transfer to a hospital capable of “rescue” angioplasty.⁹ The researchers had recruited 840 of the required 1200 patients when the study was terminated early owing to inadequate funding. Although the study was underpowered and a difference in treatment effects cannot be excluded with certainty, the analysis is meaningful and a real difference is unlikely (95% confidence interval for the difference in risk – 1.53 to 0.29, $P = 0.29$). This is the only study making this comparison that has ever been performed and thus, though imperfect, it is the only information available. At termination of the trial the groups were not significantly different in terms of 30 day mortality, rates of reinfarction, or stroke, which together formed the primary end point. Of the patients treated with prehospital thrombolysis only 26% required urgent “rescue” angioplasty, but by 30 days 70% of the CAPTIM thrombolysis group had undergone angioplasty.

Perhaps the most important result came from a subsequent analysis examining the impact of time to treatment, which showed a significant interaction between treatment effect and delay.¹⁰ For patients randomised more than two hours after the onset of symptoms 30 day mortality was similar in the two groups, but for those randomised within 2 hours mortality was 2.2% with prehospital thrombolysis compared with 5.7% with angioplasty. Although not significant, the trend was strongly in favour of early thrombolysis for these “golden hour” patients.

In the GRACIA study, routine angiographically guided angioplasty resulted in a marked reduction in the need for revascularisation before discharge and a 50% reduction at 12 months in the combined risk of death, reinfarction, and ischaemia needing revascularisation.¹¹ Thus, in addition to the one quarter of prehospital thrombolysis patients who are likely to require immediate “rescue” angioplasty, the rest should have rapid angiography and appropriate revascularisation.

We suggest that the United Kingdom should consider a strategy summed up by three Ps: publicity to maximise the proportion of patients treated within three hours, prehospital thrombolysis, and percutane-

ous coronary intervention either immediately or before discharge. This strategy would need greater investment in prehospital care, but, most importantly, it would depend on effective and continuing publicity aimed at minimising the time between the onset of chest pain and thrombolysis. The public needs to know about the “golden hour.”

Jonathan N Townend *consultant cardiologist*

(John.Townend@uhb.nhs.uk)

Sagar N Doshi *consultant cardiologist*

Department of Cardiology, Queen Elizabeth Hospital Birmingham, Birmingham B15 2TH

Competing interests: None declared.

- Boersma E, Maas AC, Deckers JW, Simoons ML. Early thrombolytic treatment in acute myocardial infarction: reappraisal of the golden hour. *Lancet* 1996;348:771-5.
- Juliard JM, Feldman LJ, Golmard JL, Himbert D, Benamer H, Haghighat T, et al. Relation of mortality of primary angioplasty during acute myocardial infarction to door-to-Thrombolysis In Myocardial Infarction (TIMI) time. *Am J Cardiol* 2003;91:1401-5.
- Channer KS. Primary angioplasty should be first line treatment for acute myocardial infarction: against. *BMJ* 2004;328:1256-7.
- Smith D. Primary angioplasty should be first line treatment for acute myocardial infarction: for. *BMJ* 2004;328:1254-6.
- Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. *Lancet* 2003;361:13-20.
- The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Management of acute myocardial infarction in patients presenting with ST-segment elevation. *Eur Heart J* 2003;24:28-66.
- Morrison LJ, Verbeek PR, McDonald AC, Sawadsky BV, Cook DJ. Mortality and prehospital thrombolysis for acute myocardial infarction: A meta-analysis. *JAMA* 2000;283:2686-92.
- Widimsky P, Budesinsky T, Vorac D, Groch L, Zelizko M, Aschermann M, et al. Long distance transport for primary angioplasty vs immediate thrombolysis in acute myocardial infarction. Final results of the randomized national multicentre trial-PRAGUE-2. *Eur Heart J* 2003;24:94-104.
- Bonnefoy E, Lapostolle F, Leizorovicz A, Steg G, McFadden EP, Dubien PY, et al. Primary angioplasty versus prehospital fibrinolysis in acute myocardial infarction: a randomised study. *Lancet* 2002;360:825-9.
- Steg PG, Bonnefoy E, Chabaud S, Lapostolle F, Dubien PY, Cristofini P, et al. Impact of time to treatment on mortality after prehospital fibrinolysis or primary angioplasty: data from the CAPTIM randomized clinical trial. *Circulation* 2003;108:2851-6.
- Fernandez-Aviles F, Alonso JJ, Castro-Beiras A, Vazquez N, Blanco J, Alonso-Briales J, et al. Routine invasive strategy within 24 hours of thrombolysis versus ischaemia-guided conservative approach for acute myocardial infarction with ST-segment elevation (GRACIA-1): a randomised controlled trial. *Lancet* 2004;364:1045-53.

Drugs for Alzheimer's disease and related dementias

Clear rules about stopping treatment in individual patients are needed

Papers p 874

The article by Ballard et al in this issue (p 874) offers an opportunity to discuss the role of drugs in the treatment of Alzheimer's disease and related dementias.¹ This investigator driven randomised clinical trial has tested the hypothesis that the atypical neuroleptic quetiapine and the cholinesterase inhibitor rivastigmine would be better than placebo for treating agitation in institutionalised patients in severe stages of Alzheimer's disease. Using measures of agitation (the Cohen-Mansfield agitation inventory) and cognition (the severe impairment battery) appropriate for this stage of dementia, the authors showed that agitation improved equally in the

three arms of the trial but a measurable decline in cognition occurred in patients taking quetiapine. They conclude that these two drugs seemed of no benefit in patients with dementia and agitation in institutional care, and that quetiapine should not be used as alternative treatment to risperidone or olanzapine in people with dementia.

Showing the benefit of drugs on behaviour has been difficult in nursing home settings. Patients with moderate to severe Alzheimer's disease living in the community who were treated with the cholinesterase inhibitor donepezil over 24 weeks have shown an improvement, compared with placebo, in the total

BMJ 2005;330:857-8

score as well as on the apathy, depression, and anxiety items of the neuropsychiatric inventory.² However, when the same drug and outcome were used, no such benefit occurred for patients at a similar severity of disease living in a nursing home setting.³ Is this difference related to an observer bias, since behavioural problems in dementia are best assessed by interviewing informants who know the patient well—for example, are family members better than professional caregivers at detecting behavioural changes?⁴ This is not an issue in Ballard et al's study since all treated patients lived in institutions, and recent data showed good correlation between informant rating and direct observation of behaviours.⁵

Was it appropriate to target agitation in this study? Clearly yes, since agitation is one of the behaviours most commonly related to severity in dementia of various causes and has a marked impact on caregivers,⁶ and because uncertainty exists about the best management of agitation, pharmacological or otherwise.⁷

Does the publication by Ballard et al mean that rivastigmine and quetiapine should be avoided in dementia? Evidence from a recently published randomised controlled trial shows that rivastigmine is useful and well tolerated in dementia associated with Parkinson's disease,⁸ and in an open label trial quetiapine has been shown to improve psychotic symptoms and cognition in this condition.⁹ The evidence for efficacy of rivastigmine and other cholinesterase inhibitors in mild to moderate Alzheimer's disease is established, even by the current report from the National Institute for Clinical Excellence.¹⁰ The issue is whether they are worth their costs from society's point of view.

From a clinical perspective, cholinesterase inhibitors are helpful in the management of many of the symptoms associated with dementia for individual patients. The art of treatment is to use the right drug for the right symptoms at the proper stage of disease,

starting low and going slow. Perhaps clear stopping rules for drugs used in dementia based on evidence from randomised controlled trials and taking into account individual patients' responses to treatment will resolve the current debate about drugs for Alzheimer's disease and related dementias. Ballard et al have added useful information to the body of evidence from randomised controlled trials.

Serge Gauthier *professor of psychiatry, neurology and neurosurgery, and medicine*

McGill Center for Studies in Aging, 6825 LaSalle Blvd, Verdun (Montréal), Québec, Canada H4H 1R3
(Serge.gauthier@mcgill.ca)

Competing interests: SG has accepted honorariums for lectures and is on the scientific advisory board of most companies doing research in dementia including Pfizer, Novartis, Janssen-Cilag, Neurochem, Lundbeck, Merz, Roche, Lilly.

- 1 Ballard C, Margallo-Lana M, Juszcak E, Douglas S, Swann A, Thomas A, et al. Quetiapine and rivastigmine and cognitive decline in Alzheimer's disease: randomised double blind placebo controlled trial. *BMJ* 2005; 330:874-7.
- 2 Gauthier S, Feldman H, Hecker J, Vellas B, Ames D, Subbiah P, et al. Efficacy of donepezil on behavioral symptoms in patients with moderate to severe Alzheimer's disease. *Int Psychogeriatrics* 2002;14:389-404.
- 3 Tariot PN, Cummings JL, Katz IR, Mintzer J, Perdomo CA, Schwam EM, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of donepezil in patients with Alzheimer's disease in the nursing home setting. *J Am Geriatr Soc* 2001;49:1590-9.
- 4 Aalten P, de Vugt ME, Lousberg R, Korten E, Jaspers N, Senden B, et al. Behavior problems in dementia: as factor analysis of the neuropsychiatric inventory. *Dement Geriatr Cogn Disord* 2003;15:99-105.
- 5 Cohen-Mansfield J, Libin A. Assessment of agitation in elderly patients with dementia: correlations between informant rating and direct observation. *Int J Geriatr Psychiatry* 2004;19:881-91.
- 6 Senanarong V, Cummings JL, Fairbanks L, Mega M, Masterman DM, O'Connor SM, et al. Agitation in Alzheimer's disease is a manifestation of frontal lobe dysfunction. *Dement Geriatr Cogn Disord* 2004;17:14-20.
- 7 Profenno LA, Tariot PN. Pharmacologic management of agitation in Alzheimer's disease. *Dement Geriatr Cogn Disord* 2004;17:65-77.
- 8 Enre M, Aarsland D, Albanese A, Byrne EJ, Deuschl G, De Deyn PP, et al. Rivastigmine for dementia associated with Parkinson's disease. *N Engl J Med* 2004;351:2509-18.
- 9 Juncos JL, Roberts VJ, Evatt ML, Jewart RD, Wood CD, Potter LS, et al. Quetiapine improves psychotic symptoms and cognition in Parkinson's disease. *Movement Disorders* 2003;19:29-35.
- 10 National Institute for Health and Clinical Excellence (NICE). *Appraisal consultation document: Alzheimer's disease—donepezil, rivastigmine, galantamine and memantine (review)*. www.nice.org.uk/page.aspx?o=245912 (accessed 11 Apr 2005).

Human and veterinary medicine

Theme issue will look at ways in which doctors and vets can work together

Traditionally, human medicine and veterinary medicine tend to be viewed separately. Doctors treat people, and vets look after animals. Of course differences exist between the two types of patients and options for treatment. Euthanasia, for example, tends not to be looked on favourably in humans, whereas in veterinary medicine it might be the best approach. Similarly, culling infected individuals or those suspected of being infected is not an option for controlling an outbreak of infectious disease in humans but may well be so in animals. Doctors usually have the advantage over vets in that they can talk to their patients; for vets, life would be so much easier if their patients could talk.

Despite the differences between the two professions they have common interests and share challenges. Vets and doctors are having to work together more and more—for example, over fears that avian

influenza could be the harbinger of a human pandemic¹ and over control of food borne zoonoses.

Without adequate safeguards, diseases of people and animals can now move more quickly around the world. Controls and contingency plans must be drawn up in tandem, whether the disease threat is natural, as with SARS, or caused by humans, as in a potential bioterrorist attack. Antimicrobial resistance also presents challenges to doctors and vets alike.

With increasing urbanisation we can easily forget the extent to which people depend on animals. In the developing world many people rely on animals for food and transport (whether of people or goods)—and the health of those animals can mean the difference between life and death. Closer to home, livestock are important economically but animals are also a source of companionship. Half of all households in the United Kingdom own a pet (www.pfina.com/public/

BMJ 2005;330:858-9