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International comparisons of acute myocardial infarction

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In conclusion, although Anagnostou and colleagues provide further evidence that OIT is a potential treatment for food allergy,⁴ more high-quality data are needed. It is important to understand that OIT research cannot be rushed, and is years away from routine clinical use. Investigative groups need time to refine protocols, revalidate data, understand the mechanisms of OIT, and minimise adverse effects. This must be done without added pressure or heightened expectations to quickly produce a marketable therapy.

Matthew J Greenhawt

The University of Michigan Food Allergy Center, Division of Allergy and Clinical Immunology, Ann Arbor, MI 48106, USA
mgreenha@med.umich.edu

I am a member of the Educational Advisory Council for the National Peanut Board and have consulted for Deerfield Industries.

- 1 Gupta RS, Springston EE, Warrier MR, et al. The prevalence, severity, and distribution of childhood food allergy in the United States. *Pediatrics* 2011; **128**: e9–17.
- 2 European Academy of Allergy and Clinical Immunology (EAACI). Food Allergy and Anaphylaxis Public Declaration. Switzerland: European Academy of Allergy and Clinical Immunology, 2013. <http://www.eaaci.org/attachments/FoodAllergy&AnaphylaxisPublicDeclarationCombined.pdf> (accessed Dec 5, 2013).
- 3 Moran TP, Vickery BP, Burks AW. Oral and sublingual immunotherapy for food allergy: current progress and future directions. *Curr Opin Immunol* 2013; **25**: 781–87.
- 4 Anagnostou K, Islam S, King Y, et al. Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial. *Lancet* 2014; published online Jan 30. [http://dx.doi.org/10.1016/S0140-6736\(13\)62301-6](http://dx.doi.org/10.1016/S0140-6736(13)62301-6).
- 5 Buchanan AD, Green TD, Jones SM, et al. Egg oral immunotherapy in nonanaphylactic children with egg allergy. *J Allergy Clin Immunol* 2007; **119**: 199–205.
- 6 Hofmann AM, Scurlock AM, Jones SM, et al. Safety of a peanut oral immunotherapy protocol in children with peanut allergy. *J Allergy Clin Immunol* 2009; **124**: 286–91.
- 7 Skripak JM, Nash SD, Rowley H, et al. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2008; **122**: 1154–60.
- 8 Jones SM, Pons L, Roberts JL, et al. Clinical efficacy and immune regulation with peanut oral immunotherapy. *J Allergy Clin Immunol* 2009; **124**: 292–300.
- 9 Blumchen K, Ulbricht H, Staden U, et al. Oral peanut immunotherapy in children with peanut anaphylaxis. *J Allergy Clin Immunol* 2010; **126**: 83–91.
- 10 Anagnostou K, Clark A, King Y, Islam S, Deighton J, Ewan P. Efficacy and safety of high-dose peanut oral immunotherapy with factors predicting outcome. *Clin Exp Allergy* 2011; **41**: 1273–81.
- 11 Burks AW, Jones SM, Wood RA, et al. Oral immunotherapy for treatment of egg allergy in children. *N Engl J Med* 2012; **367**: 233–43.
- 12 Varshney P, Jones SM, Scurlock AM, et al. A randomized controlled study of peanut oral immunotherapy: clinical desensitization and modulation of the allergic response. *J Allergy Clin Immunol* 2011; **127**: 654–60.
- 13 Sampson HA. Peanut oral immunotherapy: is it ready for clinical practice? *J Allergy Clin Immunol Pract* 2013; **1**: 15–21.
- 14 Narisety SD, Skripak JM, Steele P, et al. Open-label maintenance after milk oral immunotherapy for IgE-mediated cow's milk allergy. *J Allergy Clin Immunol* 2009; **124**: 610–12.
- 15 Keet CA, Seopaul S, Knorr S, Narisety S, Skripak J, Wood RA. Long-term follow-up of oral immunotherapy for cow's milk allergy. *J Allergy Clin Immunol* 2013; **132**: 737–39.



International comparisons of acute myocardial infarction

Sheng-Chia Chung and colleagues¹ report in *The Lancet* that, in their comparison of short-term outcomes in patients with acute myocardial infarction, unadjusted 30-day mortality was more than a third higher in the UK than in Sweden during 2004–10. They suggest that this difference is due largely to the divergent speed of implementation of policy initiatives to improve care. Chung and colleagues compared the UK data with those for Sweden because the two countries have similar health systems for, and spending on, acute myocardial infarction, but diffusion of evidence-based changes to practice and new technologies has been notably quicker in Sweden.

Records for 119 786 patients in Sweden and 391 077 in the UK were assessed. This fundamental prognosis research,² which used whole-country data, showed much higher unadjusted mortality in patients with acute myocardial infarction in the UK than in Sweden: 30-day mortality was 10.5% (95% CI 10.4–10.6) in the UK and 7.6% (7.4–7.7) in Sweden. The UK to Sweden standardised

mortality ratio was 1.37 (1.30–1.45), which suggests that more than 11 000 deaths due to acute myocardial infarction might have been avoided during the period of the study. Importantly, although the difference in mortality rates decreased over time, mortality was always higher in the UK, even in clinical subgroups such as those defined by troponin concentration or ST-segment elevation. After standardisation for the Swedish casemix by use of a 17-variable model that took into account patients' risk at baseline, UK 30-day mortality decreased by around 3%. This finding suggests that factors from the point of first medical contact to 30 days from hospital admission differentially affect outcomes.

Chung and colleagues explored what factors might account for the international differences in mortality. Their findings imply that between-country differences in the use and dissemination of treatments recommended in guidelines was an important factor, as they noted that in the UK the uptake of primary percutaneous coronary

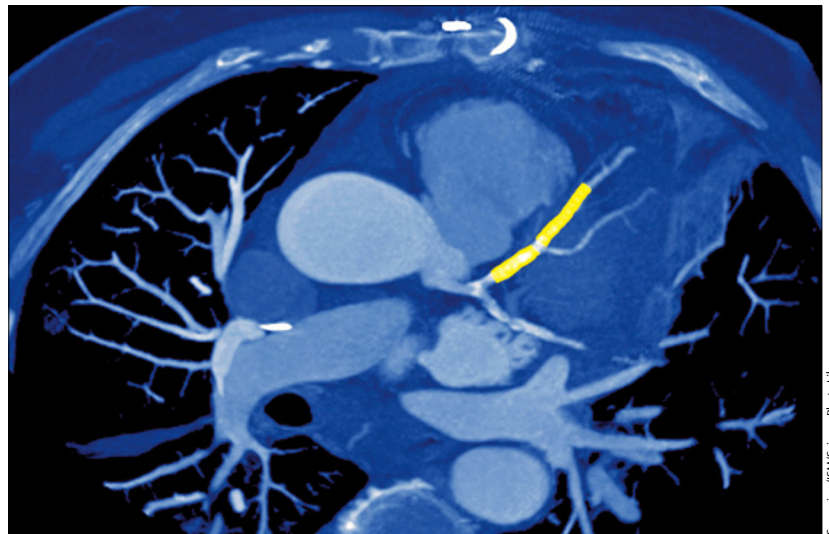
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intervention (PCI) was lower at the starting point and prescribing rates for β blockers at discharge were lower than in Sweden.

Implementation of cardiovascular evidence-based practice in the UK has been reported to lag behind that of other countries. Laut and colleagues^{3,4} compared diffusion of primary PCI across countries in the European Union and found that England was a late and low adopter. Yet, in Chung and colleagues' study,¹ prescription of statins and angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers at discharge was greater in the UK than in Sweden, which suggests that unless primary PCI and β blockers have a stronger association with survival than these treatments, other factors might lead to differences in mortality. Although estimates equally favoured reduced 30-day mortality for primary PCI over that for thrombolysis in Sweden and the UK, in line with other studies,⁵ the associations between statins, angiotensin-converting-enzyme inhibitors, and angiotensin-receptor blockers are not provided by the authors. Moreover, if the UK had adopted Swedish levels of use of primary PCI and β blockers, the standardised mortality ratio would only have reduced to 1.31, with primary PCI leading to around 2000 and β blockers to less than 50 lives saved over the 7 years of study. When the use of in-hospital treatments was considered in addition to casemix, the standardised mortality ratio decreased but did not reach unity.

The restricted improvement in standardised mortality ratio after adjustment for imbalanced treatments suggests that factors outside hospital-based cardiac interventions are also important. Indeed, Chung and colleagues' study highlights the similarities between the UK and Sweden for thrombolysis and primary PCI process measures and that, overall, reperfusion rates were higher in the UK than in Sweden (77% vs 71%). The difference in mortality rates, however, was upheld after matching by propensity score. This finding is not surprising because the scores were derived from the same 17-factor model. For these reasons, unmeasured factors, such as imbalanced case ascertainment, unmeasured confounders, non-modelled covariates or missing data, and hospital care systems are probably responsible for the international difference in mortality.

Aspects of health care, such as a patient's appropriateness for therapy and drug adherence, might have differed between the UK and Sweden. These data, which



CT scan showing stents (yellow) in coronary artery

are not routinely collected in national electronic health-care records, could have influenced the UK mortality rates. In an attempt to mitigate bias due to absent data in one source but recorded elsewhere, the authors imputed missing data. This approach, however, is unlikely to have alleviated all systematic bias and would not account for data missing by design. The modelling of latent classes could have offered greater insight into the effects of unmeasured factors. Furthermore, the authors undertook an asymmetric analysis intended to assess what would have happened if UK patients had been transferred to Sweden, but the results of a bi-directional simulation might have been more informative.

Nonetheless, through highlighting the prospect of a substantial excess of deaths in the UK compared with Sweden, Chung and colleagues have drawn our attention to the need for further comparative effectiveness research for acute myocardial infarction. Efforts to improve cardiovascular outcomes in the UK should, therefore, concentrate on data enhancement through the linkage of electronic health-care records and the early and systematic implementation of evidence-based therapies across the National Health Service. The authors reveal large international inequalities in the management and outcomes for these patients. Despite substantial reductions in early mortality rates after acute myocardial infarction, cardiovascular disease remains one of the biggest killers in developed countries.^{6,7} The prevention of premature cardiovascular death must, therefore, continue to be a priority for research.

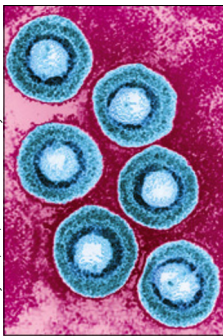
*Chris P Gale, Keith A A Fox

Division of Epidemiology and Biostatistics, University of Leeds, Leeds LS2 9JT, UK (CPG); Department of Cardiology, York Teaching Hospital, York, UK (CPG); and Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK (KAAF)
c.p.gale@leeds.ac.uk

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- 1 Chung S-C, Gedeberg R, Nicholas O, et al. Acute myocardial infarction: a comparison of short-term survival in national outcome registries in Sweden and the UK. *Lancet* 2014; published online Jan 23. [http://dx.doi.org/10.1016/S0140-6736\(13\)62070-X](http://dx.doi.org/10.1016/S0140-6736(13)62070-X).
- 2 Hemingway H, Croft P, Perel P, et al. Prognosis research strategy (PROGRESS) 1: a framework for researching clinical outcomes. *BMJ* 2013; **346**: e5595.
- 3 Laut KG, Gale CP, Pedersen AB, Fox KA, Lash TL, Kristensen SD. Persistent geographical disparities in the use of primary percutaneous coronary intervention in 120 European regions: exploring the variation. *EuroIntervention* 2013; **9**: 469–76.
- 4 Laut KG, Gale CP, Lash TL, Kristensen SD. Determinants and patterns of utilization of primary percutaneous coronary intervention across 12 European countries: 2003–2008. *Int J Cardiol* 2013; **168**: 2745–53.
- 5 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.
- 6 Gale CP, Cattle BA, Woolston A, et al. Resolving inequalities in care? Reduced mortality in the elderly after acute coronary syndromes. The Myocardial Ischaemia National Audit Project 2003–2010. *Eur Heart J* 2011; **33**: 630–39.
- 7 Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2095–128.

Prevention of varicella: time for two-dose vaccination



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Live-attenuated varicella zoster virus (VZV) vaccines have been available for decades, but their potential to reduce disease worldwide has not been fully realised. Few countries have incorporated varicella vaccination into public programmes, even though rapid and large decreases in varicella deaths and admissions have been achieved in the USA and Australia.^{1,2} One reason for reluctance to vaccinate is that, despite high efficacy of 88–100% reported in the randomised controlled trials of one-dose live-attenuated monovalent varicella vaccines in children (Varilrix, GSK³ and Varivax, Merck⁴), field effectiveness has turned out to be lower at 72–81%.^{5,6} In view of persisting disease transmission, some countries, such as the USA and Germany, now recommend a two-dose schedule. Frustratingly, a paucity of empirical data on extent of enhanced protection expected from a second vaccination⁷ has made estimation of cost-effectiveness difficult. This absence of information has been the main reason for countries such as Australia continuing a one-dose programme.⁸

In *The Lancet*, Roman Prymula and colleagues⁹ present results of the first randomised clinical trial to assess protection against varicella of two vaccine doses, using the four-in-one live-attenuated measles-mumps-rubella-varicella (MMRV; Priorix-Tetra, GSK) vaccine. Although MMRV vaccines have been approved since the mid-2000s, protection was assumed only on the basis of much the same immunogenicity as the component vaccines. This industry-funded study was done in 5803 toddlers aged 12–22 months across ten European countries where

varicella remains endemic. Participants were divided into three groups; all children received consecutive doses of study vaccines given 6 weeks apart, thereby controlling for the number of injections. The first group received two doses of MMRV; the second group had first a dose of measles-mumps-rubella (MMR; Priorix, GSK) vaccine followed by monovalent varicella vaccine (Varilrix, GSK); and the third (control) group had two doses of MMR.

Strengths of the study include 3 years of active follow-up (during which about 20% of all children reported exposure to varicella) and virological case-confirmation using VZV-PCR. Efficacy of one dose of varicella vaccination was in line with, if not a little lower than, expectations at 65.4% (97.5% CI 57.2–72.1) against disease of any severity and 90.7% (85.9–93.9) against moderate-severe disease, whereas two-dose MMRV prevented varicella in 94.9% (92.4–96.6) of children and was almost completely protective against moderate-severe disease (99.5% [97.5–99.9]). The risk of breakthrough varicella (defined as wild strain varicella occurring more than 42 days after vaccination) was 6.9 times (95% CI 4.9–9.8) less likely with two doses of MMRV than with one dose of varicella vaccine. As expected, immunogenicity of two-dose vaccination compared with one dose was also greater, at 42 days after vaccination and persisting for 2 years of follow-up.

This study reinforces that in most vaccine recipients, irrespective of receipt of one or two doses, varicella is a mild disease with fewer and less severe varicella lesions and fever than occurs in unvaccinated children.

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