of cardiac arrest is potentially reversible, it might be worthwhile to try for a little longer.

*Jerry P Nolan, Jasmeet Soar
Royal United Hospital NHS Trust, Bath BA1 3NG, UK (JPN); and Southmead Hospital, North Bristol NHS Trust, Bristol, UK (JS)
jerry.nolan@nhs.net

JPN is editor-in-chief of *Resuscitation* (honorarium received). JS is an editor of *Resuscitation* (honorarium received).

1 Lippert FK, Raffay V, Georgiou M, Steen PA, Bossaert L. European Resuscitation Council guidelines for resuscitation 2010 section 10. The ethics of resuscitation and end-of-life decisions. *Resuscitation* 2010; **81:** 1445–51.
2 Morrison LJ, Kierzek G, Diekema DS, et al. Part 3: ethics: 2010 American Heart Association guidelines for cardiopulmonary resuscitation and emergency cardiovascular care. *Circulation* 2010; **122:** S665–75.
3 van Walraven C, Forster AJ, Parish DC, et al. Validation of a clinical decision aid to discontinue in-hospital cardiac arrest resuscitations. *JAMA* 2001; **285:** 1602–06.
4 Goldberger ZD, Chan PS, Berg RA, et al, for the American Heart Association Get With The Guidelines—Resuscitation (formerly the National Registry of Cardiopulmonary Resuscitation) Investigators. Duration of resuscitation efforts and survival after in-hospital cardiac arrest: an observational study. *Lancet* 2012; published online Sept 5. http://dx.doi.org/10.1016/S0140-6736(12)60862-9.
5 Shih CL, Lu TC, Jerng JS, et al. A web-based Utstein style registry system of in-hospital cardiopulmonary resuscitation in Taiwan. *Resuscitation* 2007; **72:** 394–403.
6 Christenson J, Andrusiek D, Everson-Stewart S, et al. Chest compression fraction determines survival in patients with out-of-hospital ventricular fibrillation. *Circulation* 2009; **120:** 1241–47.
7 Stiell IG, Brown SP, Christenson J, et al. What is the role of chest compression depth during out-of-hospital cardiac arrest resuscitation? *Crit Care Med* 2012; **40:** 1192–98.
8 Idris AH, Guffey D, Aufderheide TP, et al. Relationship between chest compression rates and outcomes from cardiac arrest. *Circulation* 2012; **125:** 3004–12.
9 Carr BG, Kahn JM, Merchant RM, Kramer AA, Neumar RW. Inter-hospital variability in post-cardiac arrest mortality. *Resuscitation* 2009; **80:** 30–34.
10 Heradstveit BE, Sunde K, Sunde GA, Wentzel-Larsen T, Heltne JK. Factors complicating interpretation of capnography during advanced life support in cardiac arrest—a clinical retrospective study in 575 patients. *Resuscitation* 2012; **83:** 813–18.
11 Parnia S, Nasir A, Shah C, Patel R, Mani A, Richman P. A feasibility study evaluating the role of cerebral oximetry in predicting return of spontaneous circulation in cardiac arrest. *Resuscitation* 2012; **83:** 982–85.
12 Chen YS, Lin JW, Yu HY, et al. Cardiopulmonary resuscitation with assisted extracorporeal life-support versus conventional cardiopulmonary resuscitation in adults with in-hospital cardiac arrest: an observational study and propensity analysis. *Lancet* 2008; **372:** 554–61.

EXAMINATION of new drug-eluting stents—top of the class!

Published **Online** September 3, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61021-6

See **Articles** page 1482

The introduction of drug-eluting stents was heralded as a key development in cardiovascular medicine because of the large relative and absolute reductions in repeat coronary procedures compared with bare-metal stents (BMS). After initial exuberance with drug-eluting stents, reports emerged of a dark side—increased rates of stent thrombosis.[1] A meta-analysis of the randomised data of first-generation drug-eluting versus bare-metal stents confirmed this adverse signal.[2] Concern was greatest in acute myocardial infarction, since the baseline risk of stent thrombosis was known to be higher than in stable coronary artery disease, and therefore, any higher propensity for stent thrombosis with drug-eluting stents might be further amplified.[3] In *The Lancet*, Manel Sabate and colleagues[4] carefully examine the topic in the EXAMINATION trial.

The EXAMINATION investigators randomly assigned 1498 patients with ST-segment elevation myocardial infarction to receive the second-generation everolimus-eluting stents (EES) or BMS.[4] At 1-year follow-up, the primary endpoint of all-cause death, any recurrent myocardial infarction, or any revascularisation was 11·9% (89 of 751 patients) in the EES group versus 14·2% (106 of 747 patients) in the BMS group (difference −2·34 [95% CI −5·75 to 1·07]; p=0·19). The rate of cardiac death, target vessel myocardial infarction, or target lesion revascularisation was 5·9% in the EES group versus 8·4% in the BMS group (p=0·05). Target lesion revascularisation was significantly reduced with EES from 5·0% with BMS to 2·1% with EES (p=0·003), consistent with previous trials of drug-eluting stents, including in acute myocardial infarction. A significant reduction in stent thrombosis was noted (0·5% with EES *vs* 1·9% with BMS for definite stent thrombosis and 0·9% with EES *vs* 2·5% with BMS for definite or probable stent thrombosis; p=0·019 for both). This reduction in stent thrombosis with EES to a third of the rate with BMS is a major advance in the treatment of acute myocardial infarction.

Critics will contend that EXAMINATION did not show superiority for EES in the primary endpoint. Although no significant reduction was noted, the primary endpoint was numerically lower. The reduction in target lesion revascularisation reported in the study is meaningful to patients. Repeat percutaneous coronary intervention and particularly coronary artery bypass grafting are events that patients would like to avoid. Beyond the inconvenience, financial costs, and risks of a repeat procedure, some

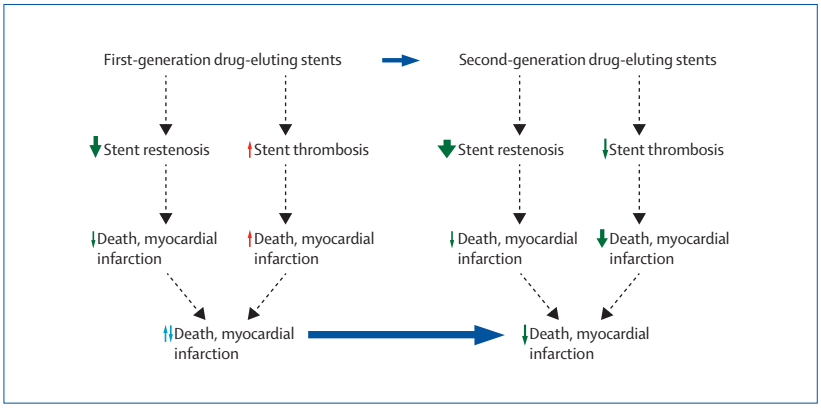

Figure: **Theoretical framework by which second-generation drug-eluting stents might decrease risk of myocardial infarction and cardiovascular death compared with bare metal stents, even though first-generation drug-eluting stents did not**

observational data also exist that suggest restenosis is not always benign and might be associated with an acute coronary syndrome, even in the absence of overt stent thrombosis.[5,6] Thus, reduction in target lesion revascularisation in a large enough sample with long-term follow-up might be expected to reduce future risk of myocardial infarction or death, especially if no counterbalancing elevated risk of stent thrombosis exists.

The actual reduction in stent thrombosis in EXAMINATION would also be expected to reduce ocurrence of myocardial infarction and death in a large population, since stent thrombosis often results in myocardial infarction or death. Of concern, a patient-level meta-analysis[3] showed an increased risk of very late stent thrombosis and reinfarction with first-generation drug-eluting stents in acute myocardial infarction.[3] Also of note, with closer scrutiny in recent years, even BMS have been shown to have a very low, but not zero, risk of delayed stent thrombosis.[7,8] Indeed, although a follow-up longer than that in the study will be insightful and necessary, the 1-year stent thrombosis findings from EXAMINATION mean that EES should be the benchmark for future studies of stent platforms, whether they are drug-eluting, bioabsorbable, or some other innovative variation.

The results of EXAMINATION are buttressed by recent meta-analyses,[9,10] which showed reduced rates of stent thrombosis with EES compared with BMS in a broad population of patients with coronary artery disease.[9,10] If this observation is true and not due to differences in duration of dual antiplatelet therapy, it potentially redefines all previous comparisons of percutaneous coronary intervention versus coronary artery bypass surgery and of percutaneous coronary intervention versus medical therapy. With proper selection of patients, the large reduction in restenosis and secondary ischaemic events with first-generation drug-eluting stents seemed to counterbalance any excess mortality due to the small increase in stent thrombosis, such that the first-generation drug-eluting stents did not raise mortality compared with BMS, nor did they lower it.[11] However, the reduced rates of stent thrombosis with EES compared with BMS, and the reduction in repeat revascularisation, would be expected in a large enough trial to translate into reduced rates of myocardial infarction and death (figure). In fact, observational data already suggest that second-generation drug-eluting stents are associated with lower rates of restenosis, stent thrombosis, and death than either first-generation drug-eluting stents or BMS.[12]

Thus, the findings of EXAMINATION might fundamentally change the risk-benefit calculus when weighing the role of percutaneous coronary intervention across a variety of indications. For example, COURAGE[13] showed similar rates of death or myocardial infarction in patients with stable coronary artery disease randomly assigned to initial percutaneous coronary intervention compared with patients assigned to medical therapy in the BMS era, but perhaps use of second-generation drug-eluting stents would have more clearly tipped the balance in favour of percutaneous coronary intervention. Of course, this hypothesis will need to be confirmed prospectively in randomised trials, but if it is borne out, the role of percutaneous coronary intervention could expand greatly. Regardless, in patients currently with indications for percutaneous coronary intervention such as acute coronary syndromes or severe stable angina, the second-generation of drug-eluting stents couples better efficacy with increased safety compared with either BMS or first-generation drug-eluting stents, which should lead to greatly improved outcomes in patients undergoing percutaneous coronary intervention.

Deepak L Bhatt
VA Boston Healthcare System, Brigham and Women's Hospital, and Harvard Medical School, Boston, MA 02132 USA
dlbhattmd@post.harvard.edu

I have been a member of the advisory board for Medscape Cardiology; a member of the board of directors for Boston VA Research Institute and Society of Chest Pain Centers; a Chair for American Heart Association Get With The Guidelines Science Subcommittee; received honoraria from the American College of

Cardiology (Editor, *Clinical Trials*, *Cardiosource*), the Duke Clinical Research Institute (clinical trial steering committees), Slack Publications (Chief Medical Editor, *Cardiology Today Intervention*), and WebMD (CME steering committees); received research grants from Amarin, AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Medtronic (co-PI of SYMPLICITY HTN-3 renal denervation trial), Sanofi-Aventis, and the Medicines Company; and I have done unfunded research with FlowCo, PLx Pharma, and Takeda. I serve on the steering committee of the OPTIMIZE trial that is randomising patients receiving the ENDEAVOR zotarolimus-eluting stent to either 3 or 12 months of clopidogrel.

1 McFadden EP, Stabile E, Regar E, et al. Late thrombosis in drug-eluting coronary stents after discontinuation of antiplatelet therapy. *Lancet* 2004; **364:** 1519–21.

2 Bavry AA, Kumbhani DJ, Helton TJ, Borek PP, Mood GR, Bhatt DL. Late thrombosis of drug-eluting stents: a meta-analysis of randomized clinical trials. *Am J Med* 2006; **119:** 1056–61.

3 De Luca G, Dirksen MT, Spaulding C, et al. Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. *Arch Intern Med* 2012; **172:** 611–21.

4 Sabate M, Cequier A, Iñiguez A, et al. Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. *Lancet* 2012; published online Sep 3. http://dx.doi.org/10.1016/S0140-6736(12)61223-9.

5 Chen MS, John JM, Chew DP, Lee DS, Ellis SG, Bhatt DL. Bare metal stent restenosis is not a benign clinical entity. *Am Heart J* 2006; **151:** 1260–64.

6 Walters DL, Harding SA, Walsh CR, Wong P, Pomerantsev E, Jang IK. Acute coronary syndrome is a common clinical presentation of in-stent restenosis. *Am J Cardiol* 2002; **89:** 491–94.

7 Sarkees ML, Bavry AA, Galla JM, Bhatt DL. Bare metal stent thrombosis 13 years after implantation. *Cardiovasc Revasc Med* 2009; **10:** 58–59.

8 Doyle B, Rihal CS, O'Sullivan CJ, et al. Outcomes of stent thrombosis and restenosis during extended follow-up of patients treated with bare-metal coronary stents. *Circulation* 2007; **116:** 2391–98.

9 Bangalore S, Kumar S, Fusaro M, et al. Short and long-term outcomes with drug eluting and bare metal coronary stents: A mixed treatment comparison analysis of 117 762 patient-years of follow-up from randomized trials. *Circulation* 2012; **125:** 2873–91.

10 Palmerini T, Biondi-Zoccai G, Della Riva D, et al. Stent thrombosis with drug-eluting and bare-metal stents: evidence from a comprehensive network meta-analysis. *Lancet* 2012; **379:** 1393–402.

11 Bavry AA, Bhatt DL. Appropriate use of drug-eluting stents: balancing the reduction in restenosis with the concern of late thrombosis. *Lancet* 2008; **371:** 2134–43.

12 Sarno G, Lagerqvist B, Frobert O, et al. Lower risk of stent thrombosis and restenosis with unrestricted use of 'new-generation' drug-eluting stents: a report from the nationwide Swedish Coronary Angiography and Angioplasty Registry (SCAAR). *Eur Heart J* 2012; **33:** 606–13.

13 Boden WE, O'Rourke RA, Teo KK, et al. Optimal medical therapy with or without PCI for stable coronary disease. *N Engl J Med* 2007; **356:** 1503–16.

Job strain as a measure of exposure to psychological strain

Published **Online** September 14, 2012 http://dx.doi.org/10.1016/S0140-6736(12)61512-8

See **Articles** page 1491

Although work contributes to material wellbeing and might be beneficial to health, strain caused by qualitative or quantitative elements of an individual's work can be harmful to a person's physical or mental health. Karasek and colleagues' 1981 job-strain model[1] was a breakthrough in the epidemiology of work-related psychosocial factors and diseases. The model suggested that high job demands plus low individual control over those demands would contribute an essential part of the psychological load that might lead to stress and, therefore, an increased risk of development of cardiovascular and mental diseases, particularly in industrial work environments.[2,3] The model was noteworthy in its ability to predict potential risks[4]—eg, the prevalence of antidepressant drug use and sickness absence in the Finnish working population.[5,6]

In *The Lancet*, Mika Kivimäki and colleagues[7] report findings from their collaborative meta-analysis of individual participant data from 197 473 European men and women without pre-existing coronary heart disease. 30 214 participants (about 15%) reported job strain. The investigators measured exposure to job strain (high demands and low control) on the basis of just one baseline assessment (done between 1985 and 2006), noting an association between job strain and coronary heart disease across age groups, sexes, socioeconomic strata, and regions, and after adjustments for socioeconomic status, and lifestyle and conventional risk factors. The sex-adjusted and age-adjusted hazard ratio for job strain versus no job strain (all other combinations of demands and control) was 1·23 (95% 1·10–1·37). The investigators used data from both unpublished (1·16, 1·02–1·32) and published (1·43, 1·15–1·77) studies to minimise publication bias; however some bias still seems to be present, but with no material effect on the conclusions. Furthermore, the study sought to reduce bias owing to reverse causation by exclusion of disease events that occurred in the first 3 years (1·31, 1·15–1·48) and 5 years (1·30, 1·13–1·50) of follow-up.

The article's appendix provides data for alternative measures of job strain in four categories: low strain (low demands and high control), passive (low demands and low control), active (high demands and high control), and high strain (high demands and low control). Only a few studies have reported the possible synergistic effect of high demands and low control.[2,8] The hazard ratios were 0·93 (95% CI 0·89–0·98) for high control and 1·02 (0·96–1·08) for high demands. With the combination of high control and low demands as comparator, the hazard ratios were 1·12 (0·99–1·27) for low demands and low control, 1·06 (0·94–1·19) for high demands and high control, and 1·28 (1·11–1·48) for