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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]

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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 practi-

cally 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 pharmacokinetics 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.

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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-

tom onset achieved greater neurologic recovery and experienced less disability than patients who received placebo. Additional data published by the NINDS investigators[3] and the US Food and Drug Administration medical officer's review of data submitted in support of a new drug application,[4] show a significant in baseline stroke severity between the tPA-treated and placebo groups in the NINDS trial. Statistical correction for this baseline imbalance has not been provided in published reports and commentaries concerning this trial. Because baseline stroke severity has a significant effect on stroke outcome, I believe that accurate interpretation the results of the NINDS trial, or any similar trial, is not possible without using a statistically appropriate analytic equation to account for the differences in stroke severity between the trial groups.

The TOAST stroke trial[5] demonstrated that very small differences in baseline stroke severity have large effects on stroke outcome. I applied stroke outcome information derived from this trial to the NINDS data.[6] My analysis indicates that the difference in stroke outcome between the treatment and placebo groups in the NINDS trial may be accounted for solely by the baseline imbalance in stroke severity between the groups.

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[The authors respond:]

Mann draws attention to 2 important points: (1) stroke outcome depends heavily on initial stroke severity as measured by the National Institutes of Health Stroke Scale (NIHSS), and (2) baseline imbalances in stroke severity could potentially affect the results of a stroke trial. However, the assertion that the NINDS tPA trial results are invalid is incorrect.

The original NINDS trial publication (1995)[1] reported the treatment and placebo groups to be well balanced in terms of initial stroke severity (median NIHSS 14 v. 15). According to further data published 5 years later in a post-hoc analysis,[2] it does appear that there were more patients in the tPA group with mild stroke (NIHSS 0–5) and fewer patients with very severe stroke (NIHSS > 20) compared to placebo. This imbalance was evident primarily in the 91–180 minute onset-to-treatment cohort and less prominent in the 0–90 minute cohort or in the entire study cohort. No baseline imbalances were in favour of the tPA group for patients with moderate or severe stroke (NIHSS 6–10, 11–15, 16–20). Mann speculates that the positive results of the NINDS trial were driven by this baseline imbalance in stroke severity. However, the actual data do not bear this out.

We obtained data directly from the NINDS investigators to clarify this issue (see Table 1). These data show that even if one excludes the subgroups with baseline imbalances (NIHSS 0–5 or > 20), the efficacy of tPA in the NINDS trial still holds true — a 16.6% absolute benefit for patients with moderate severity stroke (NIHSS 6–10) and a 10.4% absolute benefit for patients with severe stroke (NIHSS 11–20). This is reassuring since in clinical practice the major target of tPA therapy is patients with moderate to severe deficits. The overall benefit of tPA, therefore, does not appear to be driven by baseline imbalances in the very mild or very severe subgroups.

Contrary to Mann's speculation that there might be an excessive benefit in

Table 1: Three-month stroke outcomes in the NINDS tPA stroke trial by baseline stroke severity

	Baseline		90-day NIHSS score of 0–1				90-day mRS score of 0–1				Unadjusted odds ratio for favourable outcome (95% CI)
NIHSS score	% of placebo patients (n = 312)	% of tPA patients (n = 312)	% of placebo patients	% of tPA patients	Absolute benefit, % (95% CI)	NNT	% of placebo patients	% of tPA patients	Absolute benefit, % (95% CI)	NNT	
0–5	5.1	13.5	62.5	69.1	6.6 (–20.9 to 34.1)	15	81.3	78.6	–2.7 (–25.5 to 20.1)	–37	1.12 (0.36 to 3.49)
6–10	26.6	21.8	34.9	51.5	16.6 (0.9 to 32.2)	6	45.8	67.7	21.9 (6.5 to 37.3)	5	2.33 (1.32 to 4.09)
11–20	43.6	44.6	16.9	27.3	10.4 (0.7 to 20.1)	10	21.3	34.5	13.2 (2.7 to 23.7)	8	1.68 (1.05 to 2.67)
> 20*	24.7	20.2	2.6	6.4	3.8 (–3.2 to 10.8)	26	3.9	9.5	5.6 (–2.8 to 14.0)	18	1.45 (0.64 to 3.33)

Note: NIHSS = National Institutes of Health Stroke Scale, mRS = modified Rankin scale, CI = confidence interval, tPA = tissue plasminogen activator, NNT = number needed to treat.
*The 95% CI, derived using the normal approximation to the binomial distribution, for this group may not be valid owing to small number for each treatment group.