

Second, the investigators performed an intention-to-treat analysis only, which gives a conservative estimate of the effect size and hence bias toward a conclusion of noninferiority, when a per-protocol analysis is generally preferred.¹⁰

Finally, neither the AFFIRM trial¹ nor the noninferiority study² defined or reported compliance. Poor compliance can create bias toward a conclusion of “no difference” in both cases and would be of particular interest in assessing life-long therapies with recognized adverse effects.

Mario L. de Lemos

Provincial Drug Information
Coordinator
British Columbia Cancer Agency
Vancouver, BC

References

1. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002; 347:1825-33.
2. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834-40.
3. Cain ME. Atrial fibrillation — rhythm or rate control [editorial]. *N Engl J Med* 2002;347:1822-3.
4. Kovacs KA. Long-term management of atrial fibrillation: Rhythm or rate control? *CMAJ* 2003;168(5):591-2.
5. Nattel S. Rhythm versus rate control for atrial fibrillation management: what recent randomized clinical trials allow us to affirm [editorial]. *CMAJ* 2003;168(5):572-3.
6. Atrial fibrillation follow-up investigation of rhythm management — the AFFIRM study design. The Planning and Steering Committees of the AFFIRM study for the NHLBI AFFIRM investigators. *Am J Cardiol* 1997;79(9):1198-202.
7. Fuster V, Ryden LE, Asinger RW, Cannom DS, Crijns HJ, Frye RL, et al. ACC/AHA/ESC guidelines for the management of patients with atrial fibrillation: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines and Policy Conferences (Committee to Develop Guidelines for the Management of Patients with Atrial Fibrillation) developed in collaboration with the North American Society of Pacing and Electrophysiology. *Circulation* 2001;104:2118-50.
8. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH E9. *Statistical principles for clinical trials*. London: European Agency for the Evaluation of Medicinal Products; 2000 Jul 20.
9. Committee for Proprietary Medicinal Products. *Points to consider on multiplicity issues in clinical trials*. London: European Agency for the Evaluation of Medicinal Products; 2002.
10. International Conference on Harmonisation of

Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH). ICH E9. *Statistical principles for clinical trials*. London: European Agency for the Evaluation of Medicinal Products; 1998 Feb 5.

Competing interests: None declared.

[Dr. Nattel responds:]

Mario de Lemos raises several points concerning the trials of atrial fibrillation management that I discussed in my commentary.¹

First, he asks whether a type II error might have occurred in the AFFIRM trial,² given the difference between the planned sample size and study enrolment.³ The selection of appropriate sample size always involves estimating a clinically relevant difference and calculating the sample size needed to detect this difference with acceptable power. The sample size was reduced to 4060 to ensure sufficient power to reliably detect a difference of 30%, which was felt to be a minimally important clinical difference.⁴ The mortality rate in AFFIRM was marginally higher (by 15%, $p = 0.08$) in the rhythm-control group. The primary finding of AFFIRM was that a rate-control approach is not inferior to a rhythm-control approach. A larger sample size (and 5300 patients might not have been sufficiently large) might have detected a statistically significant increase in mortality rate with rhythm control; however, the investigators judged that the differential impact of a significant p value for this small effect was not sufficient to justify the substantial additional cost (and the potential detrimental effect of exposing additional patients to nonsuperior and more complex rhythm-control therapy) of extending the trial.

De Lemos also states that the efficacy of rate control was within the upper bound of the 95% confidence limit of that of rhythm control in the trial by Van Gelder and associates.⁵ However, those authors did not use efficacy as an endpoint. Their primary endpoint was a composite index of cardiovascular death, heart failure, thromboembolic complications, bleeding, pacemaker implantation and severe adverse drug reactions. In fact, the primary endpoint

(which was a negative outcome) was more prevalent in the rhythm-control group, with the 90% 2-sided confidence limit barely including a neutral effect.

De Lemos further argues that it is unclear whether the rhythm-control strategy was a suitable active comparator. This statement seems to miss the point of the trials, which was to compare the 2 widely used approaches to therapy for atrial fibrillation: rate versus rhythm control. Both studies used patient populations in which recurrence was deemed likely, so a placebo group might not have been ethical in light of presently accepted medical practice.

De Lemos also criticizes use of an intention-to-treat analysis, rather than a per-protocol analysis (in which only events while the patient is receiving active therapy are analyzed), which he claims “is generally preferred.” In fact, the weight of clinical trials opinion favours intention-to-treat analyses. The simplest way to understand the advantage of an intention-to-treat approach is to imagine a therapy that has a neutral effect on outcome but a high frequency of side effects in high-risk patients. Such a drug would be discontinued in many high-risk patients. With a per-protocol analysis, there would be an appearance of a better outcome among patients maintaining therapy, but this would be due to the drop-out of high-risk patients rather than a direct benefit.

Finally, de Lemos criticizes the AFFIRM² and Van Gelder and associates⁵ trials for not defining compliance. Because both trials assessed approaches to therapy (rate versus rhythm control), compliance would have been difficult to define. It would presumably include such standard measures as taking prescribed medication, but also reporting of events, acceptance of cardioversion when prescribed, and even physician-based components such as vigour of pursuit of heart-rate and sinus-rhythm endpoints.

It must be kept in mind that the goal of these studies was to compare 2 widely used strategies in a clinically relevant context, a goal that was largely

achieved. It is true that as physicians we prefer “positive” trials because they leave us with a sense of a conclusive message. However, both the AFFIRM² and Van Gelder and associates⁵ trials did yield a conclusive and important message, that for presently available approaches to atrial fibrillation therapy, rate control is not inferior overall to rhythm control. It is debatable whether larger studies that achieved a statistically significant *p* value would have provided any more practical information.

Stanley Nattel

Department of Pharmacology and Therapeutics
McGill University
Montréal, Que.

References

1. Nattel S. Rhythm versus rate control for atrial fibrillation management: what recent randomized clinical trials allow us to affirm [editorial]. *CMAJ* 2003;168(5):572-3.
2. Wyse DG, Waldo AL, DiMarco JP, Domanski MJ, Rosenberg Y, Schron EB, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.
3. Atrial fibrillation follow-up investigation of rhythm management — the AFFIRM study design. The Planning and Steering Committees of the AFFIRM study for the NHLBI AFFIRM investigators. *Am J Cardiol* 1997;79(9):1198-202.
4. Baseline characteristics of patients with atrial fibrillation: the AFFIRM Study. *Am Heart J* 2002;143:991-1001.
5. Van Gelder IC, Hagens VE, Bosker HA, Kingma JH, Kamp O, Kingma T, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med* 2002;347:1834-40.

Competing interests: None declared.

First-use risks

Eric Wooltorton¹ has written a balanced article in response to the warning on Diane-35 and the risk of venous thromboembolism issued by Health Canada.

Caution is always required in prescribing estrogen-progestin combinations, whether for contraception, postmenopausal hormone replacement or treatment of acne. However, the risk attributed to preparations containing cyproterone acetate in comparison with other preparations may have been exaggerated by not taking first-time use into

account. This effect has been estimated² to increase the risk of venous thromboembolism 10-fold in the first year of oral contraceptive use, regardless of preparation. The research letter of Vasilakis-Scaramozza and Jick,³ which was used by Health Canada to support the increased risk, provided adjusted odds ratios for venous thromboembolism, but no reference is made to first-time use as a potential factor. That report described a total of 128 subjects (cases and controls) who had used levonorgestrel-containing preparations and 42 subjects (cases and controls) who had used preparations containing cyproterone acetate. In the first group, only 9 (7%) had used the preparation for 6 months or less, whereas in the second group, a much larger proportion (12 or 29%) had used the drug for 6 months or less. Among patients with this short duration of use, there is a greater probability of first-time use. Thus, the proportion of women using an estrogen-progestin combination for the first time appears to have been higher in the group receiving preparations containing cyproterone acetate, which might account for some or all of the greater risk of venous thromboembolism in that group.

Timothy C. Rowe

Gynaecologist and Associate Professor
University of British Columbia
Vancouver, BC

References

1. Wooltorton E. Diane-35 (cyproterone acetate): safety concerns. *CMAJ* 2003;168(4):455-6.
2. Suissa S, Blais L, Spitzer WO, Cusson J, Lewis M, Heinemann L. First-time use of newer oral contraceptives and the risk of venous thromboembolism. *Contraception* 1997;56:141-6.
3. Vasilakis-Scaramozza C, Jick H. Risk of venous thromboembolism with cyproterone or levonorgestrel contraceptives. *Lancet* 2001;358:1427-9.

Competing interests: Dr. Rowe has received speaker fees from Wyeth, Organon, and Berlex Canada.

QALYs: the best option so far

Iwould like to challenge Maurice McGregor's argument in a recent commentary¹ that because the quality-

adjusted life-year (QALY) has “severe limitations,” it is not useful for cost-utility analyses.

To support his argument that the QALY is not meaningful, McGregor quotes a seminal work emphasizing the difficulty of using a single measurement to evaluate different health outcomes.² However, this same text recommends the continued use of the QALY while researchers develop potentially better tools.³

McGregor also argues that the QALY is not valid because it “frequently violates societal concerns for fairness in the allocation of health care resources.” Such ethical concerns have been expressed before, but alternatives to circumvent them are still relatively nascent, and “the conventional QALY remains the dominant approach.”²

McGregor then contends that the QALY is not reliable because utility estimates vary with the method used. However, variability can occur in any research. Consider how frequently clinical studies yield conflicting results. A more pertinent question is whether this variability is truly fatal to interpreting cost-effectiveness analyses.

McGregor next argues that the QALY is not relevant because there is “no unanimity as to whose viewpoint should be used when making societal policy decisions.” This does not make the QALY irrelevant — it merely means that research is needed to clarify the issue.

McGregor's final argument is more a general cautionary statement: “When the studies with which the cost-utility analysis in question can be compared are not identified, the cost-utility analysis should clearly not be used in health policy decisions.” However, the same can be said in any field: comparators should always be identified. Furthermore, comparing one cost-effectiveness ratio with another is no different from using league tables based on number-needed-to-treat to evaluate the clinical effectiveness of interventions.³

Without doubt, the QALY is an imperfect outcome measure. Nonetheless, despite acknowledging its weaknesses,