

# The Medical Post

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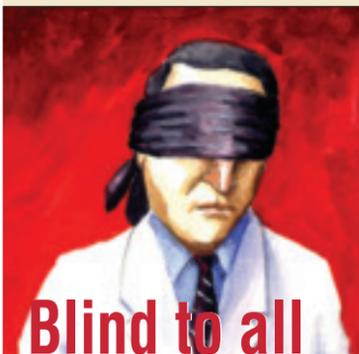
NOVEMBER 14, 2006

## A happy side-effect?

Smokers who had been prescribed statins to prevent coronary artery disease may enjoy an unforeseen benefit: a slower deterioration in their lungs. This was one of many studies presented at the annual meeting of the American College of Chest Physicians 23

## CME push

The Society of Rural Physicians of Canada is working to bring more—and more relevant—courses to doctors in some of Canada's more remote areas 62

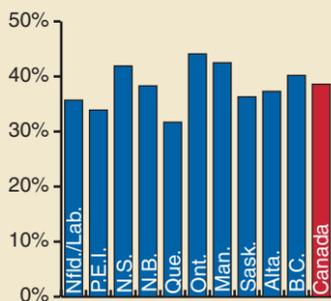


## Blind to all the signs

Sometimes a doctor can miss the truth about a patient even when the correct diagnosis is right in front of him 39

## Snapshot

Projected government health expenditure as a proportion of total government programs, 2005/06. For more on trends in health spending, see page 8



Source: CIHI



Bristol-Myers Squibb/Charlotte Raymond

**Flickers of light in the darkness** With almost one-quarter of adults afflicted with AIDS, HIV has devastated the tiny African nation of Lesotho. Here, patients receive care at the Senkatana Centre, which combines medical care with community support programs sponsored by Bristol-Myers Squibb. Dr. Val Rachlis of Toronto visited Lesotho recently and found while there are bright lights of hope in the work of volunteers and the establishment of this centre, he questions whether the developed world is doing enough. See story page 46

## Revenge of the stents

*New data analyses reaffirm benefits, safety of drug-eluting models*

by Andrew Skelly

**TORONTO** | Drug-eluting coronary stents have received a lot of bad press lately, with reports the two first-generation devices are associated with increased risks of death and myocardial infarction. But new analyses of clinical trial data have failed to back those findings.

The new reports do confirm a small increased risk of thrombosis one to four years after implantation of drug-eluting stents (DES), but

interventional cardiologists say this risk is balanced by lower rates of restenosis—and they point out that longer use of antiplatelet therapy with ASA and clopidogrel (Plavix) may help address the problem.

The latest stent thrombosis controversy heated up earlier this year with presentations at the American College of Cardiology annual meeting in Atlanta and the World Congress of Cardiology in Barcelona suggesting increased mortality and MI risks with the

see Late | page 85

## Online MD ratings draw fire from CMPA

*Letter reminds Web group about Canadian libel laws*

by Alison DeLory

**OTTAWA** | “The worst of the worst. He butchered me,” is how one anonymous patient rated his or her Canadian physician at www.RateMDs.com.

Other unflattering comments on the Web site, which invites anyone to share a good or bad experience or opinion of a doctor, included: “Are you planning to commit suicide? Go to this doctor and he will kill you.”

The Canadian Medical Protective Association (CMPA) considers these statements defamatory and has successfully pressured the California administrators to delete them from the site. But other comments that remain posted include:

• “Very argumentative and ignores what is being explained to him.”

• “Her level of knowledge appears to be mediocre . . . she didn't take responsibility for a mistake she clearly made.”

These comments and more are on the Web site next to the names of Canadian doctors.

see Web | page 84

## Workers' comp deal divides B.C. specialists, FPs

by Ann Graham Walker

**VANCOUVER** | The British Columbia Medical Association board has endorsed it, the BCMA's Society of Specialist

Physicians and Surgeons (SSPS) has sent out an e-mail asking their members to endorse it—but a proposed new Workers' Compensation Board agreement is raising howls from

general practitioners who say they weren't properly consulted. B.C.'s Society of General Practitioners is calling for members to vote against it. GPs make up just less than 50% of BCMA

membership.

The new WCB (now called WorkSafeBC) agreement has been under negotiation for 15 months. There were

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# Late risks offset by early benefits

from | page 1

two currently approved DESs: Boston Scientific's paclitaxel-eluting Taxus stent and Cordis Corporation's sirolimus-eluting Cypher stent.

In response, the two companies released all the raw data from the key clinical trials of these devices to the Cardiovascular Research Foundation (CRF), a group that helped conduct the trials and is primarily affiliated with Columbia University Medical Centre in New York.

Those data, presented last month at the CRF's annual Transcatheter Cardiovascular Therapeutics (TCT) symposium in Washington, D.C., comprised four Cypher and five Taxus randomized trials compared with bare metal stents (BMS). Neither meta-analysis showed increased risks of death or MI

with the DES compared with BMS. However, the Cypher was associated with significantly higher rate of stent thrombosis from one to four years after implantation: 0.6% in 870 patients versus zero in the 878 patients who received a bare metal stent. Similarly, the Taxus showed a late stent thrombosis rate of 0.7% in 1,749 patients, compared with 0.2% in 1,757 BMS patients, a statistically significant difference.

Dr. Martin Leon, presenter of the Taxus data, told reporters at the meeting that there has been a "hysterical over-reaction" to the studies presented in Barcelona. "The results that were reported at the European congress represented an incomplete data set," said Dr. Leon, chairman emeritus of the CRF and associate director of the Centre for Interventional Vascular

Therapy at Columbia University Medical Centre.

"Patients are not being harmed with the use of drug-eluting stents, and any small increase that may occur in heart attacks and deaths after one year is offset by a reduction of those similar events before one year, associated with the dramatic decrease in the frequency of restenosis."

## Safer stents coming

However, Dr. Gregg Stone, presenter of the Cypher data and chairman of the CRF, noted the clinical trials of both devices were restricted to patients with simple to moderately complex lesions, and registry data suggest annual late stent thrombosis rates may be closer to 0.50%, compared with 0.15% to 0.20% in the clinical trials. "I think we do need safer, more effective

drug-eluting stents, and the companies are working, now that they realize there is this problem, on developing those devices," said Dr. Stone, also at Columbia.

Canadian interventional cardiologists who spoke with the *Medical Post* agreed the recent bad publicity over late stent thrombosis had been blown out of proportion, and that the issue can be addressed through longer antiplatelet therapy and improved technology.

"There's been a lot of fear propagated as a result of this," said Dr. Eric Horlick, an interventional cardiologist at Toronto General Hospital who was at the TCT symposium in Washington. He said cardiologists at the meeting reported that patients were asking to have their drug-eluting stents removed, believing they were a "time bomb." He himself had one patient write him a letter about the issue.

"This (late stent thrombosis)

is a problem that affects a very, very small number of patients who receive drug-eluting stents. I think we're very sensitive to it, and we do have strategies to prevent this from happening, such as treating with a longer duration of Aspirin and clopidogrel, such as choosing the patients carefully," for example, by ensuring they are willing and able to comply with long-term clopidogrel therapy.

He pointed out the clinical trials of the Cypher and Taxus stents were done with three to six months of clopidogrel plus ASA, but the typical practice is to continue dual therapy for a lot longer. "Many people, including myself, especially if we do complex procedures, will give at least one year of clopidogrel. . . . Some people are keeping their patients on indefinite clopidogrel in combination with Aspirin, because of the concern about late stent thrombosis."

However, Dr. Marino Labinaz, a Heart and Stroke Foundation spokesman and director of cardiac catheterization and interventional cardiology at the University of Ottawa Heart Institute, pointed out that Ontario's drug benefit program pays for only one year of clopidogrel, and other provinces have much shorter coverage periods for the medication, which costs between \$2 and \$3 a day. "Some patients who have to pay for it complain about the cost," he said in an interview.

Dr. Labinaz agreed the late stent thrombosis controversy "has been a bit premature and a bit sensationalized."

## Drug-eluting stents costly

He pointed out DES are at least two to three times more expensive than BMS, and in Canada are usually reserved for patients with a high risk of restenosis. Consequently, they account for a much lower proportion of coronary stenting procedures than the 80% to 90% rates at some European and U.S. centres. Funding for the devices varies by province, and allows hospitals to use them in anywhere from 10% to 50% of stenting procedures, he estimated.

Dr. Labinaz said one possible explanation for late stent thrombosis in DES is that the released medication delays the growth of tissue over the stent, and the exposed surface of the device may promote clotting. "With the current technology, maybe we're inhibiting (healing) a bit too much." However, patient-specific factors, or factors related to stent placement, could also be contributing to the increased risk.

Both physicians emphasized the importance of uninterrupted antiplatelet therapy, even when patients undergo dental procedures and, depending on the bleeding risks, surgery. "A little bit of extra bleeding pales in comparison to having a stent thrombosis with a potential fatal heart attack as a result," Dr. Labinaz said.

In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in the treatment of postmenopausal osteoporosis, endoscopies performed during the study revealed no dose dependent pattern in the number of patients with positive endoscopic findings or in the anatomical location of abnormalities detected.

### Less Common Clinical Trial Adverse Drug Reactions

The following adverse drug reactions were reported in ≤1% of patients who received ACTONEL for all indications.

Uncommon (0.1-1.0%): duodenitis, iritis

Rare (<0.1%): abnormal liver function tests, glossitis

### Abnormal Hematologic and Clinical Chemistry Findings

Asymptomatic mild decreases in serum calcium and phosphorus levels have been observed in some patients (see ACTION AND CLINICAL PHARMACOLOGY, Pharmacodynamics).

Rare cases of leukemia have been reported following therapy with bisphosphonates. Any causal relationship to either the treatment or to the patients' underlying disease has not been established.

### Post-Market Adverse Drug Reactions

**ACTONEL:** Very rare (<1 report per 10,000 new prescriptions): hypersensitivity and skin reaction, including angioedema, generalized rash, and bullous skin reactions, some severe.

A number of cases of osteonecrosis (primarily of the jaw) have been reported in patients receiving treatment with bisphosphonates. Osteonecrosis has other well documented multiple risk factors. It is not possible to determine if these events are related to bisphosphonates, to concomitant drugs or other therapies (e.g. chemotherapy, radiotherapy, corticosteroids), to the patient's underlying disease or to other co-morbid risk factors (e.g. anaemia, infection, pre-existing oral disease) (see WARNINGS AND PRECAUTIONS, General).

### DRUG INTERACTIONS

#### Overview

No specific drug-drug interaction studies were performed with ACTONEL. Animal studies have demonstrated that risedronate is highly concentrated in bone and is retained only minimally in soft tissue. No metabolites have been detected systemically or in bone. The binding of risedronate to plasma proteins in humans is low (24%), resulting in minimal potential for interference with the binding of other drugs. In an additional animal study, there was also no evidence of hepatic microsomal enzyme induction. In summary, ACTONEL is not systemically metabolized, does not induce cytochrome P<sub>450</sub> enzymes and has low protein binding. ACTONEL PLUS CALCIUM is therefore not expected to interact with other drugs based on the effects of protein binding displacement, enzyme induction or metabolism of other drugs.

#### Drug-Drug Interactions

Patients in the risedronate clinical trials were exposed to a wide variety of commonly used concomitant medications (including NSAIDs, H<sub>2</sub>-blockers, proton pump inhibitors, antacids, calcium channel blockers, beta-blockers, thiazides, glucocorticoids, anticoagulants, anticonvulsants, cardiac glycosides) without evidence of clinically relevant interactions.

Drug	Reference	Effect	Clinical Comment
Acetylsalicylic acid (ASA)	CT	Among ASA users, the incidence of upper gastrointestinal adverse events were similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, ASA use was reported by 31% of patients.
		Among ASA users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in postmenopausal women, ASA use was reported by 56% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups.
Antacids/supplements which contain polyvalent cations (e.g., calcium, magnesium, aluminum and iron)	T	Interference with the absorption of ACTONEL.	Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION).
Hormone replacement therapy	CT	No clinically significant effect.	If considered appropriate, ACTONEL may be used concomitantly with hormone replacement therapy.
H <sub>2</sub> -blockers and proton pump inhibitors (PPIs)	CT	Among H <sub>2</sub> -blockers and PPIs users, the incidence of upper gastrointestinal adverse events was similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, 21% used H <sub>2</sub> -blockers and/or PPIs.
		Among H <sub>2</sub> -blockers and PPIs users, the incidence of upper gastrointestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL Once-a-Week and daily dosing regimens in postmenopausal women, at least 9% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups used H <sub>2</sub> -blockers and/or PPIs.
Non-steroidal anti-inflammatory drugs (NSAIDs)	CT	Among NSAIDs users, the incidence of upper gastrointestinal adverse events was similar between the ACTONEL-treated patients and placebo-treated patients.	Of over 5700 patients enrolled in the ACTONEL 5 mg daily Phase III osteoporosis studies, 48% used NSAIDs.
		Among NSAIDs users, the incidence of upper gastro-intestinal adverse experiences was found to be similar between the weekly- and daily-treated groups.	In the 1-year study comparing ACTONEL 35 mg Once-a-Week to ACTONEL 5 mg daily in postmenopausal women, 41% of patients in the ACTONEL 35 mg Once-a-Week and 5 mg daily groups used NSAIDs.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

Drug	Reference	Effect	Clinical Comment
Iron	T	Calcium may interfere with the absorption of iron.	Iron and calcium should be taken at different times of the day.
Bisphosphonates	T	Decreased absorption of the bisphosphonate may occur.	Such medications should be administered at a different time of the day (see DOSAGE AND ADMINISTRATION).
Tetracyclines	CT	Calcium carbonate may interfere with the absorption of concomitantly administered tetracycline preparations.	Tetracycline preparations should be administered at least two hours before or four to six hours after oral intake of calcium carbonate.
Digoxin	T	Hypercalcemia may increase the toxicity of cardiac glycosides.	Patients should be monitored with regard to electrocardiogram (ECG) and serum calcium levels.
Phenytoin	T	May form a nonabsorbable complex with calcium.	Administration times of these medications should be separated by at least 3 hours.
Thyroid hormones: Levothyroxine	CT	Concomitant intake of levothyroxine and calcium carbonate was found to reduce levothyroxine absorption and increase serum thyrotropin levels. Levothyroxine may adsorb to calcium carbonate in an acidic environment, which may block its absorption.	Levothyroxine should be administered on an empty stomach and calcium should be taken with food. Monitor serum TSH in patients taking calcium and adjust dose accordingly.
Fluoroquinolones (e.g. ciprofloxacin, moxifloxacin, ofloxacin)	CT	Concomitant administration of a fluoroquinolone and calcium may decrease the absorption of the fluoroquinolone.	Administration times of these medications should be separated by several hours.
H <sub>2</sub> Blockers (e.g. cimetidine, famotidine, ranitidine)	T	Concomitant intake can cause decreased absorption of calcium.	Calcium should be taken with food to maximize absorption.
Proton Pump Inhibitors (e.g. lansoprazole, omeprazole, rabeprazole sodium)	T	Concomitant intake can cause decreased absorption of calcium.	Calcium should be taken with food to maximize absorption.
Systemic Glucocorticoids	T	Calcium absorption may be reduced and excretion increased when calcium is taken concomitantly with systemic glucocorticoids.	Additional calcium supplementation may be considered in patients taking long-term systemic glucocorticoids.
Vitamin D (e.g. calcitriol, ergocalciferol, doxercalciferol)	CT	Absorption of calcium may be increased when given concomitantly with vitamin D analogues.	Ensure adequate vitamin D intake through diet or supplements for optimal calcium absorption.
Thiazide Diuretics	C	Reduced urinary excretion of calcium has been reported during concomitant use of calcium carbonate and thiazide diuretics.	Serum calcium should be monitored during concomitant use with thiazide diuretics, particularly in hyperparathyroid patients.

Legend: C = Case Study; CT = Clinical Trial; T = Theoretical

#### Drug-Food Interactions

Clinical benefits may be compromised by failure to take ACTONEL on an empty stomach. For dosing information see DOSAGE AND ADMINISTRATION.

#### Drug-Herb Interactions

Interactions with herbs have not been studied.

#### Drug-Laboratory Interactions

Bisphosphonates are known to interfere with the use of bone-imaging agents. Specific studies with ACTONEL have not been performed.

#### DOSAGE AND ADMINISTRATION

##### Dosing Considerations

- Patients should receive supplemental calcium and vitamin D if dietary intake is inadequate (see WARNINGS AND PRECAUTIONS, General).
- Food and medications containing polyvalent cations (e.g., calcium, magnesium, aluminum, and iron) can interfere with the absorption of ACTONEL. Therefore, food and other medications should be administered at a different time of the day (see Recommended Dose and Dosage Adjustment and DRUG INTERACTIONS).
- The ACTONEL tablet should be swallowed whole while the patient is in an upright position and with sufficient plain water (≥120 mL) to facilitate delivery to the stomach. Patients should not lie down for at least 30 minutes after taking the medication (see WARNINGS AND PRECAUTIONS, General).
- Other calcium-containing medications (e.g., multivitamins, antacids) should be administered at a different time of the day to prevent an interaction with ACTONEL and to maximize ACTONEL absorption.
- It is recommended that patients receive at least 1200-1500 mg calcium per day from all sources, as well as a vitamin D intake of at least 400-800 IU. ACTONEL PLUS CALCIUM provides 500 mg Calcium and does not contain any vitamin D.
- ACTONEL PLUS CALCIUM is appropriate for additional supplementation of 500 mg of calcium for 6 out of 7 days, in conjunction with dietary and multivitamin intake, in patients whose calcium intake is 700-1000 mg/day. In patients who have a low daily calcium intake (i.e. less than 700 -1000 mg/day) or who require vitamin D supplementation, it may be advisable to prescribe ACTONEL 35 mg and a higher dose of calcium and/or vitamin D.

##### Recommended Dose and Dosage Adjustment

For all indications and doses: The patient should be informed to pay particular attention to the dosing instructions as clinical benefits may be compromised by failure to take the drug according to instructions. Specifically, ACTONEL should be taken on an empty stomach at least 30 minutes before consuming the first food, drink (other than plain water) and/or any other medication of the day. The tablet should be swallowed whole – do not chew.

The calcium tablet should be taken with food.