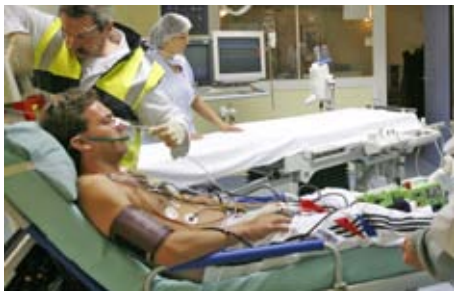
These letters are selected from rapid responses posted on bmj.com. Selection is usually made 12 days after print publication of the article to which they respond.

bmj.com To submit a rapid response go to any article on bmj.com and click "respond to this article"

LETTERS



SPL

OXYGEN IN MYOCARDIAL INFARCTION

Maintain normoxaemia until more evidence is available

Atar's advice to give oxygen to non-hypoxaemic patients with myocardial infarction is worrying.[1] There is no evidence that normobaric hyperoxaemia is beneficial in myocardial infarction, but a non-significant increase in death and a significant increase in aspartate aminotransferase has been reported.[2] Oxygen was given routinely to normoxaemic patients with strokes until it was shown to increase mortality significantly in patients with mild and moderate strokes.[3] The logical response for both conditions is to confine oxygen treatment to those who are hypoxaemic.[4 5]

Myocardial ischaemia is usually due to lack of blood flow rather than oxygen. Farquhar et al reported a mean reduction in coronary artery blood flow of 8-29% with increased coronary vascular resistance and reduced myocardial oxygen consumption in five studies where oxygen was given to patients with heart disease.[6] Giving oxygen to normoxaemic patients (saturation 96-98%) can increase blood oxygen content by only 2-4%, which cannot compensate for reduced coronary blood flow of 8-29%.

High dose oxygen is given to most survivors of cardiac arrest, but hyperoxaemia was associated with an increased risk of death compared with normoxaemia and hypoxaemia.[7]

The British Thoracic Society (BTS) guideline for emergency oxygen use recommends that oxygen should be given to patients with heart attack (and patients with angina) only if they are hypoxaemic to aim for a near normal saturation range of 94-98%.[4] This guideline was endorsed by the British Cardiovascular Society, 21 other societies, and the National Institute for Health and Clinical Excellence (NICE).[5]

Atar states that the use of oxygen for patients with angina is "undisputed," contradicting the BTS and NICE guidelines. He offers no evidence other than "custom and practice" to support continuation of a treatment with strong physiological evidence and weak clinical evidence of harm but no proved benefit.

B Ronan O'Driscoll consultant respiratory physician, Salford Royal University Hospital, Salford M6 8HD
ronan.o'driscoll@srft.nhs.uk
Luke S Howard consultant chest physician, Hammersmith Hospital, Imperial College Healthcare NHS Trust, London W12 0HS
Anthony G Davison consultant chest physician, Southend University Hospital, Westcliff on Sea SS0 0RY

Competing interests: The authors are the lead authors of the British Thoracic Society guideline for emergency oxygen use in adult patients (2008).

1 Atar D. Should oxygen be given in myocardial infarction? *BMJ* 2010;340:c3287. (17 June.)
2 Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *BMJ* 1976;i:1121-3.
3 Rønning OM, Guldvog B. Should stroke victims routinely receive supplemental oxygen? A quasi-randomized controlled trial. *Stroke* 1999;30:2033-7.
4 O'Driscoll BR, Howard LS, Davison AG; British Thoracic Society. BTS guideline for emergency oxygen use in adult patients. *Thorax* 2008;63(suppl 6):vi1-68.
5 National Institute for Health and Clinical Excellence. Chest pain of recent onset: Assessment and diagnosis of recent onset chest pain or discomfort of suspected cardiac origin. http://guidance.nice.org.uk/CG95.
6 Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009;158:371-7.
7 Kilgannon JH, Jones AE, Shapiro NI, Angelos MG, Milcarek B, Hunter K, et al; Emergency Medicine Shock Research Network (EMShockNet) Investigators. Association between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA* 2010;303:2165-71.

Cite this as: *BMJ* 2010;341:c3715

Author's reply

I principally recommend following guidelines, even when the studies supporting their recommendations might be weak. In fact, only around 10% of all guideline recommendations in cardiology are based on class A evidence. Let us therefore examine what the three authoritative societies in cardiology recommend in their guidelines.

The 2004 guideline on ST elevation myocardial infarction from the American Heart Association and American College of Cardiology gives a class IIa recommendation to the use of oxygen.[1] It states that "it is reasonable to administer supplemental oxygen to all patients with uncomplicated ST elevation myocardial infarction during the first 6 hours." There is very little literature covering this topic, hence the level of evidence is C.

The 2008 guideline on ST elevation myocardial infarction from the European Society of Cardiology states that "oxygen 2-4 l/min by mask or nasal prongs should be administered to those who are breathless or who have any features of heart failure or shock."[2]

It is important to repeat that there is no convincing evidence of harm about giving oxygen in myocardial infarction. None of the five studies selected in the review by Farquhar et al,[3] irrespective of how profoundly O'Driscoll and colleagues rely on its conclusions,[4] dealt with patients with myocardial infarction.

Dan Atar professor and head of cardiology, Department of Cardiology B, Oslo University Hospital Ullevål and Faculty of Medicine, University of Oslo, Oslo 0407, Norway
dan.atar@online.no

Competing interests: None declared.

1 Antman EM, Anbe DT, Armstrong PW, Bates ER, Green LA, Hand M, et al. ACC/AHA guidelines for the management of patients with ST-elevation myocardial infarction—executive summary: a report of the American College of Cardiology/American Heart Association. *Circulation* 2004;110:588-636.
2 Van de Werf F, Bax J, Betriu A, Blomstrom-Lundqvist C, Crea F, Falk V, et al. Management of acute myocardial infarction in patients presenting with persistent ST-segment elevation: the Task Force on the Management of STSegment Elevation Acute Myocardial Infarction of the European Society of Cardiology. *Eur Heart J* 2008;29:2909-45.
3 Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, et al. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J* 2009;158:371-7.
4 O'Driscoll BR, Howard LS, Davison AG. Maintain normoxaemia until more evidence is available. *BMJ* 2010;341:c3715.

Cite this as: *BMJ* 2010;341:c3717

GUMS AND HEART DISEASE

Healthy gums, healthy heart?

It is hard to know from de Oliveira and colleagues' national survey whether lack of toothbrushing causes cardiovascular disease.[1] Brushing regularly may reduce the inflammation caused by periodontal disease, or people who do not brush their teeth take less care of themselves in other ways.

Although a 70% increased risk sounds quite large, absolute rates may be more useful in assessing risk. The unadjusted data show:

- 59 people out of 538 (10.9%) who brushed their teeth less than once a day developed cardiovascular disease over about eight years
- 188 people out of 2850 (6.6%) who brushed their teeth once a day developed cardiovascular disease over eight years
- 308 people out of 8481 (3.6%) who brushed their teeth twice a day developed cardiovascular disease over eight years.

This study did not establish a cause and effect relation between oral health and cardiovascular disease. However, in theory these data equate

to about 73 cardiovascular events in every 1000 (10.9% minus 3.6%) being prevented by brushing teeth twice a day for eight years instead of brushing less than once a day (unadjusted). Expressed another way, only 14 people would need to do this for eight years to prevent one event (number needed to treat=14). The analysis suggests that these people would probably have other healthy habits.

Good oral hygiene is important in helping to prevent gum disease and tooth decay, regardless of its effect on cardiovascular risk. Equally, following a healthy diet and doing regular physical activity are all important, proved ways to prevent the risk of cardiovascular disease.

C Albert Yeung consultant in dental public health, NHS Lanarkshire, Hamilton ML3 0TA
albert.yeung@lanarkshire.scot.nhs.uk

Competing interests: None declared.

1 de Oliveira C, Watt R, Hamer M. Toothbrushing, inflammation, and risk of cardiovascular disease: results from Scottish Health Survey. *BMJ* 2010;340:c2451. (27 May.)

Cite this as: *BMJ* 2010;341:c3710

UNINTENDED EFFECTS OF STATINS

Yellow card reports add to data

Like Hippisley-Cox and Coupland,[1] our retrospective study using yellow card data submitted to the Medicines and Healthcare products Regulatory Agency (MRHA) from 2002 to 2006 found that lipid lowering drugs are often reported in association with drug induced renal toxicity. They came third after recognised nephrotoxins such as non-steroidal anti-inflammatory drugs and drugs acting on the renin-angiotensin system and ahead of loop diuretics, potassium sparing diuretics, and aldosterone antagonists.

On further investigation, we found the average age to be 68.59 years (SD 11.40), higher than that reported by Hippisley-Cox and Coupland. Men are reported more often than women, but this may reflect targeted prescribing of statins in men because of the higher risk of cardiovascular disease. Unfortunately, data on comorbidities and coprescription of other drugs are limited, so we cannot comment on the influence of these factors (table).

Frequency of occurrence of drugs (as BNF subsection) reported to the Medicines and Healthcare products Regulatory Agency 2002-2006 for renal toxicity*

Drug	Total (%)	Mean (SD) age (years)	Male sex (%)
Non-steroidal anti-inflammatory drugs (10.1.1)	260 (17.5)	69.18 (18.53)	45.1
Drugs affecting renin-angiotensin system (02.5.5)	217 (14.6)	74.7 (11.96)	42.5
Lipid lowering agents (2.12.00)	141 (9.5)	67.96 (10.34)	66.0

*In total, 1484 yellow cards reported renal toxicity during 2002 to 2006.

These data cannot be used to ascribe absolute risk, but they are in keeping with the trends observed. As stated in the accompanying editorial,[2] our understanding of the unintended effects of statins continues to develop and yellow card reports add to this pool of information that may help to influence future prescribing decisions (www.yellowcard.gov.uk).

Katherine Davidson senior pharmacist, Royal Infirmary of Edinburgh, Edinburgh EH16 4SA
Sheena Kerr lead pharmacist
Moira Kinnear head of pharmacy education research and development , Western General Hospital, Edinburgh EX4 2XU
D Nicholas Bateman professor in clinical toxicology, YCC Scotland, Royal Infirmary of Edinburgh
nick.bateman@luht.scot.nhs.uk

Competing interests: None declared.

Thanks to the MHRA for allowing us access to yellow card data.

1 Hippisley-Cox J, Coupland C. Unintended effects of statins in men and women in England and Wales: population based cohort study using the QResearch database. *BMJ* 2010;340:c2197. (20 May.)
2 Alsheikh-Ali AA, Karas RH. Balancing the intended and unintended effects of statins. *BMJ* 2010;340:c2240.

Cite this as: *BMJ* 2010;341:c3697

BEVACIZUMAB AND RANIBIZUMAB

A matter of public interest

Bevacizumab is better than no treatment, photodynamic treatment, or six weekly intravitreal pegaptanib sodium in neovascular age related macular degeneration (AMD).[1] Its long term safety and whether it is as effective as ranibizumab are unknown,[2] but available data should be sufficient for the European Medicine Agency (EMA) to grant the new indication.[1 3]

However, regulatory action cannot be taken without an initiative from the company. Sometimes industry has an interest in not applying for a new indication, as is the case with bevacizumab. Bevacizumab (Avastin, Roche) and ranibizumab (Lucentis, Novartis) are derivatives of the same anti-VGEF monoclonal antibody developed and patented by Genentech. Both seem effective in AMD,[4 5] but only ranibizumab has been granted this indication, while bevacizumab is indicated only for treating some metastatic tumours. Even if the cheaper bevacizumab was proved better, or not worse, than the more expensive ranibizumab, the marketing authorisation holder of bevacizumab may decide not to apply to extend indications to AMD.

What can be done? When commercial interests hamper or even oppose public health expectations, regulatory authorities should be enabled to recognise the indications that meet patients' needs best, meaning more effectively, more safely, or at lower cost. The European Commission should amend the legislation that prevents the EMA initiating authorisation procedures independently of the pharmaceutical industry or mandating a compulsory licence for another company for a specific indication.

Silvio Garattini director
silvio.garattini@marionegri.it
Vittorio Bertele' head, drug regulatory policies laboratory, Mario Negri Institute for Pharmacological Research, via Giuseppe La Masa 19, 20156 Milan, Italy

Competing interests: None declared.

We thank Judith Baggott for editing our original rapid response.

1 Tufail A, Patel PJ, Egan C, Hykin P, da Cruz L, Gregor Z, et al. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. *BMJ* 2010;340:c2459. (10 June.)
2 Chakravarthy U. Bevacizumab for the treatment of neovascular age related macular degeneration. *BMJ* 2010;340:c2834. (9 June.)
3 Schmucker C, Ehlken C, Hansen LL, Antes G, Agostini HT, Lelgemann M. Intravitreal bevacizumab (Avastin) vs ranibizumab (Lucentis) for the treatment of age-related macular degeneration: a systematic review. *Curr Opin Ophthalmol* 2010;21:218-26.
4 Subramanian ML, Ness S, Abedi G, Ahmed E, Daly M, Feinberg E, et al. Bevacizumab vs ranibizumab for age-related macular degeneration: early results of a prospective double-masked, randomized clinical trial. *Am J Ophthalmol* 2009;148:875-82.
5 Chang TS, Kokame G, Casey R, Prenner J, Feiner L, Anderson N. Short-term effectiveness of intravitreal bevacizumab versus ranibizumab injections for patients with neovascular age-related macular degeneration. *Retina* 2009;29:1235-41.

Cite this as: *BMJ* 2010;341:c3721

Bevacizumab and the inverse postcode lottery

The use of evidence and the commissioning process of primary care trusts is the elephant in the room in the debate on the use of bevacizumab for wet age related macular degeneration.[1]

Firstly, for clinicians in private practice the evidence to use bevacizumab is more than sufficient. However, when these same clinicians work in their NHS clinics the evidence becomes insufficient.

Secondly, although primary care trusts stand to save millions of pounds by switching to bevacizumab, they as providers are reluctant to confront the ethicolegal knot of guidance from the National Institute for Health and Clinical Excellence that excludes it. Commissioners lack the necessary clout to cultivate change in clinical practice on the basis of cost implications to purchasers. Thus we are left with an "inverse postcode lottery"—NHS patients use an extortionately priced drug when a suitable cheaper alternative is available only through the private system.

Obsession with evidence based decision making and the castrated commissioning system have combined to create a perfect storm of escalating costs that no primary care trust can sustain. All change, please.

Matthew J Harris specialist registrar and academic clinical fellow in public health, London Deanery **mattjharris@yahoo.co.uk**

Competing interests: None declared.

1 Chakravarthy U. Bevacizumab for the treatment of neovascular age related macular degeneration. *BMJ* 2010;340:c2834. (9 June.)

Cite this as: *BMJ* 2010;341:c3718