clinical geneticists themselves, that the major role of medical genetics is the diagnosis of genetic problems in infants and children.

Adult Medicine "Discovers" Medical Genetics

In the past two decades, molecular diagnostics have allowed us to tackle many more diseases of mendelian inheritance of all ages of onset. We now have considerable capacity in the diagnosis of hereditary cancer,

About the Author

Dawna Gilchrist is professor of medicine in medical genetics at the University of Alberta, as well as director of the History of Medicine Program in the Faculty of Medicine and Dentistry.

neurodegenerative disease, and a host of others. And, as we decipher the genome further, we are approaching the critical database necessary to tackle those disorders of multifactorial inheritance so common to chronic adult-onset disease.

But, while the application of laboratory techniques in genetics has caught the interest of internal medicine, the use of medical geneticists has generally not. Rather, the issues of genetic diagnosis, prognosis, and management have been rolled into the subspecialties of internal medicine.

The rise of another health care provider, the MSc genetic counsellor, has paradoxically widened the gap between medical geneticists and internal medicine. While internists feel comfortable with all aspects of patient management other than specific genetic issues, they may turn to the genetic counsellor to fill the gap. Genetic counsellors are often now the sole providers of genetic information in multidisciplinary clinics that encompass genetic diagnosis, for example, oncology and neurology.

Will Medical Genetics Become a Medical Subspecialty?

Since the majority of service in prenatal concerns, dysmorphology, and metabolic genetics is in the pregnant and pediatric population, medical genetics, pediatrics, and obstetrics will continue to enjoy a close and mutually beneficial relationship. The study of heritable disorders of adult onset has already been welcomed into the basic research laboratory and, via pharmacogenetics, clinical research. But, it is likely that clinical diagnosis and management of adult-onset genetic disorders will be increasingly assumed by subspecialists in internal medicine. A potential new direction could be realized in the creation of Divisions of Molecular Medicine within Departments of Medicine, particularly with respect to the training of MDs and PhDs interested in the applications of molecular medicine to clinical medicine.

The Challenge

The new paradigm for medicine is that all disease may be defined by genetic predisposition. Internal medicine can no longer think of medical genetics as limited to the diagnosis and care of rare pediatric disorders. We must ensure that medical students are well grounded in both basic and clinical genetics, as the practice of medicine will demand that potential genetic factors be taken into consideration for all diseases. Our growing capabilities in identifying presymptomatic genetic predisposition will allow us an enhanced ability to practise truly preventive medicine. Our expanding knowledge of pharmacogenetics will allow us to finely tune therapies when disease occurs. Eventually, therapies directed at the molecular level may help us to actually cure many of the diseases we can now only ameliorate.

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EKG & U

A Christmas Conundrum

George Veenhuyzen, MD

An elderly man was admitted to hospital after a fall. He had suffered several falls in the recent past. The electrocardiogram (EKG) shown in Figure 1 was routinely performed while he was resting in bed. What is your diagnosis?

Discussion

At first glance, there appears to be a wide complex tachycardia at approximately 240 bpm. Upon closer inspection, there are narrow QRS complexes marching through the tracing at a rate of approximately 60 bpm. The correct diagnosis is provided by lead I: normal sinus rhythm! With that knowledge, the "wide complex tachycardia" cannot be related to any physiological cardiac activity and must be some sort of artifact. Sources of artifact can be exogenous (electromagnetic interference) or endogenous (originating from muscles other than the heart).

An EKG performed several minutes after a medication was administered is shown in Figure 2. What was the medication?

There appear to be negative, sawtooth flutter waves (at a rate of approximately 240 bpm) most apparent in the inferior leads. However, careful inspection, particularly of leads I, V1, and V2, reveals sinus P waves preceding every QRS complex (arrows), indicating that he is still in sinus rhythm at around 60 bpm. The right atrium cannot

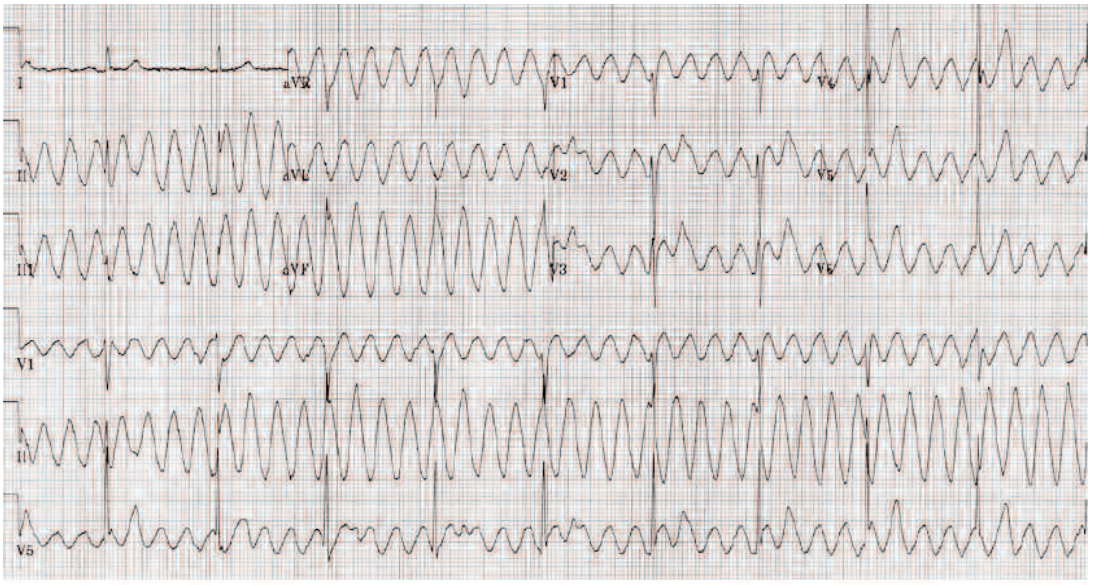

Figure 1

be in atrial flutter and sinus rhythm at the same time, so once again, the "flutter waves" must be an artifact. The rate of the artifact has not changed (around 240 cycles per minute), but it has diminished in amplitude compared with the previous EKG. What medication could diminish the magnitude of an electro-cardiographic artifact?

The salient clues include his history of falls and the frequency of the artifact (240 cycles per minute, or four cycles per second). Parkinson's disease frequently produces a tremor with a frequency of four to six cycles per second. If you surmised that the medication administered between the EKGs in Figures 1 and 2 was levodopa, you are correct!

In this case, because lead I is a clean tracing, free of artifact, we can conclude that neither upper limb is involved in the tremor. Both EKGs demonstrate that the artifact has its greatest amplitude in II, III, and aVF, which all share a lower limb electrode. Thus, apart from demonstrating that a parkinsonian tremor can masquerade as wide complex tachyar-rhythmias and atrial flutter, these EKGs also remind us that parkinsonian tremors can involve the feet.

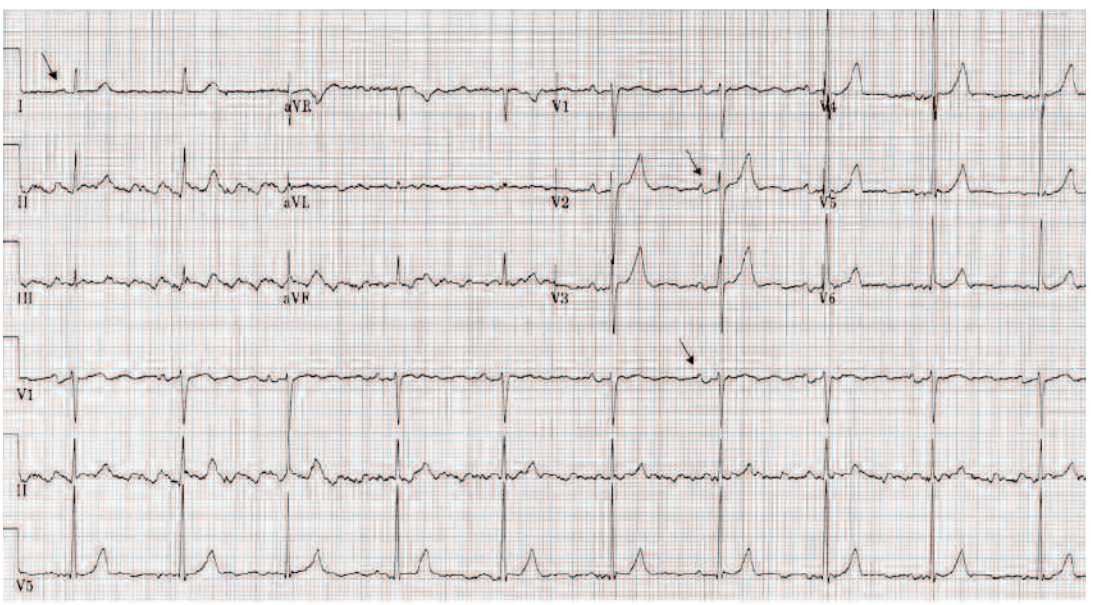

Figure 2

About the Author

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Pictures of Heart Failure Care in Complex Medical Patients: Broad Strokes or Fine Detail?

Robert C. Wu, MD, Valerie A. Palda, MD, C. Mark Cheung, MD, Ed Etchells, MD, Arlene S. Bierman, MD, Chaim M. Bell, MD

Identifying and closing gaps in heart failure care is important because of the high prevalence and comorbidity[1] and because evidence-based processes of care are well established.[2–4] Heart failure quality indicators include the prescription of angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), and beta-blockers at discharge.[3,4] However, not all patients with heart failure will benefit from specific drug therapy such as ACEI/ARB or beta-blockers. Accurate indicators consider only those patients who would expect to derive benefit from the specific drug therapy. The Canadian Cardiovascular Outcomes Research Team (CCORT) definition of this "ideal" subset of patients is "those who are eligible to receive the process of care and do not have any contraindications or other reasons not to receive the process of care."[5,6]

Patients with heart failure are more likely to be cared for by general internists than cardiologists,[5–8] and patients on general internal medicine services are older, have more comorbidities, and have potentially higher mortality.[7] Therefore, general medical inpatients with heart failure may be less likely to be ideal candidates for certain heart failure treatment.

Our objectives were (1) to determine the proportion of general medicine patients with heart failure who are ideal candidates for CCORT quality-of-care indicators for heart failure and (2) to describe the current performance of these indicators for general medical inpatients.

Methods

Setting

We studied four hospitals associated with University of Toronto: St. Michael's Hospital, Sunnybrook Health Sciences Centre, Toronto General Hospital, and Toronto Western Hospital. The study was approved by the research ethics board at each hospital.

Population

Patients admitted to general internal medicine with a primary diagnosis of heart failure in 2005 were eligible for inclusion. Patients with heart failure were identified based on the CCORT case definition criteria listed in Table 1.[3] The following modifications were made to the case definition criteria: (1) the inclusion of patients admitted to internal medicine only and (2) the removal of the exclusion criterion of a heart failure admission in the previous 3 years. While this exclusion criterion was initially designed to identify a hospitalization-naive cohort, we removed this restriction to better inform the management of internal medicine patients with heart failure, even those who have had a recent admission.

Table 1. Case Definition Criteria for Identifying Heart Failure Patients

Inclusion criteria	Most responsible diagnosis of heart failure (ICD-10 I50.0 or ICD-9 428)
	Admitted to Department of Internal Medicine
	Meets clinical validation criteria for a diagnosis of heart failure (Framingham criteria)*
Exclusion criteria	Age <20 or >105 years
	Transferred from another health care facility
	Heart failure developed as a hospital complication

ICD = World Health Organization International Classification of Diseases.

*Framingham criteria (two major or one major + two minor). Major criteria are paroxysmal nocturnal dyspnea, orthopnea, neck vein distension, elevated jugular venous pressure, rales, cardiomegaly (radiographic), pulmonary edema, third heart sound, and positive hepatojugular reflux. Minor criteria are edema, nocturnal cough, dyspnea, hepatomegaly, pleural effusion, tachycardia, and weight loss in response to diuretics.[14]

Main Measures

We used the CCORT inpatient quality indicators to create data collection forms common to all hospitals.[3] These indicators include the description of ideal candidates for the measurement of left ventricular function and the prescription of ACEIs, beta-blockers, and warfarin for atrial fibrillation at discharge (Table 2). The inpatient indicators also include the measurement of daily weights in hospital as well as discharge counselling. We modified one indicator – the documentation of left ventricular function – to keep it more in line with clinical judgment and also similar to the American College of Cardiology performance measure.[4] If assessment was performed >6 months prior to admission, it was still considered valid.

All patients were identified by hospital discharge in 2005 with a most responsible diagnosis of congestive heart failure (World Health

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Table 2. CCORT Detailed Heart Failure Process Indicator Eligibility and Exclusion Criteria

ACEI prescription at discharge	
Eligible	LV systolic dysfunction (EF <40% or equivalent grade)
	Discharged alive
Exclusions	Contraindications to ACEIs
	Moderate or severe aortic stenosis
	Bilateral renal artery stenosis
	Angioedema, hives, severe rash, other allergy or intolerance to ACEI use
	Hyperkalemia (K+ >5.5 µmol/L)
	Hypotension (SBP <90 mm Hg)
	Renal dysfunction (creatinine >200 µmol/L)
	Physician documentation of reason for nonuse (e.g., patient refusal)
	Enrolled in clinical trial testing alternatives to ACEIs
Beta-blocker for heart failure at discharge	
Eligible	LV systolic dysfunction (EF <40% or equivalent grade)
	Discharged alive
Exclusions	Conduction system disease
	Symptomatic bradycardia (HR <60 beats/min) not on beta-blocker
	Bifascicular block
	P–R interval prolongation (>0.24 s)
	Second- or third-degree AV block
	Hypotension
	Asthma
	Severe obstructive lung disease
	Physician documentation of reason for nonuse (e.g., patient refusal)
	Allergy or intolerance to beta-blocker
Warfarin at hospital discharge for atrial fibrillation	
Eligible	Atrial fibrillation during the index admission documented in chart OR principal or secondary discharge diagnosis of atrial fibrillation in administrative data
	Discharged alive
Exclusions	Contraindication to warfarin
	Any documented bleeding episode
	Liver disease
	Uncontrolled seizure disorder
	History of frequent falls
	Inability to cooperate with treatment regimen
	Pregnancy
	Physician documentation of reason for nonuse (e.g., patient refusal)
	Allergy or intolerance to warfarin

ACEI = angiotensin-converting enzyme inhibitor; AV = atrioventricular; CCORT = Canadian Cardiovascular Outcomes Research Team; EF = ejection fraction; HR = heart rate; LV = left ventricular; SBP = systolic blood pressure.

Organization International Classification of Diseases [ICD] 9 code 428 or ICD-10 code I50) and admitted to the general medicine service. Computer-generated random selection was then used to create lists of charts. We reviewed at least 50 randomly selected charts from each site. We employed two chart reviewers who had no hospital affiliation: one reviewed charts from St. Michael's Hospital and the other from Sunnybrook Health Sciences Centre, Toronto General Hospital, and Toronto Western Hospital.

Analysis

We analyzed differences in prescription rates using chi-square analyses. Confidence intervals were calculated for proportions.

Reliability of Data

We repeated data abstraction on 10% of the charts at each site to ensure reliability. Kappa was calculated on the following fields: past history of atrial fibrillation, first electrocardiogram showing atrial fibrillation, previous left ventricular function, daily weights, salt restriction, discharge counselling, and prescription of ACEIs or ARBs, beta-blockers, and warfarin at discharge. Overall kappa for interrater agreement was 0.76, representing "substantial agreement."[9]

Results

Patients

A total of 202 patients with heart failure were studied; Table 3 presents patient characteristics. We excluded 10 patients who did not meet the Framingham criteria for heart failure (see Table 1), leaving 192 patients for analysis. Sixteen patients died in hospital, leaving 176 patients for analysis of discharge processes of care. The median length of stay was 6 days. There were a slightly higher percentage of women, most patients had at least one cardiac risk factor, and 55% had known coronary artery disease.

Table 3. Patients Characteristics

	Patients
Total charts reviewed	202
Qualified (met inclusion and Framingham criteria)	192
Qualified and alive at discharge	176
Mean age, in years (SD)	78.4 (11)
Female	56%
Cardiac risk factors	
Smoking	40%
Hypertension	70%
Dyslipidemia	49%
Diabetes	44%
Patients with one or more cardiac risk factors	89%

Ideal Patients

The percent of patients that were considered ideal for ACEI/ARB or beta-blocker subgroups were 30% and 38%, respectively. The majority of patients were excluded because they either had an ejection fraction ≥40% (35%) or did not have documentation of systolic dysfunction (20%) (Table 4). For patients with atrial fibrillation ($n = 104$), 74% were considered ideal for warfarin therapy.

Prescription Rates of Target Medications at Discharge

For ideal patients, at discharge, prescription rates for ACEI/ARB and

Table 4. Reasons for Patients not Meeting the "Ideal" Definition for Pharmacological Indicators

	Reason	% (*n*)	95% CI
ACEI/ARB	No documentation of left ventricular function (previous or during inpatient admission)	20% (35)	15–26%
	Left ventricular ejection fraction ≥40%	35% (62)	29–43%
	Excluded based on contraindications or documentation of reason for nonuse	15% (27)	11–21%
	Ideal patients	30% (52)	23–37%
Beta-blockers	No documentation of left ventricular function (previous or during inpatient admission)	20% (35)	15–26%
	Left ventricular ejection fraction ≥40%	35% (62)	29–43%
	Excluded based on contraindications or documentation of reason for nonuse	7% (13)	4–12%
	Ideal patients	38% (66)	31–45%
Warfarin in atrial fibrillation	Contraindications or documentation of reason for nonuse	26% (27)	19–35%
	Ideal patients	74% (77)*	65–81%

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker.

*Of the 176 patients qualified and alive at discharge, only 104 patients had documented atrial fibrillation.

beta-blockers and were 87% and 79%, respectively (Table 5). For ideal patients with atrial fibrillation, 74% were prescribed warfarin. Prescription rates in ideal patients were statistically significantly different from those in the nonideal patients.

Nonpharmacological Processes

Regarding nonpharmacological processes, 78% of patients had a previous or an inpatient measurement of left ventricular systolic function (Table 6). Forty-two percent of all patients had left ventricular systolic dysfunction (left ventricular ejection fraction <40%). There was a large variation between hospitals in the proportion of inpatients with a measurement of left ventricular function, ranging from 28 to 72%.

Other process indicators such as daily weights and discharge counselling were documented infrequently. No hospital used standardized order sets. There was documentation of any discharge counselling for 35% of patients, while no patients (0%) had documentation of all recommended discharge counselling.

Discussion

We found that that only 30% and 38% of our patients were considered ideal for ACEI/ARBs and beta-blockers, respectively. When considering ideal patients, we found that ACEIs were prescribed 77% of the time, the combination of ACEIs and/or ARBs was prescribed 87% of the time, beta-blockers were prescribed 79% of the time, and anticoagulation for atrial fibrillation was prescribed 74% of the time. The prescription rates were significantly different between ideal and nonideal patients.

Our finding that a significant proportion of heart failure patients cared for by general internists do not meet ideal criteria has been suggested by other authors. A 1997 study of heart failure inpatients, managed by both cardiologists and internists, found that only 50% of

Table 5. Inpatient Process Indicators for Internal Medicine Patients (Pharmacological)*

	CCORT Recommended Target	All Patients	Ideal Patients	Nonideal Patients
ACEI	≥85%	61% (107/176)	77% (40/52)	54% (67/124)
ACEI/ARB	No specific target	69% (122/176)	87% (45/52)	62% (77/124)
Beta-blockers	≥50%	64% (113/176)	79% (52/66)	55% (61/110)
Warfarin for atrial fibrillation	≥85%	55% (57/104)	74% (57/77)	0% (0/27)

ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CCORT = Canadian Cardiovascular Outcomes Research Team.

*Note: Inpatient process indications were all statistically significant comparing ideal to non-ideal patients ($p < .01$).

Table 6. Inpatient Process Indicators for Internal Medicine Patients (Nonpharmacological)

	CCORT Recommended Target	Patients	95% CI
Left ventricular measurement			
Either previous or this admission	≥75%	78%	71–83%
Inpatient orders and processes			
Daily weight taken	≥90%	27%	21–34%
Salt restriction ordered	No specific target	60%	53–67%
Fluid restricted ordered	No specific target	48%	41–55%
Any discharge counselling	≥90%	35%	27–44%

CCORT = Canadian Cardiovascular Outcomes Research Team.

patients were ideal candidates for ACEI treatment.[10] Previous studies found that 44% of heart failure patients do not have systolic dysfunction and that patients with preserved systolic function are more likely to be cared for by internists.[11,12] In other domains such as colorectal screening and diabetes, many clinical practice guidelines do not capture the complexities of older patients with multiple comorbidities; universally applying standards of quality of care to these patients could result in inappropriate care.[13]

Our results highlight the importance of specific clinical information that is needed to properly judge how many patients are ideal for receiving certain medications. Such data are often not available from hospital administrative databases.[7] Overprescribing of heart failure medications could occur if the assessment of heart failure quality of care is based on all patients, ideal or not. By contrast, a narrow focus on drug prescribing for ideal patients would ignore a large proportion of complex general medical heart failure patients. If detailed clinical information is not available, then heart failure care may be better judged by measures that are applicable to the majority of patients, such as sodium restriction and counselling regarding monitoring weight and symptoms.

Conclusions

Less than half of general medical patients were ideal for specific heart failure quality measures such as ACEI/ARB or beta-blocker prescription at discharge. Failure to make the extra effort of measuring and accounting for clinical indicators that allow distinction of ideal from nonideal patients has potential implications for quality of care, hospital performance measurements, and physician engagement in quality improvement.

Acknowledgements

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Une hypertension artérielle hyperkaliémique

Vanessa Tremblay, MD, Jean-François Lajoie, MD, Luc Lanthier, MD

Le syndrome de Gordon, aussi appelé hypertension familiale hyperkaliémique ou pseudoaldostéronisme de type 2, se définit par l'association d'hypertension artérielle et d'hyperkaliémie chez un patient qui possède une fonction rénale normale. Nous présentons ici le cas d'un jeune homme qui s'est présenté avec cette association inhabituelle d'hypertension artérielle et d'hyperkaliémie.

Cas clinique

Cet homme de 29 ans nous a été adressé en clinique externe de médecine interne par son médecin de famille suite à la découverte d'une hyperkaliémie au bilan de routine. Le polystyrène sulfonate de sodium (Kayexalate) fut débuté sans effet notable sur la kaliémie. Le patient ne prenait aucun médicament ou produit naturel et sa diète ne contenait pas d'apport potassique excessif. Il ne souffrait d'aucune maladie connue, mais a abusé de l'alcool et de la cocaïne jusqu'à l'an dernier. Sa mère souffre d'hypertension artérielle, mais aucun membre de sa famille n'a de trouble potassique.

L'examen physique révélait une hypertension artérielle sur plusieurs mesures, variant de 150–170/90–110 mmHg, compliquée d'une rétinopathie hypertensive de grade 1. Le reste de l'examen physique était peu contributif.

Le bilan paraclinique confirmait une hyperkaliémie entre 5,6 et 6,8 mmol/L [normal 3,5–5,0] sans trouble électrolytique additionnel. La fonction rénale s'avérait normale avec une créatinine sérique à 79 µmol/L. Le pH sérique était normal. Une pseudohyperkaliémie a été exclue, étant donnée que la formule sanguine, les CK et la glycémie sont normaux. Le gradient potassique transtubulaire rénal fut calculé à 1,2, ce qui correspond à une excrétion rénale de potassium insuffisante, ou encore à un déficit en aldostérone. L'aldostérone sérique fut mesurée dans les limites normales à 207 pmol/L [normale 138–413], et la rénine sérique à 0,14 ng/L/s [normale 0,25–0,70].

L'ensemble du tableau clinique que présentait notre patient nous permis de conclure en la présence probable d'un syndrome de Gordon. L'hydrochlorothiazide fut débuté à 25 mg par jour, et deux jours plus tard, l'hypertension était normalisée avec des valeurs de 130/80 mmHg, ainsi que l'hyperkaliémie, qui demeura dans les valeurs normales au cours des mois suivants et ce, sans prise de Kayexalate. Un dépistage chez les autres membres de sa famille ne révéla aucun autre cas d'hypertension artérielle hyperkaliémique.

Discussion

Bien que le premier cas fût rapporté en 1964, le syndrome de Gordon fut décrit en 1970 en Australie par R.D. Gordon et coll. Depuis ce temps, plus d'une centaine de cas ont été décrits dans plusieurs pays, mais il s'agit ici du premier cas rapporté au Canada à notre connaissance. L'association des symptômes retrouvés comprend l'hyperkaliémie, l'acidose hyperchlorémique légère, qui se traduit par des bicarbonates entre 18–21 mmol/L, une filtration glomérulaire normale et, chez les adultes, le développement de l'hypertension artérielle. La petite taille, la faiblesse musculaire, l'hypoplasie des incisives, le retard intellectuel et l'hypocalciurie avec néphrolithiases peuvent accompagner ce syndrome, mais ne sont pas retrouvés dans tous les cas. La plupart des patients sont asymptomatiques, et l'investigation découle de la découverte d'une hyperkaliémie ou d'une hypertension artérielle, ou plus rarement à la suite d'un dépistage familial. Le diagnostic se pose habituellement à l'âge adulte, mais des cas de syndrome de Gordon se manifestant dès la naissance ont aussi été rapportés.

Depuis sa description, d'importants progrès ont été réalisés dans la compréhension des mécanismes physiopathologiques du syndrome de Gordon, quoique certaines incertitudes demeurent. Il s'agit d'un désordre génétique autosomal dominant. Jusqu'à maintenant, trois mutations ont été décrites, affectant les chromosomes 1q31–42, 12p13 et 17p11–q21. Toutes ces mutations semblent avoir un lien avec l'expression du cotransporteur Na-Cl sensible au thiazide, ou encore avec les kinases WNK-1 (*with no lysine [K] kinase* type 1) et WNK-4.

La kinase WNK-4, retrouvée dans le néphron distal, exerce une inhibition physiologique des canaux Na-Cl sensibles aux thiazides du néphron distal. Une mutation agit comme double inhibiteur, en produisant l'inactivation de l'inhibiteur. Une augmentation de la réabsorption de sodium et de chlore s'ensuit, créant une expansion volémique. L'hypertension artérielle en découle, ainsi que la suppression de l'axe rénine-angiotensine-aldostérone, se traduisant par un dosage de la rénine plasmatique inférieur à la normale. De plus, la quantité de sodium et d'eau atteignant le tubule collecteur est nettement diminuée, réduisant l'excrétion de potassium et d'ions H+ qui s'effectue habituellement à ce niveau en échange d'un sodium. Une autre hypothèse expliquant l'hyperkaliémie serait le rôle de WNK-4 directement sur ROMK (*renal outer medullary potassium channel)*, un des transporteurs chargés de l'excrétion du potassium dans le tubule collecteur. L'hyperkaliémie explique probablement que malgré un axe rénine-angiotensine-aldostérone supprimé, le dosage de l'aldostérone plasmatique se situe dans les limites normales ou supérieures, puisque la sécrétion d'aldostérone est aussi stimulée par l'hyperkaliémie.

Au sujet de l'auteur

Vanessa Tremblay est résidente 5 du programme de médecine interne à l'Université de Sherbrooke; internistes généralistes, Jean-François Lajoie et Luc Lanthier exercent au Service de médecine interne du Centre hospitalier universitaire de Sherbrooke, que dirige Luc Lanthier, et ils enseignent à titre de professeurs agrégés à l'Université de Sherbrooke.

Par ailleurs, la kinase WNK-1, retrouvée dans plusieurs tissus, mais particulièrement au niveau des cellules sensibles à l'aldostérone, participe aussi à l'homéostasie du chlore dans le rein. La WNK-1 favorise la réabsorption du chlore en abolissant l'effet inhibiteur de la WNK-4 sur les canaux Na-Cl. Une mutation se traduit par l'augmentation de la fonction inhibitrice de la WNK-1, favorisant l'activité des canaux Na-Cl et créant le même tableau que précédemment.

L'image clinique et physiopathologique qui en résulte est l'image miroir du syndrome de Gitelman, causé par la diminution du fonctionnement des canaux Na-Cl, et se présentant avec une hypotension, une hypokaliémie et une alcalose métabolique.

Le diagnostic du syndrome de Gordon doit s'appuyer sur les manifestations cliniques et biochimiques. Il peut être confirmé par une correction complète des anomalies métaboliques et de l'hypertension artérielle suite à la prise de diurétiques thiazidiques, et ce, dès les premiers jours du traitement. Peu importe le degré d'hypertension artérielle initial, le thiazide seul est habituellement efficace pour obtenir une normotension, bien que des doses d'hydrochlorothiazide allant jusqu'à 50 mg par jour puissent être nécessaires.

En résumé, le diagnostic d'hypertension hyperkaliémique familiale, ou syndrome de Gordon, doit être évoqué en présence d'hypertension artérielle et d'hyperkaliémie chez un patient ayant une fonction rénale normale. L'hyperfonctionnement des canaux Na-Cl du néphron distal peut facilement être renversé par les diurétiques thiazidiques qui permettent la résolution complète des manifestations de ce syndrome.

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Case Review

Unravelling the Gordonian Knot

Vanessa Tremblay, MD, Jean-François Lajoie, MD, Luc Lanthier, MD

Gordon's syndrome, also referred to as type II pseudoaldosteronism, is characterized by hypertension and hyperkalemia in a person with normal renal function. We describe here the case of a young man who presented for treatment with this rare association of hypertension and hyperkalemia.

Clinical Case

A 29-year-old man was referred to us after a routine check-up by his family doctor detected hyperkalemia. Sodium polystyrene sulfonate (Kayexalate) was started, without benefit. The patient was not taking any medications or natural products, and his diet was not high in potassium. He did not have any known illness, but he had abused alcohol and cocaine up until the previous year. His mother had hypertension, but no members of his family had abnormal potassium levels.

His physical examination revealed hypertension (based on repeated measurements), ranging from 150–170/90–110 mm Hg, complicated by grade I hypertensive retinopathy. The remainder of the physical examination was unremarkable.

Laboratory testing confirmed serum potassium levels between 5.6 and 6.8 μmol/L (normal range 3.5–5.0 mmol/L) , and no other electrolyte abnormalities. Renal function was normal, with serum creatinine at 79 mmol/L. Serum pH was normal. Pseudohyperkalemia was excluded because the complete blood count, creatine kinase, and blood glucose levels were normal. The renal transtubular potassium gradient was calculated at 1.2, indicating insufficient renal potassium excretion, or even an aldosterone deficit. Serum aldosterone (207 pmol/L, normal range 138–413 pmol/L), and serum renin (0.14 ng/L/s, normal range 0.25–0.70 ng/L/s) were both normal.

Our patient's clinical presentation suggested the diagnosis of Gordon's syndrome. Hydrochlorothiazide was started at 25 mg daily. Two days later, his blood pressure came down to 130/80 mm Hg. Potassium values were normal during the following months without the use of Kayexalate. A review of family members did not uncover other cases of hyperkalemic hypertension.

Discussion

Although the first case was reported in 1964, Gordon's syndrome was described in 1970 in Australia by R.D. Gordon et al. Since then, more than 100 cases have been described in several countries, but our patient is the first reported case in Canada, to the best of our knowledge. Features of the syndrome include hyperkalemia, a slight hyperchloremic acidosis (bicarbonates 18–21 mmol/L), a normal glomerular filtration rate and, in the case of adults, hypertension. Small body size, muscular weakness, hypoplasia of the incisors, educational retardation, and hypocalciuria with nephrolithiasis can accompany this syndrome in some cases. The majority of patients are asymptomatic. The diagnosis is usually made when the patient is an adult, but cases of newborns with Gordon's syndrome have been reported.

Subsequent to its initial description, significant progress has been made in understanding the physiopathological mechanisms of Gordon's syndrome, although some uncertainties linger. The syndrome is an autosomal dominant genetic disorder. Until now, three mutations have been described involving chromosomes 1q31–42, 12p13, and 17p11–q21. All these mutations seem to have a link with the expression of the thiazide-sensitive Na-Cl co-transporter, or even with WNK1 kinase (*with no lysine [K] kinase* type 1) and WNK4 kinase.

WNK4 kinase, located in the distal nephron, physiologically inhibits the thiazide-sensitive Na-Cl channels of the distal nephron. A mutation acts as a double inhibitor by deactivating the inhibitor. An increased absorption of sodium and chlorine ensues, creating a fluid expansion. This results in hypertension and the suppression of the renin-angiotensin-aldosterone axis, evidenced by a below-normal plasma renin activity. In addition, the supply of sodium and water to the collecting tubule is sharply decreased, thus reducing the potassium and H^+ ion excretion normally achieved here by means of a sodium exchange. Another hypothesis explaining the hyperkalemia points to the direct effect that WNK4 has on the *renal outer medullary potassium channel* (ROMK), one of the transporters responsible for potassium excretion in the collector tubule. Hyperkalemia probably explains why, despite a suppressed renin-angiotensin-aldosterone axis, plasma aldosterone activity is normal or above normal since aldosterone secretion is also stimulated by hyperkalemia.

Moreover, WNK1 kinase, found in several tissues but especially near aldosterone-sensitive cells, also contributes to the homeostasis of chlorine in the kidney. WNK1 promotes the absorption of chlorine by abolishing the inhibitory effect of WNK4 on the Na-Cl channels. A mutation is evidenced by the increase of the WNK1 inhibiting function, which fosters Na-Cl channel activity and creates the same clinical presentation as above.

The resulting clinical and physiopathological picture is the mirror image of Gitelman's syndrome, which results from reduced functioning of the Na-Cl channels and is evidenced by hypotension, hypokalemia, and metabolic alkalosis.

A diagnosis of Gordon's syndrome must be based on clinical and biochemical manifestations. It may be confirmed by a complete correction of the metabolic anomalies and hypertension within days by treatment with thiazide diuretics. Regardless of the initial level of hypertension, thiazide alone is usually effective in achieving normotension, although hydrochlorothiazide in doses up to 50 mg per day may be necessary.

In summary, familial hyperkalemic hypertension, or Gordon's syndrome, must be diagnosed if a patient with normal renal function presents with hypertension and hyperkalemia. The hyperfunctioning of the distal nephron's Na-Cl channels can easily be reversed with thiazide diuretics, which allow for the complete resolution of this syndrome's manifestations.

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My First Year in Practice

An interview with Laura Heemskerk, MD

Hector Baillie: Where are you from, and where did you do your training, Laura?
Laura Heemskerk: I'm actually from Prince Rupert, British Columbia, but grew up in Victoria. I went to medical school at UBC; then did my internal medicine residency and fellowship in Calgary.

HB: You chose to become a general internist. What influenced you in this decision?
LH: I had originally gone into internal medicine with the intention of doing oncology. I had Hodgkin's lymphoma in first-year medical school and felt that my personal experience would help me provide good care for my patients. Although I loved oncology, I realized it would be difficult for me to work only with cancer patients and began looking for something else. I enjoyed most rotations but was always a little frustrated when I was told to ignore an issue because it didn't pertain to that subspecialty. I wanted to stay broadly focused. In addition, I have a strong interest in medical education and found that GIM offers an abundance of teaching opportunities. Calgary has many great role models in GIM who are active, interesting people and excellent teachers and who I got along with very well. This, and the wealth of job opportunities in GIM in Canada, helped me decide.

HB: Where did you work in your first year?
LH: My husband and I decided to move to St. John's, Newfoundland, after residency. Brian is from Newfoundland and was excited to return there as an emergency physician. I had a locum position at the Health Science Hospital at Memorial University as a general internist. In the first month, there was a shortage of hematologists, so I became the attending physician on the inpatient hematology service. This was followed by a month on the medicine service, where there were excellent opportunities for teaching.

I moved on to a locum position in Calgary, where I had trained. Returning to a familiar environment was certainly more comfortable. I spent some time on the medical teaching team, in outpatient clinics and on the consult service. We considered staying in Calgary, but there were no long-term positions for an emergency physician. Since both of us had trained in Lethbridge, Alberta, and knew what to expect, we decided to move there. It is close to Waterton and Fernie – so we knew there would be good places to enjoy our time off! The Chinook Health Region offered us positions that suited our lifestyle and our professional goals, and in November 2006 we bought a house and began work.
Lethbridge is a semirural town of 80,000 people. As an internist, I have a broad scope of practice that includes intensive care, general medicine call, outpatient general medicine, preoperative assessment, and a heart function clinic. I also coordinate family practice and GIM resident training programs. All in all, it is busy but very rewarding.

HB: Did you feel your residency prepared you well for community GIM?
LH: GIM is a different entity in different places, between sites, between hospitals, and between provinces. I think it's hard to prepare someone for all types of GIM practice. When I took my fellowship, I planned to stay in Calgary – however, I was able to make the transition to a community hospital with only a moderate amount of stress. If I had known in advance that I would be practising so much critical care, I would have done some extra training. A few times I've felt out of my depth, but a phone call to an intensivist in Calgary was usually all I needed. Initially, I was nervous doing procedures, but then realized I had done most of them in my residency training. It would have been nice to have extra training in endocrinology and cardiology, where Lethbridge lacks subspecialty support. As far as the business of medicine is concerned, I joined an office when I moved here, which helped a lot. My fellowship director had me shadow bill during my "junior attending" rotations, so I had some idea of what to do.

HB: What was your most interesting case? Your worst moment?
LH: My most difficult case was a 16-year-old girl, 32 weeks pregnant, that I admitted to the ICU with hypoxemic respiratory failure. She had ARDS from an influenza A and B coinfection. I had already been on call for 36 hours when she arrived at the hospital in extremis. Once intubated, she proved difficult to oxygenate, despite optimal ARDSNet settings. Since she was too unstable for transport to Calgary, and lacking an oscillator and nitric oxide, I spent the rest of the night managing her with advice from my colleagues in Calgary. We discussed ventilator settings and recruitment manoeuvres and anguished over whether she would be better off if we delivered the baby. In the morning, she was unchanged but able to be helivac'ed to Calgary. My worst moment – telling her mother that, despite our efforts, she and the baby might not survive. Miraculously, she did, and became one of my most interesting cases! They delivered her baby and put her on ECMO for over 2 weeks. Her ARDS gradually resolved, and she began to improve. Not surprisingly, she had many complications from this illness but is now medically doing quite well.

HB: What would you have done differently, knowing what you know now?
LH: With a practice in Lethbridge, I would have liked more ICU training. That being said, training has to end sometime and I was ready to see what the "real world" was all about. I think, in retrospect, that I should have eased into practice at a more gradual pace. This might have reduced some of the stress of my first year. I took on anything I was asked to, and ended up being really busy right away. It was overwhelming, and I had to back out of some commitments until I felt more comfortable.
I also wish I had invested in real estate in Calgary when I moved there 6 years ago!
HB: Don't we all! Thanks for your thoughts.

Venous Examination for the Internist

Margot R. Roach, MD

Examination of the *internal jugular vein for pressure and pulsation* is part of heart examination. This vein has no valves, so the right atrial pressure can be accurately measured. Since all veins collapse to a large extent when not full, the upper level of the distended vein gives the pressure and the atrial pulsation is visible at the junction. The a wave is synchronous with right atrial contraction, vanishes with atrial fibrillation, and is amplified with tricuspid stenosis. The v wave is produced by ventricular contraction and is amplified with the reflux of blood into the atrium with tricuspid insufficiency (Figure 1). Other waves can be recorded but are not visible. The examination should be started with the patient horizontal and the vein full, and then the head of the bed raised until pulsation appears. The vertical distance from there to heart level is the venous pressure.

If the neck is short, or obese, it may be difficult to see the internal jugular vein. If so, the venous pressure, but not the waves, can be estimated crudely but when the *hand veins* collapse. The arm is first hung down over the side of the bed, then slowly raised (with the wrist pronated and elbow straight) until the veins just collapse. The venous pressure is roughly the vertical distance from there to the heart. There are valves in the arm veins; these prevent accurate measurements, and venous pulses are not visible.

All veins are *compliance vessels*.[1] They collapse when empty (Figure 2) and distend as the blood volume increases, with little change in pressure (Figure 3). Normally the veins hold about 64–75% of the total blood volume, and much of this is in the *splanchnic bed* – which cannot be examined. The *cutaneous veins* are important for heat regulation. They dilate if skin or core temperature increases, allowing heat loss to the surrounding air. Failure to do so puts the patient at risk of heat stroke. The *muscular veins* are a crucial part of the series circuit that carries blood from the limbs back to the heart. Disease here is of major importance as thrombosis can lead to pulmonary embolus and, in the presence of arterial disease or severe edema, can further reduce circulation. Varicosities, particularly in the legs, can predispose to edema, thrombosis, venous ulcers, and postphlebitic syndrome. The last two will be discussed in the next paper, on microcirculation. In orthopedic patients particularly, internists are often consulted pre- and postoperatively to prevent these complications. Remember that venous pressure is low in the horizontal position, yet may approach 100 mm Hg when a tall person stands up. By contrast, the intracranial venous pressure is lower when standing.

Phlebitis is easily diagnosed as it leads to pain, heat, and tenderness. The most common cause in hospital is from the administration of intravenous drugs, usually in the arms. *Thrombosis* (with or without phlebitis) is more common if venous flow is stagnant, starting near the valves, and spreads proximally. Unless thrombosis is associated with phlebitis, it rarely is painful or tender. Obstruction increases capillary

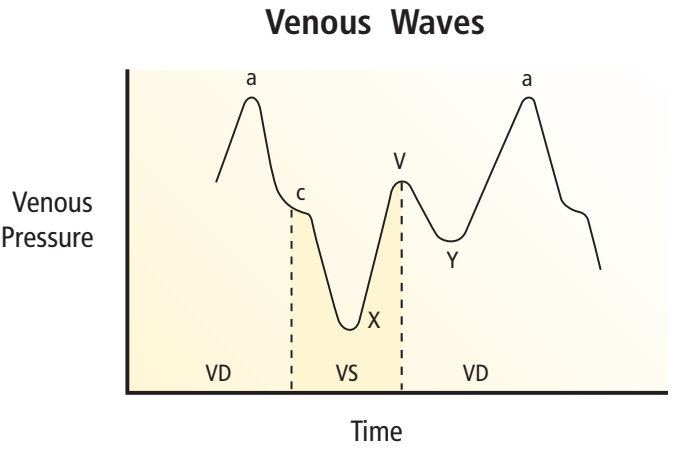

Figure 1. Venous pulsation as recorded by a pressure transducer. Only the a and v waves are visible on physical examination. A waves are larger in tricuspid stenosis, v waves in tricuspid insufficiency. VD = ventricular diastole; VS = ventricular systole.

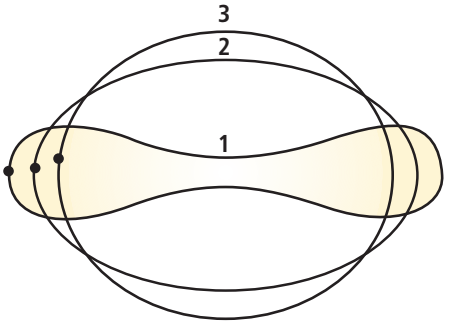

Figure 2. Virtually all veins collapse if incompletely filled. However, there are usually small open channels shown at the edges here that allow the venous column to be continuous and so act as a siphon. The vein is biconcave at low pressure (1), then elliptical when partially filled (2), and then distended and almost circular (3).

About the Author

Margot 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 at 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.

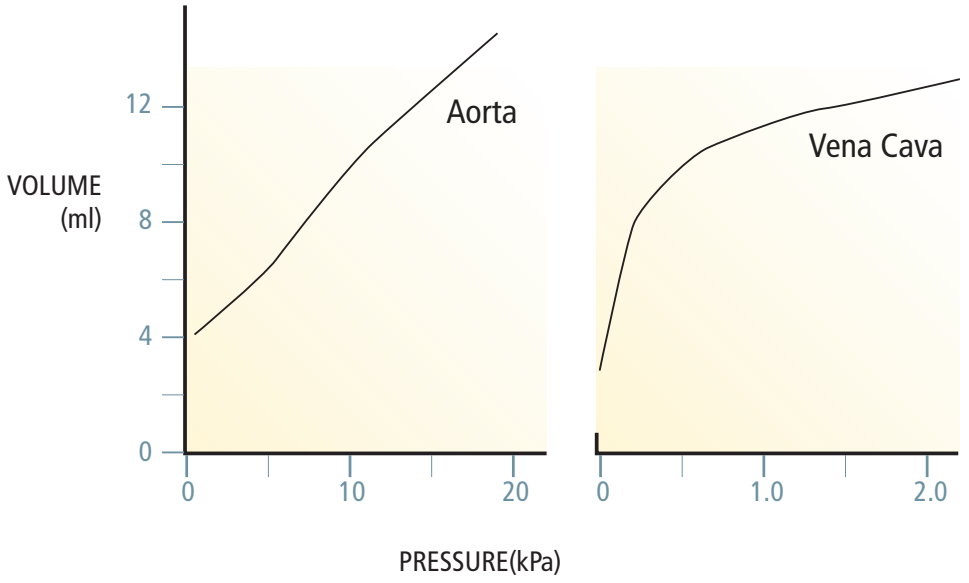

Figure 3. Comparison of the volume-pressure curves of rabbit aorta and vena cava. Note the difference in pressure scale (1 kPa = 13.3 mm Hg). Modified from Burton.[2] I obtained similar shaped curves from human common iliac arteries and veins (unpublished). Note that the aortic curve is linear, while the vena caval one is very nonlinear, with the inflection point where the slope changes, coinciding with the time when the vein is first fully distended, and then stretching minimally before it becomes very stiff and the pressure in it rises dramatically (personal observation).

pressure, and edema results. *Because of the risk of pulmonary embolus, it is crucial to diagnose it early*. The most subtle sign, in my experience, detectable several days before the leg is clinically swollen with pitting edema, is what I call the "Roach sign" – since I have not read of it elsewhere. As fluid moves out of the vessels, the surrounding tissue becomes viscoelastic rather than elastic. This means that, unlike a rubber ball that, if tapped, recovers as fast as the finger is removed, it is more like bread dough, or new bread, which does not recover quickly. Successive light taps do not feel the same as the recovery is more sluggish than normal. You can test this by comparing tapping a new firm mattress and a soft pillow. In a patient compare the two legs, or different regions of the same leg. It takes practice but is well worth learning. Later, pitting will develop, and later still increased girth. Girth should be measured at least once a day, with the early morning measurement being the most reliable. It is important to put ink marks front and back on the leg in three spots below the knee and one mid-thigh so that measurements are always made in the same location. Obviously, if the patient is bedridden, the ankle edema seen in upright or sitting patients is less apt to develop, but instead it will be on the dependent undersurface of the leg.

Homan's sign (pain in the calf on sudden dorsiflexion of the ankle) is usually positive if there is an element of phlebitis but may not be so if there is primarily thrombosis. The same is true of the *pressure cuff test*, in which a cuff is placed on the calf and inflated to determine the level and pressure at which pain is produced. ***I believe this test should never be carried out as it is very prone to dislodge the clot and lead to an embolus.*** Distension of the vein can loosen the clot, which may then travel caudally when the cuff is deflated.

Normal veins are compressible and so not palpable unless greatly distended. However, *thrombosed veins are not compressible* and so are easy to feel unless there is a lot of edema or the patient is very obese. In the posterior calf, they are best felt with the ankle plantar flexed and the knee and hip flexed to relax the overlying muscle. Again, ***be cautious so as not to dislodge a loose clot***. In the groin they are best fell with the hip and knee flexed.

Veins have nonlinear *pressure-volume curves*, that is, pressure is constant until the vein is filled; then with a rapid rise in pressure, there is a *marked increase in length with only a small change in diameter*. This is in contrast to arteries, which distend more in diameter than in length (and so can become aneurysmal). This increase in the length of veins explains the tortuosity so commonly seen in varicose veins. Note that the vein is only visible when it is distended, so it is important to examine the leg veins in both the supine and vertical positions. The superficial veins are most often varicose, and this overdistension makes the valves joining them to the deep veins incompetent; they fill from the deep veins, which normally empty as the muscles around them contract. Once the deep vein empties, the superficial veins empty into them. Normally, the superficial leg veins empty with walking, whereas they fill in patients who have varicose veins. This decreases flow from the legs and therefore predisposes to stagnant flow and resulting thrombosis. Previous venous disease, elevated venous pressure (right heart failure or increased intra-abdominal pressure), and hypercoagulable states also predispose to thrombosis and should be assessed preoperatively and, if possible, corrected. Pressure stockings help decrease filling of the superficial veins and thereby improve flow in the deep veins. Frequent ankle flexion helps the muscle pump improve flow in the deep veins.

Venous ulceration and postphlebitic syndrome are late stages of venous disease and are usually associated with alterations in the venules. This will be discussed in a subsequent article, "The Examination of Microcirculation."

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Heart Failure in Older Adults

George A. Heckman, MD, Catherine Demers, MD, Robert S. McKelvie, MD, David B. Hogan, MD

Despite a decline in overall cardiovascular mortality in developed countries, the burden of heart failure (HF) has continued to rise.[1,2] HF affects over 1% of the Canadian population, and its prevalence rises sharply with increasing age.[3–5] Population aging and the longer survival of patients with cardiovascular disease are the primary factors underlying its rising prevalence.[1,2,6] The mortality, morbidity, and economic costs of HF are substantial. [7] It is the most common cause of hospitalization among patients aged 65 years and over, while patients aged 75 years and over account for two thirds of total hospital days for HF.[8,9] One-year mortality following a first hospitalization for HF exceeds 30%.[10] Among older patients with comorbidities such as diabetes mellitus, renal insufficiency, peripheral vascular disease, and dementia, mortality rates can exceed 60% during the year following hospitalization.[10,11]

Treatment recommendations for HF in older patients are typically extrapolated from the results of large clinical trials, which often excluded them,[12] as well as from smaller trials and observational studies.[13] Using standard strategies for HF in older patients, many of whom suffer from other conditions, raises concerns about polypharmacy. Few studies have examined the impact of HF therapy on outcomes such as functional impairment and cognitive decline, which may be of greater relevance to older patients than prolonging life. The purpose of this article is to review some of the challenges encountered in managing older patients with HF, with particular emphasis on frailty, functional decline, and cognitive impairment (CI).

Heart Failure, Frailty, and Functional Decline

Frailty is a state of increased vulnerability due to reduced physiological reserve.[14,15] Following a stressful event, such as a hospitalization, frail individuals are at increased risk of adverse outcomes including progressive loss of their ability to perform basic and instrumental activities of daily living (ADLs).[16–18] Overburdened caregivers, particularly spouses, of frail seniors also face an increased risk of adverse health consequences, including death.[19]

There is an association between frailty and HF. Sarcopenia, the loss of muscle mass, is a common feature of both frailty and chronic HF. In both, it is associated with reduced physical activity.[20,21] In the Cardiovascular Health Study, a large group of community-dwelling seniors (mean age 72.7 years) underwent an extensive cardiovascular and frailty assessment.[22] The investigators found that patients with a past history of HF were more likely to be categorized as frail (odds ratio [OR] 7.51).

Patients hospitalized with HF often experience functional decline and require ongoing assistance following discharge. A 1-year prospective study of 178 older (mean age 75.6 years) patients discharged from an acute care facility found that those with HF were more likely to develop further dependency in ADLs (OR 2.07).[23] A review of US Medicare claims revealed that 13% of patients required home care services after a first hospitalization with HF.[24] Nearly 11% of older patients (mean age 75 years) hospitalized with HF in Nova Scotia were discharged to a long-term care facility.[25]

Frail patients with HF are more likely to present in an atypical manner.[1,26,27] Sedentary patients may not experience exertional dyspnea, and edema may accumulate over the sacrum rather than at the ankles. Edema is also not a specific sign as it can arise from venous insufficiency, treatment with calcium-channel blockers, reduced oncotic pressure due to malnutrition, or pulmonary disease. Nonspecific sleep disturbances may occur instead of classic orthopnea or paroxysmal nocturnal dyspnea. Nocturia can reflect the mobilization of peripheral edema in the recumbent position.[28,29] A study of older hospitalized patients showed that atypical presentations (i.e., delirium, functional decline, falls, and decreased mobility) occurred in 59% of frail patients compared with 25% of other patients ($p < .001$).[26] Cardiovascular disorders, including HF, accounted for approximately one third of their underlying diagnoses (personal communication from Kenneth Rockwood, Department of Medicine, Dalhousie University).

Heart Failure and Cognitive Impairment

Cognition refers to the intellectual abilities required to function independently within one's environment. It includes memory, language, attention, visuospatial ability, and executive functions such as abstract thinking, planning, problem solving, insight, and judgment.[30] Syndromes of CI can be differentiated based on their time course. Delirium is a syndrome of acute and fluctuating CI, often precipitated by an underlying illness such as acute HF.[31] Delirium can be reversible if the underlying precipitant is diagnosed and treated, although recovery may take months and may never be complete.[31] Chronic CI is referred to as *dementia* if it interferes with a person's independence and as *mild cognitive impairment* (MCI) or *cognitive impairment not demented* (CIND) if independent function is retained despite documented cognitive deficits.[32]

Older patients with HF have an increased risk for CI. Cross-sectional studies using global cognitive measures such as the Mini-

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Mental State Examination (MMSE) show that its prevalence in hospitalized older patients with HF is greater than that found among patients without HF and may exceed 50%.[33–35] The severity of the CI correlated with the severity of left ventricular systolic dysfunction[33,34] and NYHA symptoms.[35] Many of these patients may have been suffering from delirium. In addition, older patients with HF are at increased risk of chronic CI.[36–39] In a randomly selected community sample, over 1,000 older participants (mean age 74 years) were assessed for both a history of HF and CI (as determined by their MMSE score).[36] A history of HF was associated with an increased risk of CI (adjusted OR 1.96). In the Italian Longitudinal Study, those with a history of HF were more likely to have CIND (OR 1.73).[37] The Helsinki Aging Study followed 650 randomly selected community-dwelling seniors.[38] A history of HF was associated with a higher risk of cognitive decline over 5 years (relative risk [RR] 1.83). Finally, in the Kungsholmen project, community-dwelling seniors (mean age 82 years) were followed up for 5 years.[39] None had a prior history of dementia, while 205 had a history of HF. Those with a history of HF were more likely to develop dementia during follow-up (hazard ratio [HR] 1.84).

CI in HF patients increases the risks of rehospitalization, progressive disability, and mortality.[40–43] This might arise because CI interferes with the ability of patients with HF to adequately self-manage their illness. Cognitive domains impaired in patients with HF include memory, attention, processing speed, learning, and executive function.[44] These deficits may interfere with a patient's ability to adhere to a prescribed lifestyle and dietary restrictions, medications, and regular weighing and to recognize symptoms of decompensated HF. If delirium develops early in the course of HF, initiation of appropriate HF therapy may be delayed. Patients may not recognize their illness (and take appropriate action) and health care providers may fail to recognize HF as the precipitant of the delirium. Rehospitalization for HF has been associated with both medication mismanagement and the failure to recognize early symptoms and to seek timely medical attention.[45–50]

Assessing Elderly Patients with HF

The association of frailty, functional impairment, and CI with HF in older patients has important clinical ramifications. HF should be considered in the differential diagnosis of patients presenting with atypical signs and symptoms.[26] When assessing such a patient, it is important to obtain collateral information regarding baseline cognitive function and ability to perform ADLs. The CSHA Clinical Frailty Scale (Table 1), a brief seven-item instrument, can be used to assess the patient's degree of frailty.[51] An important step in the evaluation of CI in a hospitalized patient is to determine its onset.[31] The Confusion Assessment Method (CAM) (Table 2) is a simple yet accurate screening instrument for delirium.[52] Even among patients whose clinical status has improved sufficiently to consider hospital discharge, clinicians should consider looking for CI by using a brief cognitive measure. The Montreal Cognitive Assessment (MoCA) may be more sensitive than other brief measures such as the MMSE in detecting subtle yet important degrees of CI.[53] The MoCA requires little training to administer, and a short version can be performed in about 5 minutes.

Table 1. The CSHA Clinical Frailty Scale

1. Very fit – robust, active, energetic, well motivated, and fit; these people commonly exercise regularly and are in the most fit group for their age
2. Well – without active disease but less fit than people in category 1
3. Well, with treated comorbid disease – disease symptoms are well controlled compared with those patients in category 4
4. Apparently vulnerable – although not frankly dependent, these people commonly complain of being "slowed up" or having disease symptoms
5. Mildly frail – with limited dependence on others for instrumental activities of daily living
6. Moderately frail – help is needed with both instrumental and noninstrumental activities of daily living
7. Severely frail – completely dependent on others for activities of daily living, or terminally ill

Table 2. Confusion Assessment Method (CAM): A Diagnosis of Delirium Requires Features 1 and 2 Coupled with 3, 4, or Both

1. Acute onset and fluctuating course – information obtained from a reliable source
2. Inattention – difficulty focusing attention
3. Disorganized thinking – disorganized, incoherent, rambling/incoherent conversation, illogical/unclear reasoning, and unpredictable switching
4. Altered level of consciousness – anything but alert

Managing Elderly Patients with HF

Evidence from small randomized trials and observational data consistently supports the benefits of standard HF therapies, particularly angiotensin-converting enzyme (ACE) inhibitors and beta-blockers, in older patients.[13] ACE inhibitors may be particularly effective in maintaining function and protecting cognition.[44,54] Following HF guidelines such as the Canadian Cardiovascular Society Recommendations on Heart Failure will lead to the use of multiple medications. A medication review is essential to ensure optimal HF therapy and to minimize the risk for adverse drug reactions and interactions. Nonsteroidal anti-inflammatory drugs including cyclo-oxygenase 2 inhibitors, thiazolidinediones (glitazones), antiarrhythmic drugs, and first-generation calcium channel blockers should be used cautiously, if at all.[13] Older patients receiving HF combination therapy should be followed up closely for changes in renal function and fluid/electrolyte abnormalities. The experience seen in Ontario, where following the publication of RALES (Randomized Aldactone Evaluation Study) there were an estimated 560 additional hospitalizations and 73 deaths from hyperkalemia in 2001 alone, underlines the importance of appropriate prescribing and close monitoring.[55]

Hospitalized patients with HF with risk factors for delirium such as pre-existing CI should be identified. Simple and cost-effective manoeuvres have been shown to prevent up to 40% of incident cases.[56] For patients with significant CI, clinicians should target their educational interventions to cognitively intact caregivers.[13] Adherence to prescribed therapy may be improved through the use of aids (i.e., dosettes or blister packs that are filled weekly and supervised by a

pharmacist or caregiver) coupled with ensuring adequate social support through family members or visiting nurses.[57] Referral of frail older patients to multidisciplinary HF management programs or specialized geriatric services should be considered, though the continued involvement of their primary care physician is essential.[13]

Conclusion

The course of HF can be complicated in older patients by concomitant frailty and CI. Understanding the nature and impact of geriatric syndromes on the assessment and management of HF is critical to optimal delivery of care to these patients. The potential for clinical improvements in the severity and expression of these and other geriatric syndromes underscores the importance of optimizing HF therapies in these patients.

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CanMEDS in Practice: A Template to Optimize Patient Care

Sharon E. Card, MD, Heather Ward, MD, Anne PausJenssen, MD, Lisa PausJenssen, MD, Jenny Basran, MD, William Dust, MD

Background

In the fall of 2005, the Orthopedic Trauma Service was amalgamated, from three acute care sites to one major teaching hospital in Saskatoon. This service included a high proportion of elderly patients with hip fractures, many of whom had serious medical comorbidities. As the workload on this service increased, there was a corresponding demand for general internal medicine (GIM) and geriatric medicine consultations. Both GIM and orthopedics residents were concerned about the impact such a change would have on their own educational objectives. Concurrently, geriatrics noted several areas where they felt the knowledge base of both resident groups was suboptimal.

Action Plan

The program directors of both orthopedics and GIM met to review issues. They agreed that they shared many educational and patient concerns, and they decided to develop a solution that would improve patient care and enhance resident education (and satisfaction). It was recognized that their shared concerns were linked to each of the CanMEDS competencies, and that these could be used as a template to identify problems and propose solutions (Table 1).

Conclusion

Feedback from both residents and attendings, for all services involved, indicated a much improved work environment and a perceived improvement in patient care. We encourage others to think of CanMEDS competencies not only as something to teach our residents but as a tool that can be used to improve patient management on our wards.

Table 1. CanMEDS Competencies: Examples of Concerns and Solutions

CanMEDS Competencies and Objectives	Mutual Identified Concerns	Solutions
Medical expert	• Perceived excess VTE • Delirium treatment suboptimal	• VTE prophylaxis routine initiated • Co-educational sessions
Communicator	• Timely consult questions not communicated to GIM • GIM not communicating plans and concerns effectively	• Sessions to review nature/constraints of each service • Orthopedic clinical nurse specialist liaison between services
Collaborator	• Two specialties not working together efficiently • Discharge plans not always complete	• Improved direct communication encouraged • GIM encouraged to supplement discharge summaries
Manager	• Team-based skills poor • Time-management skills problematic for GIM residents	• Specific communication of OR scheduling and priority patients requested • Orientation emphasized importance of triage
Health advocate	• Patient cohort who could not advocate for selves and were at risk for care gaps	• Jointly advocate for improved resources for this vulnerable patient group
Scholar	• Teaching workload of both faculties heavy • Potential research opportunities lost	• Joint educational sessions introduced and evaluated • Joint research projects encouraged
Professional	• Heavy workload tended to have specialties "blame" each other	• Understand each others' perspectives and roles to enhance patient care via group sessions with introduction of roles

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The Use of Estimated Glomerular Filtration Rate in Clinical Practice

Bryce A. Kiberd, MD, Steven D. Soroka, MD

The purpose of this review is to acquaint the reader with several caveats when using estimated glomerular filtration rate (eGFR) and clarify current recommendations for nephrology referral within this context.

Serum creatinine reflects a breakdown of muscle and has been used for decades as a way to measure kidney function. There is a large variation in kidney function from person to person for any given creatinine, particularly in young versus old, male versus female, and those who are healthy versus those with disease. The relationship is not linear such that small creatinine increases within the normal range of values (60–85 µmol/L) translate into considerable reductions in function, while larger increases (200–300 µmol/L) may reflect small changes in function. In both males and females, more than half of the kidney function is lost well before the creatinine reaches 150 µmol/L. Since the important measure of interest is the patient's GFR (kidney function), it makes sense to convert creatinine to an estimate of GFR (essentially the amount of fluid filtered by all the glomeruli per unit of time). Currently, there are two formulas: the well-known (and Canadian-made) Cockcroft-Gault equation and the more recently derived Modification of Diet in Renal Disease (MDRD) eGFR.[1,2] The four-variable MDRD eGFR requires knowledge of the patient's age, sex, and race and is reported as millilitres per minute per 1.73 m^2. This equation is emerging as the preferred method for estimating GFR as it is slightly more accurate and the patient's body weight is not required.[3]

How Accurate Is the eGFR?

The eGFR depends heavily on the serum creatinine. There is a relatively small day-to-day laboratory variation but a larger day-to-day biological variation (hydration, activity, diet, etc.) in the measurement of serum creatinine. This variability can result in sizeable variations in reported eGFR for some patients. Intercurrent illness or medications (i.e., nonsteroidal anti-inflammatory drugs) may also impact on function and result in transient increases in creatinine, which may translate into fluctuations of eGFR of >30 mL/min. This variation also limits the ability to detect small but significant changes in kidney function over time. Therefore, clinicians should perform several measurements if an abnormally low GFR is detected.

The formulas assume a steady state since only one creatinine value is used. To be indicative of chronic kidney disease (CKD), the eGFR should be low for >3 months. Recent studies show that eGFR accurately estimates the true GFR for kidney disease patients within 30% about 70% of the time and within 50% about 90% of the time.[4] For a true GFR of 60 mL/min/1.73 m^2, the eGFR may be outside the range of 42–78 mL/min/1.73 m^2 30% of the time. The equations are at best an approximation.

Is One Estimating Equation Better for Calculating eGFR?

The most common estimating equation is the Cockcroft-Gault formula. This formula has been widely used and validated, and clinical decisions on drug dosing are based on this method. It does require body weight, but there is no race correction. It is not quite as accurate (within 30% about 60% of the time) as the MDRD eGFR and is expressed as millilitres per minute (no body surface correction).[4] Both formulas perform better when the true GFR is <60 mL/min/1.73 m^2, although there is still considerable variation between 50 and 60 mL/min/1.73 m^2.[5] Both tend to underestimate function in healthy people but overestimate function in certain patients, including those with cirrhosis, the hospitalized, paraplegics, amputees, and those with malnourishment or cachexia.[5–7] The estimating equations are not as accurate in children or during pregnancy.[5,8] Most centres with nuclear medicine facilities can perform plasma clearances with radioisotope markers; however, even these are not perfect compared with traditional urinary clearance methods, and this degree of accuracy is not required in most clinical situations.

At What Level of GFR Should a Patient Be Referred to a Specialist?

The Canadian Society of Nephrology website has information available to internists and general practitioners.[9] Patients who should be referred include those with normal function but with significant proteinuria; those with acute kidney failure; those with CKD who cannot achieve ideal blood pressure (<130/80 mm Hg) control or tolerate an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB); and those with a progressive decline in function, especially if the cause is unknown. Because of the high risk of progression in patients with an eGFR of <30 mL/min/1.73 m^2, the nephrology community recommends referral to assess risk, prepare for dialysis or transplantation, and treat complications associated with kidney disease (anemia, hyperphosphatemia, acidosis, and hypocalcemia). These complications may occur at higher levels of

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Table 1. Classification of Chronic Kidney Disease by Severity

Stage	Description	GFR (mL/min/1.73 m^2)	Related Terms
1	Kidney damage with normal or ↑ GFR	≥90	Albuminuria, proteinuria, hematuria
2	Kidney damage with mild ↓ GFR	60–89	Albuminuria, proteinuria, hematuria
3	Moderate ↓ GFR	30–59	Early renal insufficiency
4	Severe ↓ GFR	15–29	Late renal insufficiency
5	Kidney failure	<15 (or dialysis)	Renal failure, end-stage renal disease, uremia

GFR = glomerular filtration rate.
Modified from Levey AS et al.[10]

eGFR, between 30 and 45 mL/min/1.73 m^2, and may be an indication for earlier referral.

In Addition to eGFR, What Other Factors Should Clinicians Be Aware of When Assessing ESRD Risk?

Table 1 shows the present classification scheme for CKD.[10] Presumably, patients with lower GFRs are at a greater risk for progression. However, a low eGFR is seen in many elderly patients (>75), who often will not progress to kidney failure but die of other causes.[11] Patients with CKD stages 1 or 2 (eGFR or >90 and 60–89 mL/min/1.73 m^2 and proteinuria) may be at a greater risk for progression than some patients at stage 3. In the MRFIT study, 1+ proteinuria on dipstick was associated with a bigger risk for end-stage renal disease (ESRD) than a low GFR.[12] The presence of both proteinuria and low GFR was associated with an even greater risk than either alone. Diabetes mellitus greatly increases the risk for progression to ESRD.[13] These higher at-risk patients benefit from an early initiation of ACE inhibitor therapy and control of blood pressure long before the eGFR falls below 60 mL/min/1.73 m^2.

Conclusion

We hope this brief discussion highlights the rationale for the use of eGFR and the important caveats when interpreting laboratory values. It is interesting to see that ESRD incidence rates have started to stabilize in Canada since 2000.[14] Some believe that better blood pressure control and more widespread use of ACE inhibitors/ARBs is the reason for this observation. However, there remain large numbers of inadequately treated patients. Increasing risk factors in the population such as obesity and diabetes mellitus may cause ESRD rates to increase again. Increased detection of CKD will have no impact without adequate treatment. It is this treatment gap that requires attention at all levels, including adaptation of healthy lifestyles and the administration of proven therapy at the specialty and primary care levels.

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Observations on the Transfusion Threshold at the Intensive Care Units of a Tertiary Care Teaching Hospital

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Anemia is a common problem in intensive care units (ICUs); 70% of patients admitted to US ICUs in 2000 had a hemoglobin level <120 g/L in the 48 hours following admission. Of these, 50% were <100 g/L.[1] Causes of this anemia are numerous: hemorrhage, extracorporeal circuits, inflammation leading to diminished erythropoietin production and alterations of iron store use, direct marrow infection, disseminated intravascular coagulation, and nutrition deficiency. Blood sampling is also a significant contributing factor for anemia in the ICU. Vincent et al. have shown that an average of 41 mL/d was lost through blood sampling; sicker patients have more blood loss from blood sampling.[2] Clinical consequences of anemia, when very severe (hemoglobin <60 g/L) are associated with decreased oxygen-distribution capacity and have been shown to be a critical component in mortality.[3]

Hebert et al.[4] compared a restrictive transfusion strategy (hemoglobin 70–90 g/L) with a liberal one (hemoglobin 100–120 g/L). In this study, the restrictive strategy was at least as effective and maybe superior to the liberal one, excluding patients with active coronary heart disease. Blood transfusions are not without consequences. Even if occurrence is low, viral infections can occur, albeit infrequently, as well as blood transfusion reactions and transfusion-related acute lung injury. Increased susceptibility to bacterial infection might be a genuine consequence. Shorr et al.[5] showed that one transfusion of red blood cells (RBCs) doubles the risk of acquired bacteremia. According to Taylor et al.,[6] it raises the risk up to six times of getting a nosocomial infection. It is actually thought that this can happen through depressed immune function in recipients of an RBC transfusion. However, no reduction in severe nosocomial infection was documented in this study, which compared the clinical outcome of patients before and after the Canadian Universal Leukoreduction Program.[7] Even if not associated with infections, there still exists a relationship between transfusion and poor outcome.[1,2,6,8,9] Given this literature, we undertook this study to determine if the restrictive use of RBC transfusion – that is, keeping the hemoglobin level between 70 and 90 g/L – has been translated in the practice of medical teams working in the ICUs of the Centre Hospitalier Universitaire de Sherbrooke (CHUS).

Study Design

This prospective observational cohort study was performed in the medical and surgical ICUs of the CHUS between September 25 and November 18, 2005. The CHUS, Hôpital Fleurimont, is a 400-bed tertiary care teaching hospital consisting of 30 adult intensive care beds distributed in two units: medical (16) and surgical (14). Patients receiving RBC transfusion during their ICU stay were identified by the in-hospital blood bank. Exclusion criteria were patients <18 years old, those who were pregnant, those with active bleeding (defined as a clinical evidence of bleeding with a >30 g/L drop in hemoglobin in the 12 hours preceding the transfusion or the need for three or more RBC units at the same time), those with chronic anemia (hemoglobin <90 g/L measured in the month preceding the admission), and those with an ICU stay expected to be <24 hours. The research ethics committee approved this study.

Objectives

The primary end point of our study was to determine the threshold for RBC transfusion. Secondary end points were to document if the severity of the disease and the presence of coronary artery disease (CAD) influenced the transfusion threshold. We also wanted to identify the reasons why the medical team transfused their patients, and to determine whether an informed consent had been documented in the medical chart prior to transfusion.

Data Collection

Data were collected on transfusion events, defined as the set of transfusions administered on the basis of one hemoglobin level, until the hemoglobin was checked again. For each transfusion event, we noted age, sex, location before admission to the ICU (regular ward, emergency room, operating room, referring centre), admission diagnosis, and comorbidities. We also calculated the Acute Physiology and Chronic Health Evaluation II (APACHE II) score at the time of admission, the need for mechanical ventilation or hemodialysis, and the use of vasopressors at the time of the transfusion. We recorded the hemoglobin level before transfusion and the number of RBC units that were prescribed for each event. We also took note of the medication associated with bleeding and immunosuppressive medications that

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might have had a toxic effect on bone marrow. The reasons for transfusing patients were set into four categories: preoperative, comorbidities (CAD, heart failure, advanced age, shock), sepsis, and low hemoglobin. The latter category was reserved for cases where no indication was found in the medical chart.

Statistical Analysis

The statistical analysis was made with SPSS 14.0 software. Transfusion thresholds are reported as means ± standard deviations. A *t*-test was used to compare the transfusion thresholds. The proportion of transfusions given to patients with a hemoglobin >70 g/L was analyzed with a chi-square test, using a two-sided alpha level of .05. The *t*-test was also selected to evaluate the influence of CAD on the transfusion threshold, with a two-sided alpha level of .0167 (after Bonferroni correction). A Pearson correlation was used to look for a link between APACHE II scores and the transfusion threshold.

Results

During the 2-month period of our study, there were 183 transfusion events, for a total of 223 RBC units administered. Of these, 59 events were excluded, leaving a total of 124 transfusion events. Reasons for exclusion were active bleeding (48), chronic anemia (7), ICU length of stay <24 hours (2), or mixed reasons (2). In 107 events, a sole RBC unit was prescribed, leaving 17 events with the prescription of two RBC units without checking the hemoglobin level after the first unit.

Baseline characteristics of patients included in the study are described in Table 1. The number and location of transfusion events are described in Table 2. Table 3 shows the transfusion thresholds in both ICUs. The APACHE II score did not influence the transfusion threshold, but there was a significant difference in the thresholds between CAD and non-CAD patients. Patients with coronary artery bypass grafts (CABGs) ($n = 39$) were transfused at hemoglobin levels of 85.3 ± 10.6 g/L, whereas the levels for non-CABG patients were 76.8 ± 10.0 g/L ($p < .0001$).

If we consider the optimal threshold for transfusion to be 70 g/L, 77% of transfusions given were over this optimal threshold (Table 4); however, the threshold was lower for non-CAD patients. There were also 15 transfusion events occurring at a threshold of 95 g/L or more.

We did not find documentation of informed consent in the charts we reviewed. The reasons for giving blood were indicated in a minority of medical charts (12 of 124): preoperative (3), shock (3), heart failure (2), CAD (2), sepsis (1), and old age (1).

Discussion

The major end point of our study was to find out the transfusion threshold in our ICUs and to compare it with the current literature. Our mean transfusion threshold was 79.6 ± 10.9 g/L, which is lower than the 86 ± 17 g/L reported in the CRIT study (which looked in the clinical practice of RBC transfusion in the United States in 2000–2001).[1]

We found a significant difference in the transfusion thresholds between the medical and the surgical ICUs, even if there were fewer events in the medical ICU. This can be explained in part by different populations of patients, such as CABG cases. Indeed, the optimal threshold for these patients remains to be determined. Some studies, either retrospective or observational, suggested a higher mortality when

Table 1. Characteristics of the Patients

	Number ($N = 124$)	%
Age (yr)	70 ± 11	–
Male	77	62
Comorbidities		
Hypertension	103	83
Dyslipidemia	78	63
Coronary heart disease		
Stable	63	51
Unstable*	23	19
Peripheral vascular disease	50	40
Diabetes	39	32
Atrial fibrillation	33	27
Congestive heart failure†	28	23
Smoking	25	20
COPD	23	19
Chronic renal failure‡	18	15
Cancer	5	4
Cirrhosis	3	2
Location before ICU Admission		
Operating room	85	68.5
Transfer from another hospital	18	14.5
Emergency department	16	13
Ward	5	4
Severity of Illness		
APACHE II score	15 ± 6	–
Mechanical ventilation	75	61
Vasopressors	58	47
Renal replacement therapy (chronic or acute)	21	17
Admission Diagnosis§		
Cardiac surgery	41	33
Coronary bypass ± valvular surgery	39	31
Valvular surgery alone	2	2
Vascular surgery	26	21
Other surgery	14	11
Shock	12	10
Gastrointestinal condition	11	9
Trauma	10	8
Pneumonia	8	6
Acute MI/unstable angina	7	6
Acute renal failure	7	6
Acute pulmonary edema	1	1
Others	5	4
Drug on Admission		
ASA	90	73
Plavix	15	12
Anticoagulation (heparin or warfarin)	6	5

APACHE II = Acute Physiology and Chronic Health Evaluation II; ASA = acetylsalicylic acid; COPD = chronic obstructive pulmonary disease; ICU = intensive care unit; MI = myocardial infarction.
*Unstable angina or recent MI.
†Left ventricular ejection fraction (LVEF) <50%.
‡Creatinine >130 µmol/L.
§For 18 transfusion events, the patients had two diagnoses on admission.

Table 2. Transfusion Events According to Each Intensive Care Unit

	Intensive Care		
	Surgical	Medical	Total
Transfusion events (%)	92 (74)	32 (26)	124
Red blood cell unit (%)	102 (72)	39 (28)	141
Patients	43	19	60*

*Two patients were transfused at both the surgical and medical intensive care units.

Table 3. Hemoglobin Threshold for Red Blood Cell Transfusion*

	Mean Hemoglobin Threshold (g/L)		
Intensive Care Unit	All Patients	Cardiac Patients	Noncardiac Patients
Surgical	82.3 ± 10.2 (n = 92)	84.4 ± 10.2 (n = 69)	75.9 ± 7.2 (n = 23)
Medical	71.6 ± 8.8 (n = 32)	76.6 ± 8.3 (n = 18)	65.1 ± 3.6 (n = 14)
Total	79.5 ± 10.9	82.8 ± 10.3	71.8 ± 8.1

*p < .0001 for hemoglobin threshold for cardiac versus noncardiac patients; p < .0001 between the two intensive care units for hemoglobin threshold for all patients and hemoglobin threshold for noncardiac patients; p = .004 between the two intensive care units for hemoglobin threshold for cardiac patients.

Table 4. Rate of Transfusion Events Occurring at a Hemoglobin Threshold >70 g/L*

	Transfusion Events at Hb >70 g/L	
Intensive Care	Percentage of All Patients	Percentage of Noncardiac Patients
Medical	50 (16/32)	7 (1/14)
Surgical	86 (79/92)	78 (18/23)
Total	77 (95/124)	51 (19/37)

*p < .0001 between the two intensive care units.

the hemoglobin is low in the perioperative period of CABG surgery.[10,11] It is somewhat difficult to determine if the excess mortality can be attributed to the anemia itself or to the number of units transfused. Indeed, a recent study showed that each unit of red cells transfused is associated with an incrementally increased risk for adverse outcomes.[9] Furthermore, another study showed that there was no increase in mortality or morbidity when the transfusion threshold was set at 80 g/L versus 90 g/L.[12] Some other factors to explain differences between the surgical and the medical units might be explored. First, the majority of patients were admitted from the operating room. Even if they were included in the study, it is still possible that they had minor bleeding not noted in the chart but that prompted the medical teams to transfuse RBCs. Secondly, the ICU staff are distinct in each ICU.

We also found a significant difference between CAD and non-CAD patients. The ideal threshold for these patients is still a matter of debate. It is known that a hemoglobin level <60 g/L in patients with CAD who refuse RBC transfusions is associated with adverse outcomes compared with similar patients without CAD.[3] Furthermore, it has been shown that patients with CAD exhibit higher mortality when they have a hemoglobin level <95 g/L in the context of critical illness.[13] In the postoperative period, anemic patients with CAD had a higher mortality than non-CAD patients.[14] These data should be interpreted cautiously because the above studies were retrospective. The only prospective study including CAD patients is the TRICC study,[4,15] where no adverse outcomes were noted in CAD patients in the restrictive strategy group; but this latter group of patients was underrepresented.

Results regarding "consent to transfuse" are more difficult to interpret. There were no detailed descriptions in the medical charts, but it is possible that transfusion had been discussed with the patient before the surgery, or with the family in the case of ICU patients. Also, the reason for transfusing patients was not well described in the charts, possibly reflecting uncertainty regarding transfusion guidelines, or just empiricism.

The limits of our study are mainly the short period of observation, the small number of transfusion events in the medical ICU, and the unicentric nature of the study. Nonetheless, this study showed us that medical literature has influenced our practice and that clinicians in our centre tend to tolerate anemia to a level of 70–80 g/L, depending on the ICU. In the absence of clear evidence, the transfusion threshold for CAD patients and CABG patients should be individualized.

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Medical Humanities

Professionalism: Use It or Lose It

Jock Murray, MD

There has been increasing concern about the concept of professionalism in the past few years, voiced in the press, in medical journals, and in university circles. The nature of professionalism has changed over time as our responsibilities to our patients and to society have changed. Centuries ago, it was based on competence; medicine was a skilled trade providing a service to those who could afford it. Later, an element of altruism shaped professionalism so that the physician's knowledge and skill served those in need. In the past century, we have added the concepts of nobility of service and the democratization of medicine, which respects the autonomy of our patients.

However, there are widespread threats to this concept. The de-professionalization of medicine has been evident for some time, and physicians are becoming disheartened. Polls over the past decade have noted that many physicians would not recommend their children, or any young person, go into medicine. A profession in which many members would not encourage the next generation to follow them is a profession in serious trouble.

Many have commented that physicians have developed a siege mentality, worn down by the "hassle factor," fearing the Barbarians at the gate, worried about marginalization of physicians, and bruised by intrusion into their decisions about patients. This is not paranoia.

There *is* an increasing desire by other parties to have physicians function as skilled employees rather than as professionals. There *are* people outside the profession who want to redefine our role of physicians in a way that serves their interests. There *are* increasing external controls over the profession and its members. There *is* a growing atmosphere of complaint and malpractice. And there *are* increasing incentives that reward physicians for serving the "system" but in ways that may not best serve our patients.

The erosion of professionalism is coupled with a public attitude that sees us in a less positive light. Some say the peak of the Golden Age of Medicine was in the 1960s. At that time, the image of the doctor was the kindly, caring physician who had new and very powerful medicines in his black bag, eager to serve his patients and his community. On TV, physicians were represented by the idealistic Dr. Kildare and Dr. Marcus Welby.

What do we have today? As the public becomes more cynical about the role of physicians and the profession, with the backdrop of corporate medicine, competing insurance companies, de-insuring tactics, rising health costs, the uninsured and malpractice, how are doctors portrayed?

We have the TV medical dramas *ER, House, Nip/Tuck, Scrubs*, and *Grey's Anatomy*, where physicians are seen as self-absorbed and egotistical, more concerned with their own problems than those of the patients; moody, rude, argumentative, uncooperative, and disrespectful, not only to each other but to the patients as well. They argue out their impassioned lives, prejudices, and conflicts in front of patients – almost as if they were not there. Such unprofessional behaviour would clearly be unacceptable in real life and would prompt official complaints and very negative trainee evaluations. It might make good TV drama, but it is an awful display of professionalism. In addition, the public see on *Nip/Tuck* technologically adept and surgically skilled but entrepreneurial plastic surgeons whose motivation seems more financial than esthetic.

And what do you make of Dr. House? Here we see a new and disturbing image of the modern doctor. Dr. House is a seriously flawed physician, who seems to enthrall the public by his Sherlock Holmesian sleuthing while lashing out at staff, belittling students, and cynically snapping questions at patients. As I leave for the hospital in the morning, I pass a billboard for *House* that has him dishevelled and scruffy, saying to a patient with serious liver disease, "You're orange, you moron!"

Unfortunately, at a time when the public is losing faith, they see every night on their TV examples of doctors lacking professionalism, acting in a manner that suggests they are not worthy of trust, and who need to be brought under control. I realize that this is just TV drama, but it

reflects a public perception and it, in turn, reinforces the idea that professionalism, if not terminally ill, is sadly in need of medical attention.

This increasingly cynical public attitude toward the medical establishment is paradoxical. At a time when medicine and physicians can do so much more, when medical science has brought such remarkable advances, the trust and faith in all of this has waned. At a time when medical schools are spending many more hours on communication skills, ethics, and humanistic attitudes, we are seen as more distant and self-serving.

The concept of professionalism involves fundamental principles and responsibilities. First, you must be *competent*. A physician must be competent to offer the appropriate care to patients, and this competence is related to clinical skills, knowledge, technical ability, humanistic attitudes, and communication skills. But competence is not enough.

Primacy of patient welfare is the moral core of professionalism. You owe your first duty to your patients. Not to yourself, your practice, or your hospital. As advocates for your patients, you must speak out and act if there are decisions being made by agencies that are clearly not in the interests of good patient care. The old term *fiduciary responsibility* indicated that medical decisions must always be in the interest of the patient. This also respects patient autonomy and the rights of patients in the health care system, and in your interactions with them.

Another core concept is *social justice*. This means we are not just dedicated to the individual patient, but we have responsibility to all patients, and to society, as part of our social contract.

Doctors don't mean to be belligerent or uncooperative in our defense of professionalism. We can be good players, we can be collaborative, and we can be effective in health care change and in making organizations effective and successful. We can work effectively in many different structures and settings, whether in academic health care systems, government agencies, or non-for-profit organizations. But we must always have in our minds that we are professionals, and we must always act in the interests of our patients.

I want to emphasize that a "call to professionalism" is not "resistance to change." It is not a veiled attempt to protect the power and status of physicians. It is not an endeavour to return to another age characterized by elitism and self-interest, the "good old days." It is a call to practise the best medicine in the best interests of our patients.

It is our responsibility as individual physicians to defend professionalism. Those who would like to alter and undermine professionalism are not bad people – they have a different professional and ethical system, and we are fooling ourselves if we think we can make them adopt *our* ethical system and espouse the fundamental principles of medical professionalism. Our fundamental concepts are appropriate to medicine, just as the ethical system of business is appropriate for business, and the ethical systems of the legal community, and the military, and the police are appropriate for their constituencies. It is when one group with an ethical system becomes involved in – or, worse still, takes charge of – another group that we have difficulty. That's why the professional and ethical system of medicine would not work for the law, governments are not good at running business, the military should not be running governments, and, dare I say it, business should not be running medicine.

Business interests and the ethics that govern them are increasingly prevalent in medical practice today. It can be good business to be conscious of patient care and professionalism, but it is not their goal. Most would not be in the complex area of patient care if it were not profitable. In fact, from a purely business point of view, professionalism and the primacy of patient care are complex, frustrating, and diverting from goals and agendas that relate to boards of directors, shareholders, bottom lines, and profits.

But we can work together. We must first recognize and respect the ethical system and goals and professional ethics of each other and not delude ourselves that they are the same. We are not going to change the ethic of business to that of medicine, or vice versa.

Henry Kissinger talked about the way things were negotiated in the world, and about an American model and a European model. The American model was to have everyone sit around the table to hammer things out until everyone agreed and thought the same. The European model was to recognize that the French would always be the French, the English the English, the Germans the Germans, and so on. They were never going to think the same. So the approach was to recognize that fact and then see how they could still work together. In the complex world of health care, involving medicine, other health professions, government, business-oriented administrators, corporations, the pharmaceutical industry, and so many others, we need a European model that recognizes the different ethical systems and goals of each other, and reaches a consensus. If things continue as they are, however, the business ethic will try to erode further the concept of medical professionalism as being a hindrance to the smooth operation of a profitable business.

It is in the interest of the patients we are privileged to serve that we defend medical professionalism. But do we understand it well enough? I'm concerned that if I stopped a medical student, resident, or practising internist and asked if he or she believed that professionalism was a fundamental belief and a sacred covenant with patients, I would hope the answer would be "Absolutely!" But if I then asked for a definition of *professionalism*, there might be some shuffling and hesitation.

I see three major steps in the call to professionalism. Firstly, our universities and medical colleges need to recognize the importance of such a fundamental issue. Secondly, doctors need to know the concepts of professionalism and act these out in our lives, our practices, and our discussions. We should all be able to list and discuss the fundamental principles of professionalism, the responsibilities and commitments, and have them burned into our heads and hearts. We are able to remember the 12 cranial nerves, the 15 major causes of fatigue, and the 26 major causes of fever of unknown origin, so surely we can remember the fundamental principles and responsibilities on which professionalism is based, when they are central to our role as physicians. We can be forgiven for not remembering the 40 different causes of headache, but not for being unaware of the elements that make us medical professionals.

And not just list them – we must know their meaning and think of them when in discussions about medicine and decisions about patient care, in meetings and committees in our hospitals, in our medical organizations, and having coffee with others in our hospitals and clinics and communities. It is not enough to have a parchment defining professionalism nailed on the wall beside the AMA Code of Ethics, or

added to the curriculum as a lecture some afternoon, between the lectures on chronic obstructive lung disease and cirrhosis. It has to be a living thing in the profession and in our educational philosophy.

If we want professionalism to flourish, we must have physicians everywhere living out the concepts of professionalism in their daily lives and practices. We must be conscious that every day, every moment, we are role models for future physicians and for what professionalism is all about. Role models have great influence. If we do it correctly, students will emulate us for the rest of their lives. If we do it incorrectly, they will copy our bad habits and teach them to the next generation.

Thirdly, we need to incorporate these principles into our educational approaches, our admission processes, and the experience in all years of medical training. We should look more diligently than we have to the admission process that selects the next generation of physicians. We often say we don't know how to select the right kind of person, just the ones with the highest marks, but I am reminded of a senior physician who said, "I could select for those qualities if I could take the student with me for a weekend in my canoe. I could then see what they were made of."

So let's buy some canoes! I'm serious. If that's the way to select the best future physicians for their personalities, attitudes, and qualities, then let's buy some canoes. In some Chinese medical schools, the prospective students must work for a year as low-level workers in a hospital before applying to medicine so that they can see what they are made of.

You may smile at the idea of medical schools putting in large orders to L.L.Bean for canoes, but if not canoes, what? We have not spent enough time on the admission process. Despite attempts to change and broaden the process, it still really guarantees that we admit the intellectually brightest young people who have attained scholastic excellence. But the person in the street knows that the brightest people don't necessarily make the best doctors. I think we are too slow in picking up on something everyone else seems to know.

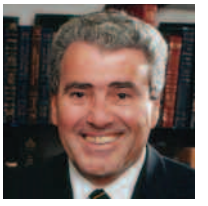
When I became dean of Medicine some 20 years ago, I first wanted to revamp our admission requirements. I knew we wouldn't take Mother Theresa unless she had organic chemistry and had gotten top grades. We made what were dramatic changes for our faculty, but the public instantly understood, and we saw results.

So, my message today is simple. We have a renewed definition of medical professionalism. Now it is up to each of us as individual physicians to know and practise our medical professionalism. If we don't know the concepts of professionalism, we will not be able to defend them, and we will see the elements of our professionalism whittled and negotiated away.

If we don't use it, we will lose it.

About the Author

T. Jock Murray is professor emeritus and the former dean of Dalhousie Medical School and former chairman of the Board of Regents of the American College of Physicians. He continues his clinical and research work in multiple sclerosis and writes on medical history and humanities.



Steroid Use in the Perioperative Period

Kelly Zarnke, MD

As an internist, you have been asked by your surgical colleagues to assess three patients prior to their upcoming surgery. In each case, the surgeon asks, "Should my patient receive perioperative steroids to avoid the risk of adrenal insufficiency?"

Mr. Anderson is scheduled to have a carpal tunnel release by the plastic surgeon at your hospital. The patient has rheumatoid arthritis and has been receiving prednisone 5 mg/d for the past 3 years. Ms. Barnes is due to have a semiurgent colectomy for refractory ulcerative colitis and has been taking prednisone 40 mg/d for the past 3 months. The patient exhibits clinical features of steroid excess and is unwell. Mr. Chan will undergo an elective total hip arthroplasty for osteoarthritis by your orthopedic surgeon. The patient has stable chronic obstructive pulmonary disease (COPD). However, he had three acute exacerbations around 6 months ago, and for each episode he received 50 mg prednisone daily for 10 days and none since.

For each of these patients, what recommendations would you offer to your surgery colleagues?

History and Pathophysiology

The adrenal extract cortisone has provided symptomatic relief to patients with rheumatoid arthritis since the late 1940s.[1] The first cases of iatrogenic adrenal insufficiency following abrupt preoperative withdrawal of chronic therapy were reported in the early 1950s.[2,3] The pathophysiology of adrenal crisis had been described almost 100 years previously by Addison. However, the application of this knowledge to the context of iatrogenic adrenal suppression and its implications in stress-induced situations were recognized only thereafter. Based on crude and preliminary estimates of maximal adrenal cortisol secretion, it is now customary practice for such patients to receive much higher doses of intravenous corticosteroids prior to, during, and often following surgical procedures.

Adrenal (or addisonian) crisis is characterized by severe and refractory intra- and postoperative hypotension. It is believed that endogenous glucocorticoids facilitate catecholamine-medicated vasoconstriction and cardiac inotropism.

The Controversy

Traditional recommendations have advised that patients on chronic steroid therapy should receive high doses of corticosteroid support perioperatively (e.g., hydrocortisone 300–900 mg). Such doses are historic, established on the basis of theoretical and pathophysiological rationales rather than empirical clinical data. More recently, various authors have argued that these conventional doses may be higher than necessary and may lead to small but significant risks of adverse effects. Lower doses of hydrocortisone may be adequate to prevent adrenal insufficiency.

The following reasons have supported traditional higher doses. First, early recommendations advocated a fourfold increase in the preoperative corticosteroid dose.[3] Thus, 300 mg of hydrocortisone per day (or equivalent) has been assumed to most closely mimic the maximal response of the adrenal gland to stresses such as surgery or trauma.[4–6] Second, adverse consequences of high-dose corticosteroids for short periods are considered to be small if not negligible. In fact, some authors have advocated a potential benefit.[7] Third, even with small risks of adverse steroid-induced sequelae, high-dose corticosteroids may be acceptable if the risk of adrenal crises is negated. Thus, Merli and Weitz, in their widely used guide to the medical management of surgical patients, espouse "lower doses of hydrocortisone [lower than 200–900 mg/d] … cannot be recommended."[8] Finally, hydrocortisone is inexpensive.

What are the arguments for a more conservative approach? First, advocates would cite the limited clinical data, as outlined below, as supporting the safety of lower doses. Second, not all surgery induces a maximal stress response. As anesthetic techniques have improved and many procedures such as cholecystectomies are now less invasive, the maximal physiological challenge is less often applicable. Third, the use of high-dose corticosteroids is not without hazards, including hyperglycemia, poor wound healing, psychostimulatory effects, aggravation of hypertension, drug interactions, and myopathy.[9,10] Given the prevalence of perioperative steroid use, the aggregate burden of adverse effects may be substantial.

What Does the Clinical Evidence Tell Us?

Among the large number of editorials and reviews of this topic, four clinical articles are helpful. Kehlet[11] reviewed 37 publications involving 57 steroid-treated patients experiencing postoperative hypotension, or death, putatively attributed to stress-induced adrenal insufficiency. The author concluded that the assignment of adrenal insufficiency as causal was highly speculative in the vast majority of cases and that convincing causal criteria was present in only three patients who received no perioperative corticosteroids. Although this review is dated, it is consistent with recent surveys that document a very low incidence of adrenal insufficiency in the perioperative setting.

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The second and third publications describe the clinical consequences in two case series of a planned conservative approach to steroid use in stress-inducing perioperative circumstances. Bromberg et al.[12] describes the outcomes of 40 renal transplant patients taking between 5 and 10 mg prednisone daily for at least 3 months. All received their usual dose of prednisone with no supraphysiological supplementation. No cases of adrenal insufficiency were reported. Hypotension occurred in seven of 40 patients, attributable to hypovolemia (fluid and blood loss), the vasodilating effect of anesthetic drugs, and/or sepsis. All hypotensive events responded to corrective interventions without additional steroids. Friedman et al.[13] studied the outcomes of 28 patients undergoing orthopedic surgery (arthroplasty, amputation) who had been taking an average of 10 mg of daily prednisone for the preceding 6 months or more. These patients were given their usual prednisone with no supplementation. There were no episodes of adrenal insufficiency and no "unexplained or unexpected" hypotension. Parenthetically, both reports suggest preoperative screening for adrenal reserve (i.e., cosyntropin testing) may be too sensitive and unreliable to be helpful for patient management.

The only randomized trial to date is by Glowniak and Loriaux.[14] Sixteen patients taking at least 7.5 mg prednisone daily for several months underwent 17 surgical procedures, mostly joint replacements and a variety of intra-abdominal procedures. All had positive cosyntropin testing in keeping with adrenal dysfunction. They were randomized to either their usual dose of prednisone or to 200 mg daily of additional perioperative cortisol. There was no statistically significant difference in blood pressure or heart rate between strategies, and the authors concluded that supraphysiological supplementation was unnecessary.

However persuasive the arguments against supraphysiological supplementation may seem, one must note important limitations in these studies. Post hoc conclusions around possible causal inferences made in Kehlet's review must be interpreted with caution. The two cited case series are small, and very few of the operative stresses would be considered severe. For example, there were few major visceral or intrathoracic procedures. Friedman et al.'s trial was limited by small sample size and a somewhat surprising asymmetric randomization. Furthermore, there was a trend toward better blood pressure in the cortisol-treated group, suggesting that caution should be exercised in making any firm conclusions.

Practical Recommendations

Despite the limitations of available evidence, a consensus opinion has emerged among editorial commentators. Most advocate using two clinical parameters to help in decision making. The first requires quantitatively defining the patient's recent or current steroid use. The second requires an estimate of the expected physiological stress induced by the specific proposed surgery.

Three patient-specific factors should be considered: the dose of steroid, the duration of steroid use, and, if applicable, the period of time since this treatment was stopped. All agree that protracted systemic exposure to greater than physiological doses of prednisone increases the risk of clinically significant adrenal suppression. Most would agree that such threshold doses would be those greater than prednisone 5 mg/d, hydrocortisone 25 mg/d, and dexamethasone 0.75 mg/d. Regarding duration, suppression of the hypothalamic-pituitary-adrenal (HPA) axis may occur with treatment courses >4 weeks. After cessation of systemic steroids, recovery of normal responsiveness of the HPA axis may take up to 9 months. Thus, patients who have received systemic steroids at greater than physiological doses for >2–4 weeks within the past 9–12 months should be considered for supplemental treatment.

What procedures warrant steroid coverage? Clearly, not all surgical procedures elicit the same stress response. Graded hormonal responses of cortisol and catecholamines reflecting the degree of surgical stress have been well documented.[15] Surgical procedures can be associated with minor, moderate, and severe surgical stresses, using procedure-specific gradients as proxies for anticipated stress. These include distal appendicular to major visceral surgeries; superficial to deep surgeries; small to large expected fluid losses or shifts; and brief to long expected durations of procedures. Examples of mild, moderate, and severe surgical stresses would be a cataract extraction, an uncomplicated arthroplasty, and coronary bypass surgery, respectively.

What Dose of Steroids Should be Used?

Using the patient- and procedure-specific information as described above, the dose of steroid supplementation varies from none to 300–400 mg/d. For patients with low-dose or remote steroid exposure undergoing a short procedure with little expected fluid losses, no supplementation is necessary. Mr. Anderson's use of low-dose prednisone (≤5 mg/d), combined with a short hand operation and minimal expected blood loss, would favour a conservative approach. Mr. Anderson should take only his usual dose of prednisone on the morning of surgery.

In contrast, most would agree that patients taking supraphysiological doses undergoing major operative procedures associated with significant blood or fluid losses should receive supplementary doses. Ms. Barnes's situation is a case in point. She will receive 200–400 mg of hydrocortisone in divided doses starting with 100 mg preoperatively and then the rest divided in q6h or q8h intervals for at least the first postoperative day.

Many patients fit between these two extremes. They are taking moderate doses of prednisone (e.g., 5–10 mg/d) or were using higher doses previously. They are scheduled to undergo a procedure expected to induce only a moderate amount of physiological stress, such as Mr. Chan's hip arthroplasty. Most would recommend making a judgment call with a "titrated dose" of hydrocortisone, such as 25–50 mg preoperatively, and one or two postoperative doses if intraoperative stress turns out to be greater than expected.

When supplementation is provided, the optimal duration of coverage is not known. Twenty-four hours will suffice for most patients; however, this may be extended for those with longer unstable postoperative courses. Hydrocortisone is most commonly used; however, therapeutically equivalent doses of dexamethasone or methylprednisolone are equally acceptable. These latter two have the pragmatic advantage of longer half-lives but the disadvantage of less mineralocorticoid effects compared with hydrocortisone.

Not all postoperative hypotension is a reflection of adrenal insufficiency. Fluid and blood loss, sepsis, vasodilating drugs, cardiac ischemia, and arrhythmias – alone or in combination – may conspire to lower blood pressure.

Summary

In summary, we should consider replacing our historic custom of supraphysiological supplementation with a more rational algorithm, one that recognizes patient factors and the physiological stresses of the proposed surgical procedure. It is unclear whether more definitive clinical data will come to light, given the heterogeneity of clinical indications for chronic steroids and the range of surgical procedures that these patients undergo.

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MedEd

Performance Assessment: The Touchstone of Learning

John Ruedy, MD

Assessment and evaluation of medical trainees and practising physicians is under increased scrutiny. Both processes share measurement methods such as multiple choice questions (MCQs), objective structured clinical examinations (OSCEs), and performance assessment, but the uses of the measurements are distinct.

For the purpose of this article, I will characterize evaluation as the measurement of how well tasks are undertaken, with *judgment* based on a comparison with predetermined standards. Evaluation is useful in providing accountability of educational programs and the credentialing of students and physicians. It is summative – a measure of what *has been* learned. On the other hand, assessment is described as the estimation of how well tasks are undertaken, with *feedback* on learning needs. Its purpose is formative – to provide the learner with help in identifying *future* learning needs.

Recently, processes of evaluation have dominated those of assessment, and there has often been a lack of clarity as to whether the purpose of the measurement is summative or formative. This has meant that formative assessment as a critical component of learning has been compromised both in education and practice.

The Need to Distinguish between Evaluation and Assessment

The distinction between the processes of evaluation and assessment is important.[1–4] Both processes have a profound influence on learning behaviours. An example of this is described in a report by Newble and Jaeger.[5] When asked which evaluation method most influenced their study habits at a time when a clinical clerkship year was first introduced,

most students identified the final MCQ examination rather than the on-the-ward assessment as the most important factor. Faculty became concerned that students withdrew from clinical exposure to prepare for this, so a clinical examination was introduced that was dependent on ward experiential learning. Over a period of 3 years, an increasing proportion of students thought that this new examination influenced their learning behaviours more than the MCQ.

Where evaluation results in potentially critical decisions for an individual's future, learners, whether students or practising physicians, are motivated to "pass the test." Every act of evaluation is a prompt for learning.[1] The evaluation method cues the learner as to what and how to learn. More emphasis on evaluation results in learning that becomes a preparation for the measurement session, not a stimulus for improved workplace performance. The more a measurement method strays from the real world of patient cares, the less the learning becomes relevant for practice.

Limitations of Processes of Measuring Knowledge and Competence

Three measurable components of interdependent skills have been described in professional education – knowledge, competence, and performance. In an insightful article, Hodges has identified some of the "hidden incompetences" fostered by current methods used to evaluate knowledge and competence.[6] These include the effects of MCQs to foster "the recognition of isolated facts rather than patterns or the synthesis of contextual information"; and OSCEs "failing to assess the integration of knowledge into performance resulting in the demonstration of inauthentic skills with superficial displays of pseudo-empathy and cursory examination skills." Students and physicians readily learn by rote the checklist items for evaluation of communication and physical examination skills on an OSCE. Their evaluation has little bearing on what the students or physicians actually do in practice. An important constraint of methods used to measure knowledge and competence is that they are carried out in an artificial environment.

There has been an impressive growth in the number and variety of measures that are available to measure knowledge (know-how) and competence ("show-how"). Establishing the validity and reliability of these methods has been fodder for three decades of medical education research. Almost all methods are resource intensive, particularly in terms of faculty time. Thus, less effort is devoted to enhancing the processes of performance assessment. Another constraint is that, with few exceptions,[7,8] there is little evidence that these methods predict the CanMEDs humanistic roles in practice.

Performance Assessment

These comments lead to a consideration of the process of what a learner or a physician actually does in practice – so-called performance assessment or, in the case of learners, in-training assessment. Newble comments, "Ward practice-based sessions provide the most desirable environment in which to assess a student. It provides the possibility of making multiple observations over a period of time and in a variety of settings."[9] Turnbull et al. have correctly observed that "as a result of the difficulties of feasibility, reliability and validity, existing approaches to in-training evaluation are neither effective, accountable, nor educational."[10] Nevertheless, there have been some reports of successful performance assessment processes.[10]

The ultimate measures of physician or student effectiveness are the actual outcomes of their interventions. Although these measures becomes easier with electronic records, they can be difficult in team-based practice or with very long-term outcomes.

Factors important in an effective performance assessment in the workplace have been identified, and these can be applied to the medical learning environment (Table 1). Of particular importance, and often ignored in medical education programs, are feedback, peer assessment, and self-assessment.

Table 1. Important Factors for Effective Workplace Performance Assessment

1.	Checklists, not global ratings
2.	Narrative descriptors of levels of performance
3.	Multiple observers
4.	Observers from diverse groups
5.	Timely recording and feedback
6.	Feedback focused on learning opportunities
7.	Effective self- and peer assessments

Adapted from Baker and Dunbar.[2]

Feedback is the feature that differentiates assessment from evaluation. Twenty-five years ago, Ende stated, "Feedback … is a key step in the acquisition of clinical skills, yet … is often omitted or handled improperly in clinical training. This can result in important consequences, some of which extend beyond the training period."[11] The same could be said today. Ende's main attributes of effective feedback (Table 2) have been reiterated recently in this journal.[12]

Table 2. Elements of Effective Feedback

1.	Well timed and expected
2.	Based on first hand data
3.	Phrased in descriptive nonevaluative language
4.	Deals with specific performances not generalizations
5.	Assessor and individual assessed work as allies with common goals

Adapted from Ende[11]

Veloski et al.[13] concluded that feedback can change physicians' clinical performance, but this can have detrimental effects if done poorly. This is likely to occur when evaluation overrides assessment and learners turn to defensive tactics – such as disparaging the source or regarding the issues as irrelevant. In addition, learners, through faulty self-assessment, may establish standards internally in such a way as to resist external efforts to modify them.

Assessment by peers is becoming an important feature of maintenance of competence and revalidation processes. Provided a sufficient number participate, peer assessment of humanistic qualities has been shown to reliably identify physicians whose performance is considerably above or below that of their peers.[14] The traditional reluctance of physicians to assess their peers can best be overcome by introducing peer assessment into undergraduate and residency curricula. In addition to preparing them for this role in practice, this

method may enhance the learners' self-assessment processes.

Physicians learn from experience enriched by reflection and study, and are guided by a recognition of gaps in their own knowledge or competence. In a self-regulated profession, continued learning is dependent on self-recognition of such learning needs. One goal of assessment of students and physicians should be to foster such future learning. To accomplish this, assessment must include guidance to self-assessment and effective supportive feedback.

Davis et al. have recently reviewed the literature on self-assessment by graduate physician-trainees and practising physicians[15] and concluded that physicians have a limited ability to self-assess. Similarly, McLeod et al. found a high correlation between patient and faculty ratings of residents' humanistic qualities but a weaker correlation between patient ratings and resident self-assessment, particularly for the qualities of responsibility and respect.[16] Feedback and peer and self-assessment thus remain challenges to effective performance assessment in medical education and practice.

Performance Assessment in Residency Programs in Canada

The Royal College of Physicians and Surgeons of Canada (RCPSC) provides leadership in delineating standards expected of the performance assessment processes in residency programs.[17] A review of the status of these processes in the residency programs of one Canadian medical school showed that most programs did not meet most of the expected criteria (Table 3). Results also suggest that processes were largely used for summative and not formative purposes. Despite updating, the RCPSC standards could be clearer on the purpose of "evaluation," insist on peer and self-assessment, and better delineate issues of quality in performance assessment processes.

Performance assessment must be emphasized at all levels of medical education and practice. Medical education research should change its focus to develop effective means of measuring performance as the key assessment process and a critical stimulus for learning. In particular, the processes of feedback and peer and self-assessment need attention. The RCPSC should continue its leadership role in outlining the criteria expected of resident assessment processes through refining its accreditation standards. Performance assessment is a critical element of learning and remains the "touchstone" of assessment processes for learners and practising physicians.

Table 3. Percentage of 23 Postgraduate Programs at a Canadian Medical School Meeting Selected Criteria of Assessment Processes

Process	Programs Meeting Criteria (%)
Forms consist of checklists	48
Forms completed more often than at the end of posting	39
Forms reflect goals and objectives	74
Formal feedback occurs regularly	78
Physician evaluators receive training	17
Other health professionals provide assessments	35
There is peer assessment	39
There is structured self-assessment	22
Patients provide recorded assessments	17

Data are from a study supervised by the author.

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About the Author

John Ruedy is a general internist and clinical pharmacologist who has served in a number of key academic positions, including chair of the Department of Pharmacology and Therapeutics, McGill University; head of the Department of Medicine at St. Paul's Hospital, Vancouver; and dean of the Faculty of Medicine, Dalhousie University. He currently serves as vice-president, Academic Affairs, Capital District Health Authority, Halifax, Nova Scotia.

Burma on Our Minds

Kerri Johannson, MD

The laughter in Burma has been silenced. On September 25, 2007, military officials arrested Par Par Lay, a 60-year-old Burmese comedian and founding member of the Moustache Brothers Comedy Troupe. His fate remains unknown. It's not the first time he has been arrested for vocal antigovernment views, and his troupe is hopeful he will be released soon. Lay is one of thousands of Burmese citizens who have been detained in the past 8 weeks for their alignment with pro-democracy views.

Me at Shwedagon Pagoda, Yangon Burma, 2003

In August this year, sparked by a government decision to cut fuel subsidies, thousands of Burmese citizens took to the streets of Yangon. The target of these early protests was the skyrocketing gas price, but what soon evolved was a nationwide pro-democracy rally. The first days were subdued, kept in check by a heavy military presence in the city as well as by the peaceful nature of the protesters. Buddhist monks joined the waves of civilian protests, and the world began to take notice. But soon brute force erupted. Soldiers beat and shot their citizens. Pagodas (Buddhist sites of worship and meditation) were surrounded and sealed off, and hundreds of monks and nuns were arrested. The whereabouts of many of these symbols of peace and compassion are still unknown. In the past few weeks, all public protests have been silenced in the wake of thousands of arrests, with detainees being released only if they sign pledges vowing not to engage in further protest. The United Nations and several human rights groups are lobbying day and night to put an end to the current military crackdown, but so far little progress has been made.

I travelled to Burma in the spring of 2003 prior to starting medical school. My purpose was to learn about Buddhism and Burmese history and to be trained in the style of Vipassana meditation that had resurfaced from this region over 2,500 years ago. My month-long experience was astounding. Never in my life have I met kinder, gentler, more compassionate people. In messages home, I continually reassured my parents that I felt safer there than I did in Canada. In fact, it was at a hotel in Rangoon that I received a telegram from my dad informing me I'd been accepted to medical school (shortly before I endured the worst gastroenteritis of my life …). Vipassana meditation changed my life, and I left Burma with a profound respect for not only Buddhism but for the Burmese people.

It is a hotly contentious issue whether foreigners should travel to this country at all, given that tourist revenues serve to fund the 19-year-old military junta. At that time, tourists arriving at Yangon International Airport had to convert US$200 into Burmese kyat, and this foreign currency would go to funding an oppressive military. Many believe it is immoral to support Burma's tourism industry, while others worry that an embargo would only deepen the plight of the average citizen.

In the northern city of Mandalay, I met the Moustache Brothers, a family of 13 actors, musicians, and puppeteers that have long been outspoken opponents of the military regime. The Moustache Brothers take their name from Par Par Lay and his brother, Lu Maw, who sport impressive handlebar moustaches. They perform *a-nyient pwe*, a traditional form of Burmese music, dance, and puppetry. Historically, such performers travelled the countryside entertaining at weddings and festivals. They were well known and respected for their satire and tongue-in-cheek humour, directed toward the ruling class. Despite the fact that since 1962 the government in power has not readily accepted any style of criticism, troupes like the Moustache Brothers have persisted. Their makeshift theatre is in the front room of their home, in a nondescript neighbourhood of Mandalay, advertised in Lonely Planet travel guides and by tuk-tuk drivers for hire. They spread their words of sociopolitical commentary through humour, dance, and American comedic idioms, while a receptive audience of foreign tourists laughs and learns.

In 1999, three members of the Moustache Brothers were imprisoned after performing for Aung San Suu Kyi, the National League for Democracy (NLD) leader and Nobel Peace Prize winner. Kyi's democratic election to office in 1990 was overruled by the military, and she has remained under house arrest for 13 of the past 18 years. For their part in supporting her, two of the brothers toiled for 5 1/2 years in a labour camp. Since their release, their work has been tolerated, provided they perform only in English and only for foreigners. Par Par Lay's recent abduction is evidence that this tolerance has run out.

One of the roles of a doctor in the CanMEDS framework is to become a health advocate, with key competencies that include the

About the Author

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promotion of health of individual patients, communities, and populations. I believe it is our duty not only as physicians but as Canadian citizens to promote this role by advocating for health rights and human rights worldwide. We have the opportunity to educate ourselves on these issues, to communicate our views to our government representatives, and to facilitate change. The parallel consequences of health rights abuses and human rights abuses are innumerable and far reaching. From a lack of clean drinking water and inadequate nutrition, to military violence and government-sanctioned prostitution, the Burmese people are suffering and will continue to suffer until the international community demands change.

The Moustache Brothers

Despite Mr. Lay's detention, the Moustache Brothers continue to perform for the few foreigners who remain in Burma, according to current online travel blogs. I can only imagine that on a night like tonight, they might recite one of Par Par Lay's favourite jokes:

Par Par Lay travels to India to get relief from a toothache. The Indian dentist wonders why the Burmese man has come all this way to see him. "Don't you have dentists in Burma?" he asks. "Yes, we do, Doctor," says Mr. Lay, "but in Burma, we're not allowed to open our mouths."

With ongoing pressure and support from the international community, that punchline may soon have to be re-written.

Instructions to Authors

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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.

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INDICATIONS AND CLINICAL USE

Chronic Stable Angina ADALAT® XL® (nifedipine) 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. ADALAT® XL® may be used in combination with beta blocking drugs in patients with chronic stable angina. However, available information is not sufficient to predict with confidence the effects of concurrent treatment, especially in patients with compromised left ventricular function or cardiac conduction abnormalities. When introducing such concomitant therapy, care must be taken to monitor blood pressure closely, since severe hypotension can occur from the combined effects of the drugs (see WARNINGS). **Hypertension** ADALAT® XL® 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 blocker has been ineffective, or has been associated with unacceptable adverse effects. ADALAT® XL® can be tried as an initial agent in those patients in whom the use of diuretics and/or beta blockers is contraindicated, or in patients with medical conditions in which these drugs frequently cause serious adverse effects. Combination of ADALAT® XL® with a diuretic has been found compatible and has shown added antihypertensive effect. Concurrent administration of low doses of ADALAT® XL® and enalapril has been shown to produce an enhanced antihypertensive effect with no additional safety concerns when compared to that observed with either of the monotherapies. Safety of concurrent use of ADALAT® XL® with other antihypertensive agents has not been established.

CONTRAINDICATIONS

ADALAT® XL® (nifedipine) is contraindicated in pregnancy, during lactation, and in women of childbearing potential. Fetal malformations and adverse effects on pregnancy have been reported in animals. An increase in the number of fetal mortalities and resorptions occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice, rats, and rabbits. Fetal malformations occurred after the administration of 30 and 100 mg/kg nifedipine to pregnant mice and 100 mg/kg to pregnant rats. In patients with hypersensitivity to ADALAT®. In patients with severe hypotension or cardiovascular shock. Nifedipine must not be used in combination with rifampicin because insufficient plasma levels of nifedipine may result due to enzyme induction.

WARNINGS

Excessive Hypotension in Patients with Angina Since ADALAT® XL® (nifedipine) lowers peripheral vascular resistance and blood pressure, ADALAT® XL® should be used cautiously in patients with angina who are prone to develop hypotension and those with a history of cerebrovascular insufficiency. Occasional patients have had excessive and poorly tolerated hypotension. Syncope has been reported (see ADVERSE REACTIONS). These responses have usually occurred during initial titration or at the time of subsequent upward dosage adjustment, and may be more likely in patients on concomitant beta blockers. If excessive hypotension occurs, dosage should be lowered or the drug should be discontinued (see CONTRAINDICATIONS). Severe hypotension and/or increased fluid volume requirements have been reported in patients receiving nifedipine, with a beta blocker, who underwent coronary artery bypass surgery using high dose fentanyl anesthesia. The interaction with high dose fentanyl appears to be due to the combination of nifedipine and a beta blocker, but the possibility that it may occur with nifedipine alone, with low doses of fentanyl in other surgical procedures, or with other narcotic analgesics cannot be ruled out. In nifedipine-treated patients where surgery using high dose fentanyl anesthesia is contemplated, the physician should be aware of these potential problems and if the patient's condition permits, sufficient time (at least 36 hours), should be allowed for nifedipine to be washed out of the body prior to surgery. The following information should be taken into account in those patients who are being treated for hypertension as well as angina. **Increased Angina and/or Myocardial Infarction** Rarely, patients, particularly those who have severe obstructive coronary artery disease have developed well-documented increased frequency, duration and/or severity of angina or acute myocardial infarction on starting nifedipine or at the time of dosage increase. The mechanism of the response is not established. Since there has not been a study of ADALAT® XL® in acute myocardial infarction reported, similar effects of ADALAT® XL® to that of immediate-release nifedipine cannot be excluded. Immediate-release nifedipine is contraindicated in acute myocardial infarction. **Beta Blocker Withdrawal** Patients with angina recently withdrawn from beta blockers may develop a withdrawal syndrome with increased angina, probably related to increased sensitivity to catecholamines. Initiation of treatment with ADALAT® XL® will not prevent this occurrence and might be expected to exacerbate it by provoking reflex catecholamine release. There have been occasional reports of increased angina in a setting of beta blocker withdrawal and initiation of nifedipine. It is important to taper beta blockers if possible, rather than stopping them abruptly before beginning ADALAT® XL®. **Patients with Heart Failure** There have been isolated reports of severe hypotension and lowering of cardiac output following administration of nifedipine to patients with severe heart failure. Thus, ADALAT® XL® should be used cautiously in patients with severe heart failure. Rarely, patients usually receiving a beta blocker, have developed heart failure after beginning nifedipine therapy. In patients with severe aortic stenosis, nifedipine will not produce its usual afterload reducing effects and there is a possibility that an unopposed negative inotropic action of the drug may produce heart failure if the end-diastolic pressure is raised. Caution should therefore be exercised when using ADALAT® XL® in patients with these conditions. **Patients with Pre-Existing Gastrointestinal Narrowing** Since the ADALAT® XL® delivery system contains a non-deformable material, caution should be used when administering ADALAT® XL® in patients with pre-existing severe gastrointestinal narrowing (pathologic or iatrogenic). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of ADALAT® XL® tablets. In single cases, obstructive symptoms have been described without known history of gastrointestinal disorders. Bezoars can occur in very rare cases and may require surgical intervention. ADALAT® XL® must not be used in patients with a Kock pouch (ileostomy after proctocolectomy).When doing barium contrast X-ray, ADALAT® XL® may cause false positive effects (e.g., filling defects interpreted as polyp).

PRECAUTIONS

Hypotension/Heart Rate Because ADALAT® XL® (nifedipine) is an arterial and arteriolar vasodilator, hypotension, and a compensatory increase in heart rate may occur. Thus, blood pressure and heart rate should be monitored carefully during nifedipine therapy. Close monitoring is especially recommended for patients who are prone to develop hypotension, those with a history of cerebrovascular insufficiency, and those who are taking medications that are known to lower blood pressure (see WARNINGS). **Peripheral Edema** Mild to moderate peripheral edema, typically associated with arterial vasodilation and not due to left ventricular dysfunction, has been reported to occur in patients treated with ADALAT® XL® (see ADVERSE REACTIONS). This edema occurs primarily in the lower extremities and may respond to diuretic therapy. With patients whose angina or hypertension is complicated by congestive heart failure, care should be taken to differentiate this peripheral edema from the effects of increasing left ventricular dysfunction. **Male Fertility** In some cases of *in vitro* fertilization, nifedipine has been associated with reversible spermatozoal biochemical changes. *in vitro* studies have shown that nifedipine may inhibit expression of mannose-ligand receptors, thus preventing the spermatozoa from attaching to the zona pellucida and impairing sperm function. In those men who are repeatedly unsuccessful in fathering a child by *in vitro* fertilization, and where no other explanation could be found, nifedipine should be considered as a possible cause. **Use in Elderly** ADALAT® XL® should be administered cautiously to elderly patients, especially to those with a history of hypotension or cerebral vascular insufficiency. **Use in Diabetic Patient** The use of ADALAT® XL® in diabetic patients may require adjustment for their control. **Use in Patients with Impaired Liver Function** ADALAT® XL® should be used with caution in patients with impaired liver function (see CLINICAL PHARMACOLOGY). A dose reduction, particularly in severe cases, may be required. Close monitoring of response and metabolic effect should apply. **Ability to Drive and Use Machines** Reactions to the drug, which vary in intensity from individual to individual, can impair the ability to drive or to operate machinery, particularly at the start of the treatment, upon changing the medication, or in combination with alcohol. **Interaction with Grapefruit Juice** Published data indicate that through inhibition of cytochrome P_{450}, flavonoids present in the grapefruit juice can increase plasma levels and augment pharmacodynamic effects of some dihydropyridine calcium channel blockers, including nifedipine (see ACTION AND CLINICAL PHARMACOLOGY). Therefore, the administration of nifedipine with grapefruit juice should be avoided. **Drug Interactions** As with all drugs, care should be exercised when treating patients with multiple medications. Dihydrophyridine calcium channel blockers undergo biotransformation by the cytochrome P_{450} system, mainly via the CYP3A4 isoenzyme. Coadministration of nifedipine with other drugs which follow the same route of biotransformation may result in altered bioavailability. Dosages of similarly metabolized drugs, particularly those of low therapeutic ratio, and especially in patients with renal and/or hepatic impairment, may require adjustment when starting or stopping concomitantly administered nifedipine to maintain optimum therapeutic blood levels. If necessary, a reduction in the dose of nifedipine may be considered. Drugs known to be inhibitors of the cytochrome P_{450} system include: azole antifungals, cimetidine, cyclosporine, erythromycin, quinidine, terfenadine, and warfarin. Drugs known to be inducers of the cytochrome P_{450} system include: phenobarbital, phenytoin, and rifampicin. Drugs known to be biotransformed via cytochrome P_{450} include: benzodiazepines, flecainide, theophylline, imipramine and propafenone. **Beta Adrenergic Blocking Agents** Concomitant administration of nifedipine and beta blocking agents is usually well tolerated, but there have been occasional literature reports suggesting that the combination may increase the likelihood of congestive heart failure, severe hypotension, or exacerbation of angina. Therefore, caution and careful monitoring of patients on concomitant therapy is recommended (see INDICATION AND CLINICAL USE and WARNINGS). **Diltiazem** Diltiazem decreases the clearance of nifedipine. The combination of both drugs should be administered with caution, and a reduction of the nifedipine dose may be considered. **Long Acting Nitrates:** Nifedipine may be safely co-administered with nitrates, but there have been no controlled studies to evaluate the antianginal effectiveness of this combination. **Digoxin:** Administration of nifedipine with digoxin may lead to reduced digoxin clearance, and therefore, an increase in the plasma digoxin level. It is recommended that digoxin levels be monitored when initiating, adjusting and discontinuing nifedipine to avoid possible "under-" or "over-"dosing with digitalis. **Coumarin Anticoagulants:** There have been rare reports of increased prothrombin time in patients taking coumarin anticoagulants to whom nifedipine was administered. However, the relationship to nifedipine therapy is uncertain. **Carbamazepine** No formal studies have been performed to investigate the potential interaction between nifedipine and carbamazepine. As carbamazepine has been shown to reduce the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme induction, a decrease in nifedipine plasma concentrations and hence a decrease in efficacy cannot be excluded. **Quinidine:** The addition of nifedipine to a stable quinidine regimen may reduce the quinidine by 50%, an enhanced response to nifedipine may also occur. The addition of quinidine to a stable nifedipine regimen may result in elevated nifedipine concentrations and a reduced response to quinidine. Some patients have experienced elevated quinidine levels when nifedipine was discontinued. Therefore, patients receiving concomitant therapy of nifedipine and quinidine, or those who had their nifedipine discontinued while still receiving quinidine,should be closely monitored, including determination of plasma levels of quinidine. Consideration should be given to dosage adjustment. **Quinupristin/Dalfopristin** Simultaneous administration of quinupristin/dalfopristin and nifedipine may lead to increased plasma concentrations of nifedipine. Upon co-administration of both drugs, blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose should be considered. **Cimetidine and Ranitidine:** Pharmacokinetic studies have shown that concurrent administration of cimetidine or ranitidine with nifedipine results in significant increases in nifedipine plasma levels (ca. 80% with cimetidine, and 70% with ranitidine). Patients receiving either of these drugs concomitantly with nifedipine should be monitored carefully for the possible exacerbation of effects of nifedipine, such as hypotension. Adjustment of nifedipine dosage may be necessary. **Cisapride** Simultaneous administration of cisapride and nifedipine may lead to increased plasma concentrations of nifedipine. Upon co-administration of both drugs, the blood pressure should be monitored and, if necessary, a reduction of the nifedipine dose considered. **Valproic acid** No formal studies have been performed to investigate the potential interaction between nifedipine and valproic acid. As valproic acid has been shown to increase the plasma concentrations of the structurally similar calcium channel blocker nimodipine due to enzyme inhibition, an increase in nifedipine plasma concentrations and hence an increase in efficacy cannot be excluded.

INFORMATION FOR PATIENTS

ADALAT® XL® (nifedipine) tablets must be swallowed whole. Patients should be advised to not chew, divide or crush the tablet as this can result in a massive immediate release of the drug. In ADALAT® XL®, the medication is packed within a nonabsorbable shell that has been specially designed to slowly release the drug so the body can absorb it. When this is completed, the empty tablet is eliminated in the stool. Administration of nifedipine with grapefruit juice should be avoided.

ADVERSE REACTIONS

Angina: In 257 chronic stable angina patients treated in controlled and long term open studies with ADALAT® XL®, adverse effects were reported in 30.0% of patients and required discontinuation of therapy in 8.5% of patients. The most common adverse effects were: edema (10.1%), headache (3.1%), angina pectoris (3.1%). The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis: Cardiovascular: Palpitation (2.3%), tachycardia, myocardial infarction, ventricular arrhythmia, extrasystoles, dyspnea, chest pain. In patients with angina, rarely, and possibly due to tachycardia, nifedipine has been reported to have precipitated an angina pectoris attack. In addition, more serious events were occasionally observed, not readily distinguishable from the natural history of the disease in these patients. It remains possible, however, that some or many of these events were drug related. These events include myocardial infarction, congestive heart failure or pulmonary edema, and ventricular arrhythmias or conduction disturbances. Central Nervous System: Dizziness (2.3%), hypoesthesia (1.2%), confusion, insomnia, somnolence, nervousness, asthenia, hyperkinesia. Gastrointestinal: Constipation (1.9%), dyspepsia (1.2%), abdominal pain (1.2%), diarrhea, nausea, melena. Genito-urinary: Impotence, hematuria, polyuria, dysuria. Musculo-skeletal: Leg cramps, paresthesia, myalgia, arthralgia. Dermatologic: Rash, pruritus. Other: Fatigue (1.2%), pain, periorbital edema. **Hypertension:** In 661 hypertensive patients treated in controlled trials with ADALAT® XL®, adverse effects were reported in 54.0% of patients and required discontinuation of therapy in 11.9% of patients. The majority of adverse effects reported occurred within the first three months of therapy. The most common adverse effects 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%), nausea (3.5%). The following adverse effects were also reported. Incidences greater than 1% are given in parenthesis: Cardiovascular: Flushing (2.4%), palpitation (2.3%), tachycardia (1.2%), chest pain (1.1%), ventricular arrhythmia, hypotension, syncope. Central Nervous System: Insomnia (1.8%), nervousness (1.8%), somnolence (1.5%), depression, tremor, decreased libido, migraine, vertigo, amnesia, anxiety, impaired concentration, twitching, ataxia, hypertonia, paresthesia, hypoesthesia. Gastrointestinal: Dyspepsia (1.5%), flatulence (1.5%), abdominal pain (1.4%), dry mouth (1.1%), diarrhea, vomiting, thirst, melena, eructation, weight increase. Genito-urinary: Impotence (1.5%), polyuria (1.5%), dysuria, nocturia, oliguria, urinary incontinence, urinary frequency, menstrual disorder. Musculo-skeletal: Arthralgia, back pain, myalgia. Special Senses: Abnormal vision, abnormal lacrimation, taste disturbance, conjuctivitis, tinnitus. Dermatologic: Rash (2.3%), pruritus (1.1%), erythematous rash, alopecia. Respiratory: Dyspnea (1.7%), bronchospasm, pharyngitis, upper respiratory tract infection, epistaxis. Other: Leg cramps (2.7%), pain (2.7%), asthenia (2.0%), face edema, gout, allergy, fever, breast pain.

DOSAGE AND ADMINISTRATION

Dosage should be individualized depending on patient tolerance and response. ADALAT® XL® (nifedipine) tablets must be swallowed whole and should not be bitten or divided. In general, titration steps should proceed over a 7-14 day period so that the physician can assess the response to each dose level before proceeding to higher doses. Since steady-state plasma levels are achieved on the second day of dosing, if symptoms so warrant, titration may proceed more rapidly provided that the patient is closely monitored. **Angina** Therapy with ADALAT® XL® should normally be initiated with 30 mg once daily. Experience with doses greater than 90 mg daily in patients with angina is limited, therefore, doses greater than 90 mg daily are not recommended. Angina patients controlled on ADALAT® capsules alone or in combination with beta blockers may be safely switched to ADALAT® XL® tablets at the nearest equivalent daily dose. Subsequent titration to higher or lower doses may be necessary and should be initiated as clinically warranted. **Hypertension** Therapy should normally be initiated with 20 or 30 mg once daily. The usual maintenance dose is 30 to 60 mg once daily. Doses greater than 90 mg daily are not recommended. Patients switched from ADALAT® PA 10 or 20 to ADALAT® XL® therapy should receive an initial dosage of ADALAT® XL® no higher than 30 mg once daily, based on previously prescribed dosing regimen. If clinically warranted, the dosage of ADALAT® XL® should be increased to 60 mg once daily. Blood pressure and patient symptoms should be monitored closely following the switch from ADALAT® PA to ADALAT® XL®. No "rebound effect" has been observed upon discontinuation of ADALAT® XL®. However, if discontinuation of nifedipine is necessary, sound clinical practice suggests that the dosage should be decreased gradually under close physician supervision.

PHARMACEUTICAL INFORMATION

Composition

ADALAT® XL® is supplied as 20, 30 and 60 mg tablets for oral administration. ADALAT® XL® 20, 30 and 60 mg tablets, in addition to the active ingredient nifedipine, contain the following inactive ingredients: polyethylene oxide, cellulose acetate, sodium chloride, hydroxypropyl methylcellulose 2910, magnesium stearate, hydroxypropyl cellulose, titanium dioxide, polyethylene glycol 3350, red ferric oxide, pharmaceutical shellac, synthetic black iron oxide.

AVAILABILITY OF DOSAGE FORMS

ADALAT® XL® (nifedipine) extended release tablets contain nifedipine in strengths of 20 mg, 30 mg and 60 mg.
ADALAT® XL® 20 mg is a dusty rose tablet imprinted with "ADALAT 20" on one side.
ADALAT® XL® 20 mg is available in blister packs of 28 and 98 tablets.
ADALAT® XL® 30 mg is a dusty rose tablet imprinted with "ADALAT 30" on one side.
ADALAT® XL® 30 mg is now available in blisters of 28 and 98 tablets.
ADALAT® XL® 60 mg is a dusty rose tablet imprinted with "ADALAT 60" on one side.
ADALAT® XL® 60 mg is now available in blisters of 28 and 98 tablets.

PRODUCT MONOGRAPH IS AVAILABLE UPON REQUEST

Reference: Product Monograph Adalat® XL®, revised August 12th, 2004. Bayer Healthcare Inc.

Bayer HealthCare
Pharmaceuticals

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

XL1253AE

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 nonnatal 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®. Such conditions, especially volume and/or sodium depletion, 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: Due to the sorbitol content in MICARDIS® (telmisartan) tablets, MICARDIS® is unsuitable for patients with hereditary fructose intolerance. **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. There is no experience regarding the administration of MICARDIS® (telmisartan) in patients with a recent kidney transplant. **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 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. Rare cases have also been reported with angiotensin II receptor antagonists including MICARDIS®. Therefore, serum lithium level monitoring is advisable during concomitant use. *Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)*: Combinations of angiotensin-II antagonists (MICARDIS®) and NSAIDs (including ASA and COX-2 inhibitors) might have an increased risk for acute renal failure and hyperkalemia. Blood pressure and kidney function should be monitored more closely in this situation, as occasionally there can be a substantial increase in blood pressure. NSAIDs (including ASA and COX-2 inhibitors) and angiotensin-II receptor antagonists exert a synergistic effect on the decrease of glomerular filtration. In patients with pre-existing renal impairment, this may lead to acute renal failure. Monitoring of renal function at the beginning and during the course of the treatment should be recommended.

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 System:** 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	8.0	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, fascitis 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 mEg/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 mEg/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 mEg/L were found in 0.6% 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, syncope/faint, insomnia, depression, stomach upset, vomiting, hypotension (including orthostatic hypotension), bradycardia, tachycardia, abnormal hepatic function/liver disorder, renal impairment including acute renal failure, hyperkalemia, dyspnoea, anaemia, eosinophilia, thrombocytopenia, weakness and lack of efficacy have been reported. The frequency of these effects is unknown. As with other angiotensin II antagonists rare cases of angio-oedema, pruritus, 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. In addition, since the introduction of telmisartan in the market, cases with increased blood creatinine phosphokinase (CPK) have been reported.

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, 15-30°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, 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 J, *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. *J Hum Hypertens* 1999;13:657-664. **2.** Neldam S *et al*. Telmisartan Plus HCTZ vs. Amlodipine Plus HCTZ in Older Patients With Systolic Hypertension: Results From a Large Ambulatory Blood Pressure Monitoring Study. *The American Journal of Geriatric Cardiology* 2006:15(3):151-160. **3.** White WB, *et al*. Effects of the angiotensin II receptor blockers telmisartan versus valsartan on the circadian variation of blood pressure: impact on the early morning period. *Am J Hypertens* 2004;17:347-353. **4.** 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. *Am J Hypertens* 2006;19:104-112. **5.** Data on file, Boehringer Ingelheim Canada Ltd. **6.** MICARDIS® Product Monograph, Boehringer Ingelheim (Canada) Ltd. August 14, 2006.

℞ MICARDIS®

TELMISARTAN 80mg AT_1 RECEPTOR BLOCKER

Boehringer Ingelheim

www.boehringer-ingelheim.ca

Boehringer Ingelheim (Canada) Ltd.
5180 South Service Rd.,
Burlington, Ontario L7L 5H4

PAAB Member R&D

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 nonnatal 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	8.0	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, fascitis 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 mEg/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 mEg/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 mEg/L were found in 0.6% 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 AT_1 RECEPTOR BLOCKER
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EZETROL®

ezetimide

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10 mg Tablet

Cholesterol Absorption Inhibitor

SUMMARY PRODUCT INFORMATION

Route of Administration	Dosage Form/ Strength	Clinically Relevant Nonmedicinal Ingredients
oral	tablet 10 mg	Lactose monohydrate

INDICATIONS AND CLINICAL USE

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

Primary Hypercholesterolemia

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

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

Homozygous Familial Hypercholesterolemia (HoFH)

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

Homozygous Sitosterolemia (Phytosterolemia)

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

CONTRAINDICATIONS

Hypersensitivity to any component of this medication.

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

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

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

WARNINGS AND PRECAUTIONS

Serious Warnings and Precautions

- hepatitis
- pancreatitis
- myopathy/rhabdomyolysis
- myalgia
- anaphylaxis (see ADVERSE REACTIONS; Post-Market Adverse Drug Reactions)

General

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

Hepatic/Biliary/Pancreatic

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

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

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.

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

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

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

Muscle Effects

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

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

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

Renal

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

Special Populations

Pregnant Women

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

Nursing Women

Studies in rats have shown that ezetimibe is excreted in milk. It is not known whether ezetimibe is excreted into human breast milk, therefore, EZETROL® should not be used in nursing mothers unless the potential benefit justifies the potential risk to the infant. Note that all statins and fenofibrate are **contraindicated** in nursing women (see the Product Monograph for the medication).

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 or fenofibrate, please refer also to the Product Monograph for that medication.

Clinical Trial Adverse Drug Reactions

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

Monotherapy

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

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

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

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

Combination with a Statin

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

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

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

Combination with Fenofibrate

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

Abnormal Hematologic and Clinical Chemistry Findings

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

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

Post-Market Adverse Drug Reactions

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

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

Anticoagulants: 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.

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 Adverse Event	Placebo (%) n=795	EZETROL® 10 mg (%) 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 Adverse Event	Placebo (%) n=259	EZETROL® 10 mg (%) n=262	All Statins** (%) n=936	EZETROL® + All Statins** (%) 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.

Fibrates: The safety and effectiveness of ezetimibe co-administered with fenofibrate have been evaluated in a clinical study (see WARNINGS AND PRECAUTIONS, ADVERSE REACTIONS and CLINICAL TRIALS, Co-administration with Fenofibrate in the product monograph); co-administration of ezetimibe with other fibrates has not been studied. Fibrates may increase cholesterol excretion into the bile, leading to cholelithiasis. In a preclinical study in dogs, ezetimibe increased cholesterol in the gallbladder bile. Although the relevance of this preclinical finding to humans is unknown, co-administration of EZETROL® with fibrates (other than fenofibrate) is not recommended until use in patients is studied.

Fenofibrate: In a pharmacokinetic study, concomitant fenofibrate administration increased total ezetimibe concentrations approximately 1.5-fold. This increase is not considered clinically significant.

Gemfibrozil: In a pharmacokinetic study, concomitant gemfibrozil administration increased total ezetimibe concentrations approximately 1.7-fold. This increase is not considered clinically significant. No clinical data are available.

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.

Recommended Dose and Dosage Adjustment

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

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/Biliary/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. The molecular target of ezetimibe is the sterol transporter, Niemann-Pick C1-Like 1 (NPC1L1), which is responsible for the intestinal uptake of cholesterol and phytosterols.

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. Administration of EZETROL® with fenofibrate is effective in improving serum total-C, LDL-C, Apo-B, TG, HDL-C, and non-HDL-C in patients with mixed hyperlipidemia.

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 or fenofibrate 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.

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NEW 2006 CANADIAN GUIDELINES For The Treatment of Dyslipidemia

RECOMMEND LOWER LDL-C TARGETS[1]

HOW CAN EZETROL® HELP YOUR PATIENTS REACH THEIR NEW TARGETS?

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, including anaphylaxis, 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.

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EZETROL® AND A STATIN:
DEMONSTRATED SUPERIOR EFFICACY THROUGH DUAL INHIBITION[2]

AN ADDITIONAL

25.8%

MEAN REDUCTION IN LDL-C

VS 2.7% WITH A STATIN ALONE FROM MEAN BASELINE LDL-C LEVELS OF 3.3 MMOL/L FOR BOTH TREATMENT GROUPS ($p<0.001$).[3,*]

*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

References: **1.** McPherson R et al. Canadian Cardiovascular Society position statement - Recommendations for the diagnosis and treatment of dyslipidemia and prevention of cardiovascular disease. Can J Cardiol 2006;22(11):913-27. **2.** Data on file, Merck Frosst/Schering Pharmaceuticals: Product Monograph—EZETROL®, 2006. **3.** Pearson TA et al. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP III goals for LDL cholesterol in hypercholesterolemic patients: The ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc 2005;80(5):587-95.

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.

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