/briefing/3677b1_03_med.doc and www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.doc.

Results of the CLASS trial as reported in *JAMA* are presented in Table 1.[3] The CLASS trial was actually a planned pooled analysis of 2 trials, one comparing ibuprofen with celecoxib and the other comparing diclofenac with celecoxib. In the *JAMA* article the CLASS trial was presented as a 6-month trial (mean duration of exposure 4 months).[3] However, the trial comparing ibuprofen with celecoxib was 15 months long (mean duration of exposure 7 months) and the trial comparing diclofenac and celecoxib trial was 12 months long (mean duration of exposure 6.5 months). A synopsis of the overall results of these 2 trials and a more complete presentation of the adverse events that occurred are presented in Table 2.

Results of the VIGOR trial are presented in Table 3. Results from the FDA Web site are virtually the same as those presented in the published version of this 9-month trial.[4] The data presented in boldface are from the FDA Web site and were not presented in the *N Engl J Med* article.[4]

The interpretation of the clinical importance of these results compared with the published data in journals is left to the reader.

James P. McCormack
Associate Professor
Faculty of Pharmaceutical Sciences
University of British Columbia
Vancouver, BC
Robert Rangno
Associate Professor
Departments of Medicine and Pharmacology
University of British Columbia
Vancouver, BC

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Table 3: Results of the VIGOR trial as published in *N Engl J Med*[4] and FDA reports

	Frequency of event (%)	
	Naproxen	Rofecoxib
Gastric or duodenal ulcers, upper gastrointestinal bleeding, perforations, obstructions	3.0	1.4*
Upper gastrointestinal bleeding, perforations, obstructions	1.0	0.4
Serious cardiovascular thrombotic events	**0.7**	**1.7***
Myocardial infarctions	0.1	0.4*
Deaths	0.4	0.5
Serious adverse events	**7.8**	**9.3**
All adverse events causing withdrawal from the trial	**15.8**	**15.9**
Specific adverse events causing withdrawal from the trial		
Cardiovascular	**0.8**	**2.7**
Congestive heart failure	**0.2**	**0.5†**
Digestive	**9.7**	**7.2**
Gastrointestinal	10.6	7.8*
Edema	**0.3**	**0.6‡**
Hypertension	**0.1**	**0.7***

Note: Data in boldface are from the FDA reports. For differences not indicated with asterisks, statistics were not reported.
*Significant difference ($p < 0.05$) as reported in the *N Engl J Med* or FDA reports.
†$p = 0.07$
‡$p = 0.06$

Safe drug prescribing

The excellent article on safe drug prescribing for patients with renal insufficiency addresses many questions that pharmacists are asked by physicians in daily practice.[1]

However, in Table 5 a statement on COX-2 selective NSAIDs would have been useful, as many physicians believe that these agents have less potential to adversely affect renal function than older nonselective agents. No evidence exists to support this belief. The new COX-2 selective agents are similar in net effects on renal prostaglandin function to the older nonselective NSAIDs.[2,3]

In addition, another nephrotoxic drug class to watch out for is radiocontrast "dyes." Exposure to intravenous radiocontrast agents for diagnostic and interventional procedures is quite common. Aside from considering non-ionic, low-osmolality agents and hydration, reasonable evidence suggests that pretreatment with oral *N*-acetylcysteine may further reduce the risk of renal damage.[4] Given its low cost and minimal toxicity, *N*-acetylcysteine should be considered in patients with renal insufficiency before they are exposed to parenteral radiocontrast agents.

Bruce Lange
Clinical Pharmacist, Nephrology
Royal Columbian Hospital
New Westminster, BC

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I read with interest the article on safe drug prescribing for patients with renal insufficiency.[1] The authors have succinctly summarized various medications that require adjustment in dosage in renal failure and others that do not require such adjustments, but I take issue with certain recommendations in Table 4 of the paper.

First, the authors describe morphine as a medication not requiring dosage adjustment in renal failure unless given in a palliative care setting. Although morphine is rapidly metabolized by the liver, it is excreted mainly in the urine as its active metabolites, morphine-3-glucuronide (M-3G) and morphine-6-glucuronide (M-6G). Both M-3G and M-6G readily cross the blood–brain barrier and bind with strong affinity to opiate receptors, exerting strong analgesic effects. In patients with renal failure or in the elderly, the ratios of M-3G and M-6G to morphine increase, making opioid toxicity, prolonged narcosis and respiratory depression more likely.[2,3] Morphine dosage must therefore be carefully controlled and adjusted in patients with renal failure.

The authors also state that angiotensin-converting enzyme (ACE) inhibitors require dosage adjustment in renal failure whereas angiotensin receptor blockers (ARBs) do not. Although these generalizations are mostly accurate, subtle pharmacokinetic differences in some agents may make them exceptions to the rule. For example, although most ACE inhibitors require dosage adjustment because they are exclusively eliminated through the kidney, fosinopril has both a renal and hepatobiliary route of elimination and thus may not require dosage adjustment in chronic renal insufficiency.[4] Similarly, most ARBs do not require dosage adjustment in renal failure because of their hepatobiliary route of elimination, but 60% of candesartan cilexetil is mainly excreted in the urine as candesartan. In patients with renal insufficiency it may be prudent to employ lower starting doses of this medication.[5]

Malvinder S. Parmar
Internal Medicine and Nephrology
Timmins and District Hospital
Timmins, Ont.

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[One of the authors responds:]

Bruce Lange's comments regarding COX-2 selective NSAIDs are quite correct and readers would be well advised to add this addendum to Table 5.[1]

Strictly speaking, radiocontrast agents are diagnostic tools and not drugs and therefore were not included in this article on safe drug prescribing. However, radiocontrast agents certainly can cause nephrotoxicity in patients with renal insufficiency. I do not think that the current published studies regarding the use of *N*-acetylcysteine in patients with renal insufficiency have conclusively established that this drug absolutely reduces the incidence of contrast nephropathy.[2] Because *N*-acetylcysteine is relatively harmless, I think that it is being used widely without adequate data.

Malvinder Parmar's comments regarding morphine dosage adjustments are quite correct when morphine is used on a regular basis. However, when morphine is used on a sporadic basis, as in postoperative pain control, I do not believe that dosage adjustment is practically required. Dosage adjustments are required when morphine is used on a regular basis such as in a palliative care setting (as reflected in Table 4).

An excellent review article by Song and White states that angiotensin receptor blockers do not require dosage adjustment in patients with renal insufficiency.[3] This includes candesartan cilexetil. Furthermore, a subsequent article by See and Stirling extensively reviewed the pharmocokinetics of candesartan cilexetil and did not find a significant alteration in patients' blood pressure response (in those with renal insufficiency) after they received multiple doses of candesartan cilexetil .[4]

As the treatment of many nonemergent conditions does not require an immediate or maximal drug response, I would hope that clinicians would start drugs at the lowest convenient dose, regardless of renal function, and increase to produce the desired response.

Joanne Elaine Kappel
Department of Nephrology
St. Paul's Hospital of Saskatoon
Saskatoon, Sask.

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tPA for acute stroke: balancing baseline imbalances

In a recent *CMAJ* article,[1] David Gladstone and Sandra Black stated that the National Institute of Neurological Disorders and Stroke (NINDS) study[2] provided valid evidence that patients treated with tissue plasminogen activator (tPA) within 3 hours of symp-