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Evidence-based healthcare 10 years on: is the National Institute of Clinical Studies the answer?

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TO THE EDITOR: The recent creation of the National Institute for Clinical Studies (NICS) is an exciting new opportunity for bridging the gap between evidence and practice.¹

In carrying out this task, NICS will be directed by the members of its Board. Balanced stakeholder representation on the Board is required for NICS to produce optimal results. At present the Board consists of nine members, of whom eight are medical practitioners. The importance of doctors in the process and implementation of quality improvement initiatives is indisputable. However, other healthcare professionals also play a central role in achieving quality health outcomes for patients.² Board membership more representative of its stakeholders would provide NICS with a broader range of perspectives, which could only be seen as beneficial.

Given the current debate surrounding ethics and evidence-based healthcare, the values and expectations of healthcare consumers also need to be taken into account.³ One of the definitions of quality in healthcare is “consistently meeting or exceeding informed customers’ opinion”.⁴ It is crucial that the consumer’s voice be heard in matters relating to healthcare research and in the implementation of quality initiatives. As the relevance and acceptability of quality initiatives undertaken by NICS will have an impact on health outcomes for consumers, it is important that such initiatives take into account the preferences of consumers. For this reason, we believe it is imperative that NICS include a consumer on its Board.

An example of successful integration of a wide range of stakeholders onto a board is the Federal Government-funded National Health Priority Action Council, with representation from State/Territory, Indigenous and consumer groups and a balanced gender mix. We hope that NICS has strategies in place to enhance stakeholder representation on its Board, as this may be a factor in determining whether or not NICS becomes another forgettable acronym.

1. Silagy C. Evidence-based healthcare 10 years on: is the National Institute of Clinical Studies the answer [editorial]? *Med J Aust* 2001; 175: 124-125.

2. Donabedian A. The quality of care: how can it be assessed? *JAMA* 1988; 260: 1743-1748.
3. Leeder S, Rychetnik L. Ethics and evidence-based medicine. *Med J Aust* 2001; 175: 161-164.
4. Headrick L, Neuhauser D. Quality health care. *JAMA* 1995; 273: 1718-1720. □

Chris A Silagy (deceased)

Professor, and Director, Monash Institute of Public Health, Monash Medical Centre, Locked Bag 29, Clayton, VIC, 3168.

IN REPLY: The Board of the National Institute of Clinical Studies (NICS) agrees strongly with Hall and Lauder that closing the gap between evidence and practice involves input from consumers. We also agree that the Board of Directors should seek to incorporate input from consumers in its strategic and operational activities.

Of equal concern to the Board is ensuring the input of other stakeholder groups also currently not reflected in the composition of Board membership. For example, nursing and allied health professions comprise about 80% of the healthcare workforce and have shown strong leadership in relation to evidence-based practice. We are keen to see such groups actively involved in all aspects of the Institute’s work.

As a Federal Government-owned company, the selection and appointment process for Board members is the responsibility of government and our constitution does not allow the Board to change its own membership. However, the Board is seeking input from both consumers and other key stakeholder groups, both through its initial consultation processes and through establishment of Board advisory groups specifically focused on consumer issues and nursing and allied health. These groups will provide direct and valued input into the strategic and operational activities of the NICS.

Our first round of consultation, with over 300 organisations, highlighted a number of areas where there are currently major gaps between evidence and practice, such as cardiac failure, various forms of cancer treatment, prevention of deep vein thrombosis in hospitalised patients, prevention of bedsores, and prescribing of psychotropic drugs for children. We are now examining ways in which the NICS might usefully help in some of these areas to identify barriers and possible solutions that can be rolled out across the healthcare system and sustained. The success of the NICS in achieving this will depend on the willingness of all stakeholders (including health professionals, consumers and managers) to work together in a constructive way. □

COX-2 inhibition and thrombotic tendency

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TO THE EDITOR: I am concerned that several statements in the article on cyclooxygenase-2 (COX-2) inhibition by Cleland and colleagues¹ do not accurately reflect the clinical data.

The authors postulate a prothrombotic tendency of celecoxib on the basis of the CLASS study (comparing celecoxib with ibuprofen or diclofenac)² and four case reports. The authors concede that celecoxib has no effect on the rate of myocardial infarction (MI) in the CLASS study (a conclusion also reached by the United States Food and Drug Administration [FDA] review of CLASS³), which would seem to contradict their hypothesis that celecoxib is prothrombotic.

Cleland and colleagues speculate that the differences between the CLASS study and the VIGOR study (which compared rofecoxib with naproxen)⁴ may be explained by low-dose aspirin use in CLASS and failure to use aspirin in 4% of patients in VIGOR with “CV [cardiovascular] risk factors”. This speculation is unfounded. In the CLASS study patients in all treatment groups who used aspirin had higher MI rates than non-aspirin users, and presumably this higher rate would have been observed in VIGOR if aspirin users had been enrolled. This higher rate is probably because aspirin use serves as a marker for increased CV risk. In patients in CLASS similar to the 4% with “CV risk factors” in VIGOR, MI rates were similar in the celecoxib and non-steroidal anti-inflammatory drug (NSAID) groups (data on file, Pharmacia) and numerically much lower than in the VIGOR study subgroup.

On the basis of these two flawed arguments, Cleland and colleagues apparently extrapolate the high rate of MI seen with the use of rofecoxib to celecoxib and suggest that high MI rates are a “class” effect. This proposal is scientifically unsound and is not supported by other clinical data, including over 12 000 patients in the celecoxib registration program (data on file, Pharmacia). No celecoxib study has shown an increased risk of MI compared with traditional NSAIDs.

The authors correctly assert there is “little clinical evidence from community use to suggest that selective COX-2 inhibition has serious unwanted effects other than those seen with standard NSAIDs”, but imply there are few community data. In fact, community use of celecoxib in Australia (at least 1.5 million

patients exposed) and worldwide (more than 20 million) has been extensive, and with this degree of exposure one would expect significant adverse event patterns to emerge. Reference to the Adverse Drug Reactions Advisory Committee and FDA database does not indicate a prothrombotic tendency of celecoxib. Further, we at Pharmacia do not consider that the four case studies presented by Cleland et al provide strong support for a prothrombotic tendency for celecoxib, especially as all patients described had diseases with high risk for thrombosis.

On the basis of a large body of controlled trial data (including CLASS) and extensive community exposure, the evidence does not show any more thrombosis with celecoxib than with NSAIDs.

Results of the CLASS and VIGOR studies clearly differ. It is clinically unjustified and scientifically unsound to suggest that rates of MI seen with rofecoxib can be ascribed to celecoxib and described as a "class effect".

1. Cleland LG, James MJ, Stamp LK, Penglis PS. COX-2 inhibition and thrombotic tendency: a need for surveillance. *Med J Aust* 2001; 175: 214-217.
2. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study. JAMA* 2000; 284: 1247-1255.
3. Throckmorton DC. FDA Center for Drug Evaluation and Research memorandum. Comparative safety of celecoxib, diclofenac and ibuprofen. Rockville, MD: FDA, 1 May 2001. <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_07.pdf>
4. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520-1528. □

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IN REPLY: The response from the Medical Director of Pharmacia to our article highlights some problems for all clinicians and independent scientists seeking to evaluate the balance of risks and benefits of pharmaceuticals and to validate the marketing messages of pharmaceutical companies. On the one hand, we lack the time and statistical resources to trawl through all data related to all trials with a test drug. On the other, our efforts to evaluate data are confounded by the publication and reporting biases associated with company-sponsored studies. In this regard, it is notable that the definitive results of CLASS¹ have not been published, although the Food and Drug Administration (FDA) review of the data is available through an FDA website,² as indicated by Fenn. While this document places data in the public domain, its location is neither within the pathway of MEDLINE search engines, nor is it known to the general body of clinicians.

As reported in the FDA presentation, CLASS was a very large, double-blind safety study of at least six months' treatment that failed to achieve its primary endpoint of reduced complicated upper gastrointestinal events with celecoxib relative to the comparator, non-steroidal anti-inflammatory drugs (NSAIDs). While an interim analysis at six months was published, with extrapolation of event rates to 12 months,³ failure to publish the final results has withheld important results from wider scrutiny. In essence, the FDA document shows no overall long-term safety advantage of celecoxib over standard NSAIDs.²

The FDA analysis⁴ of the VIGOR study⁵ also shows no overall safety advantage for rofecoxib compared with NSAID, with fewer complicated upper gastrointestinal events being offset by a highly statistically significant ($P = 0.0016$) increase in serious thrombotic cardiovascular events.

Collectively, these FDA analyses invalidate the promotion of selective cyclooxygenase-2 (COX-2) inhibitors as a safe alternative to NSAIDs, notwithstanding encouraging results from short-term trials. Further, although an increase in serious cardiovascular events was not seen in the CLASS study, its design was not optimal for detecting increased cardiovascular risk, and it is unlikely that CLASS was sufficiently powered to detect the degree of increased risk seen with rofecoxib in VIGOR. As explained in our article,⁶ unbalanced prothrombotic eicosanoid production associated with selective COX-2 inhibition (ie, a class effect) appears the most likely explanation for the increased cardiovascular events seen in VIGOR.

Finally, we wish to reassert that, for effective postmarketing surveillance, it is essential that prescribers be adequately informed about safety concerns associated with new drugs, particularly when they involve events that are common and not usually seen as unwanted drug effects.

1. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study. JAMA* 2000; 284: 1247-1255.
2. US Food and Drug Authority. NDA 20-998/S-009. Celebrex capsules (Celecoxib). Medical Officer Review. Sept 2001 <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_03_med.doc>
3. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: A randomized controlled trial. *Celecoxib Long-term Arthritis Safety Study. JAMA* 2000; 284: 1247-1255.
4. FDA Advisory Committee Briefing Document, NDA 21-042, s007, VIOXX Gastrointestinal Safety <http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b2_03_med.pdf>
5. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000; 343: 1520-1528.
6. Cleland LG, James MJ, Stamp LK, Penglis PS. COX-2 inhibition and thrombotic tendency: a need for surveillance. *Med J Aust* 2001; 175: 214-217. □

Liver biopsy in hepatitis C: reassessing its role in 2001

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TO THE EDITOR: Chronic hepatitis C (HCV) infection affects more than 200 000 Australians.¹ As the degree of hepatic fibrosis is the best predictor of morbidity, liver biopsy has a central role in management. Biopsy is also carried out to exclude additional pathology. However, because liver biopsy carries real risks and is expensive,^{2,3} debate exists as to whether liver biopsy should be performed routinely.^{3,4} Despite controversy surrounding the need to treat patients with minor histological changes,⁴ our impression is that many informed patients request treatment irrespective of liver histology. In Australia, liver biopsy is a prerequisite for antiviral therapy under the Pharmaceutical Benefits Scheme Highly Specialised Drugs Program (Box).⁵

To assess the impact of liver biopsy on management, we performed a retrospective study of patients with chronic HCV infection who underwent liver biopsy from March 1998 to December 2000. We identified 76 patients (51 men, 25 women), with a mean age of 29 years (range, 20–52 years). The biopsy was performed to stage and grade hepatitis C in all patients, and additionally to investigate a second pathology in seven patients. No alternative diagnoses were raised. Additional diagnoses (all suspected before biopsy) were confirmed in three patients and refuted in four patients. Biopsy findings were all consistent with chronic HCV infection, with some degree of fibrosis in 69 patients. There were five patients with histologically confirmed cirrhosis (including incomplete cirrhosis in three), and this was clinically evident in two patients. When S100 criteria at the time of biopsy were applied, after exclusions on clinical grounds, only one patient would have been ineligible for interferon monotherapy based on liver histology. Under current S100 criteria, nine patients would be ineligible for combination therapy, but all nine would remain eligible for monotherapy. Of our patients who attended follow-up and were HCV RNA positive, 62 of 64 patients received or are awaiting therapy.

Our results confirm the finding that liver biopsy in patients with chronic HCV infection rarely identifies alternative diagnoses.³ These data reflect the fact that