Aspirin for prevention of cardiovascular events

Is only effective in established cardiovascular disease

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RESEARCH, p 1030

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In the linked randomised controlled trial, Belch and colleagues assess whether aspirin and antioxidants, given together or separately, reduce cardiovascular events in patients with diabetes mellitus and asymptomatic peripheral arterial disease.[1]

The use of aspirin for secondary prevention of cardiovascular events in patients with coronary or cerebrovascular disease is well established and is based on extensive evidence from the Antithrombotic Trialists' Collaboration.[2] That meta-analysis found that aspirin was beneficial in patients with acute myocardial infarction or ischaemic stroke; unstable or stable angina; and those with previous myocardial infarction, stroke, or cerebral ischaemia. However, not all patients with cardiovascular disease respond to aspirin, as shown by a recent meta-analysis of aspirin trials in peripheral artery disease.[3]

In contrast, studies evaluating the possible benefits of aspirin for primary prevention in patients without cardiovascular disease have been consistently negative. A review by the United States Food and Drug Administration (FDA) of the proposed labelling of aspirin for primary prevention in 2003 evaluated five primary prevention trials and found that they were all negative for their primary end point.[4] Further examination of those trials in the higher risk subgroups (Framingham risk score greater than 8-10% a decade) and in patients with diabetes also failed to show a benefit of aspirin. On the basis of this assessment, the FDA did not extend the labelling of aspirin for primary prevention.

Subsequent to the FDA meeting, the Women's Health Study—a randomised trial of 39 876 healthy women treated with aspirin or placebo—also failed to show a significant improvement for the primary end point (prevention of non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes; P=0.13).[5] But rather than emphasising this negative conclusion, the authors focused on a subgroup analysis that led them to conclude that aspirin reduced the risk of stroke in women.

The Physicians' Health Study randomised 22 071 healthy men to aspirin or placebo and found no benefit for the primary end point of cardiovascular mortality, although a subgroup analysis found that aspirin prevented non-fatal myocardial infarction in men.[6] The major cardiovascular event rates in these two key primary prevention studies were less than 1% a year.

Despite the consistently negative evidence from trials, guidelines provide inconsistent recommendations on the use of aspirin to prevent cardiovascular events in healthy subjects at higher risk who do not have existing cardiovascular disease, particularly patients with diabetes.[7] The assumption is that the positive findings of aspirin in patients with symptomatic coronary or cerebrovascular disease can be extrapolated to these high risk populations without clinical evidence of cardiovascular disease.

Other groups at high risk include patients with markers of systemic atherosclerosis, such as peripheral artery disease. In a recent meta-analysis, an ankle brachial index of less than 0.90 (indicating peripheral artery disease) was associated with a doubling of the clinically assessed 10 year risk of major cardiovascular events after adjusting for the baseline Framingham risk score in each of the major risk groups.[8] For example, women at intermediate risk with a normal ankle brachial index had an annual risk of major cardiovascular events of 1.1%, but in women with an abnormal ankle brachial index (<0.90) the risk was 2.5% a year.

In this context, Belch and colleagues' trial compared the effects of aspirin and antioxidants (using a factorial design) on the primary prevention of fatal and non-fatal major cardiovascular events in a high risk population. Patients were eligible if they had type 1 or type 2 diabetes and evidence of asymptomatic peripheral artery disease, defined by an ankle brachial index less than 1.00. More than 1200 patients were enrolled and followed up to eight years. At baseline, participants had a mean age of 60 years and an average ankle brachial index of 0.90. The observed risk of a major cardiovascular event was 2.9% a year, much higher that that seen in the previously noted primary prevention trials (driven by age of the population and the presence of diabetes and peripheral artery disease). Patients randomised to aspirin had 116 primary fatal and non-fatal cardiovascular events compared with 117 in the control group (hazard ratio 0.98, 95% confidence interval 0.76 to 1.26). No significant difference in major cardiovascular events was seen between the antioxidant treatment group and the placebo group. Although no significant difference was seen between the rate of gastrointestinal bleeding in each group, there was a trend for a greater incidence of gastrointestinal symptoms, including dyspepsia, in patients randomised to aspirin.

Belch and colleagues' study supports the observations from six well conducted randomised control trials that found no benefit of aspirin for primary prevention, even in higher risk groups. The findings are also consistent with the previous report of no benefit

of aspirin in patients with peripheral artery disease.[3] What is striking about the negative effect of aspirin is that people in Belch and colleagues' study were at particularly high risk given their age and the presence of diabetes and asymptomatic peripheral artery disease, with an event rate of about 3% a year.

These results support the concept that risk assessment alone cannot predict which patients will benefit from aspirin. In fact, the only predictor of clinical response to aspirin is a history of a major coronary or cerebral ischaemic event, as defined by the previous meta-analysis.[2] The mechanisms of this differential response to aspirin are not known but clearly suggest that patients who respond to aspirin must have a history of clinical, symptomatic cardiovascular disease. This is in sharp contrast to the evidence that statins, for reducing concentrations of low density lipoprotein cholesterol, and drugs for treating hypertension have clinical benefit that extends to all risk groups, including those with and without cardiovascular disease. In these examples, the difference between primary and secondary prevention is only in the absolute reduction in risk because primary prevention populations have a lower absolute risk of cardiovascular events but receive the same relative benefit from the treatment.

A total of seven well controlled trials now show that aspirin has no benefit for primary prevention of cardiovascular events, even in people at higher risk. Although aspirin is cheap and universally available, practitioners and authors of guidelines need to heed the evidence that aspirin should be prescribed only in patients with established symptomatic cardiovascular disease.

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Patellofemoral pain syndrome

Usually resolves over time, and intervention offers only limited benefit

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RESEARCH, p 1034

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Patellofemoral pain syndrome is defined as pain behind or around the patella caused by stress in the patellofemoral joint. Symptoms are usually provoked by climbing stairs, squatting, and sitting with flexed knees for long periods of time. It is a common presentation in general practice and can have a big effect on patients' ability to work.[1] Physiotherapy and foot orthoses available without prescription are often used in the management of patellofemoral pain syndrome. In the linked randomised controlled trial, Collins and colleagues assess the effectiveness of foot orthoses, flat insoles, multimodal physiotherapy (patellofemoral joint mobilisation, patellar taping, quadriceps muscle retraining, and education), or a combination of foot orthoses and physiotherapy in people with this syndrome.[2]

The rationale for treatment is to correct unbalanced tracking of the patella. Knee braces, knee taping, knee sleeves, and knee straps all aim to alter the patella's tracking pattern. Some studies have shown that these strategies improve knee symptoms, although others show no significant difference compared with physiotherapy.[3 4] The most commonly recommended treatment is strengthening of the quadriceps along with avoidance of painful activities.[5] Straight leg raises are recommended to isometrically strengthen the quadriceps. One cohort study found that increasing hip muscle strength and flexibility has also been successful.[6] In this cohort study, after six weeks of hip exercises, improvement of hip muscle function was associated with good results in patellofemoral pain syndrome.

In patients with a flat foot deformity, the foot is pronated causing a compensatory internal rotation of the lower extremity that can disturb the patellofemoral mechanism. In this situation custom made foot orthoses are used to support the medial arch and restore normal leg alignment. Foot orthoses, in addition to an exercise programme, can be effective for people with patellofemoral pain syndrome.[7] On the other hand, a recent randomised trial showed no difference in outcome between eight weeks of treatment with functional foot orthoses, exercises, or orthoses combined with exercises.[8] Follow-up beyond eight weeks was not available in either of these studies, which limits their value, because patellofemoral pain syndrome tends to become a chronic problem.

The linked study by Collins and colleagues randomised 179 patients with patellofemoral pain syndrome to four interventions of six weeks' duration.[2] The flat insole group can be regarded as a control for the foot orthoses.[9] Global improvement, severity of usual and worst pain over the preceding week, the anterior knee pain scale, and the functional index questionnaire were measured at six, 12, and 52 weeks. Foot orthoses significantly improved outcomes at six weeks compared with flat inserts (relative risk 0.66, 99% confidence interval 0.05 to 1.17; number needed to treat 4, 2 to 51). At six weeks patients using foot orthoses or those who

performed a supervised exercise programme showed significant improvement compared with those using flat insoles. This study confirms the good results seen for exercise and foot orthoses in the short term.[3] At one year follow-up, all groups, including the one using flat insoles, showed a clinically meaningful improvement.

A systematic review found that exercise programmes consisting of either closed chain exercises (where the foot is in contact with a surface) or open chain exercises (where the foot is not in contact with a surface) are equally effective.[10] So far, the role of foot orthoses has not been clear. A recent systematic review found no evidence to support the use of any orthotic devices in the treatment of patellofemoral pain syndrome.[4] Collins and colleagues' study suggests that foot orthoses can be useful in the short term. They may even be cost effective compared with physiotherapy.

The study also found that all groups, including the placebo group (flat insoles) made a clinically relevant improvement over time. This probably reflects the benign natural history of this syndrome, and raises the question of whether we should interfere at all. High quality randomised controlled trials are needed to answer this question. These should compare the results of knee orthoses, foot orthoses, physiotherapy, and patients without treatment; follow-up should be for at least a year. The limited evidence for the effectiveness of orthotic devices for patellofemoral pain syndrome along with the current results should encourage future researchers to use a control group not receiving any treatment.

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Tight control of blood glucose and cardiovascular disease

A strong effect that develops slowly but persists for years

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September saw the 10th anniversary of the publication of the landmark United Kingdom Prospective Diabetes Study (UKPDS), which comprised a series of studies that have greatly improved our understanding and practice of controlling blood glucose in people with type 2 diabetes.[1] Nevertheless, intensive control in the group treated with sulphonylurea or insulin had an equivocal effect on preventing cardiovascular disease compared with conventional treatment (percentage risk reduction for myocardial infarction 16%, 95% confidence interval 0% to 19%), with the P value of 0.052 on the boundary of conventional statistical significance.[2] A study of intensive control with metformin in overweight people seemed to give clearer results (39%, 11% to 59%),[3] but the study was underpowered, and a subgroup analysis in people taking metformin plus sulphonylurea raised the potential of harm.

However, in October the results of the UKPDS 10 year follow-up study were published. These results showed that patients in the sulphonylurea or insulin group had a significant 15% reduction in myocardial infarction even though they achieved the same glucose control as patients in the less tightly controlled group over the five year extension.[4] The results reflect those of the Diabetes Control and Complications Trial in type 1 diabetes. This also found no effect of glucose control on cardiovascular outcomes (with very few events), but on 12 year follow-up it found around a 50% reduction in cardiovascular events in the previously intensive group despite equivalent blood glucose control over the 12 years.[5] In the UKPDS follow-up study, the finding for tighter control remained statistically significant with metformin, but the estimate of the risk reduction decreased towards that for sulphonylurea or insulin.[4]

At first sight these findings conflict with the three large studies of tighter blood glucose control published or presented this year (ACCORD (Action to Control Cardiovascular Risk in Diabetes), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation), and VADT (Veterans Affairs Diabetes Trial)), which found no significant benefit for cardiovascular events from tighter glucose control.[6-8] However, all three studies found that tighter glucose control reduced the risk of primary cardiovascular disease by 10% but were underpowered at their stopping point to detect a significant result. VADT is yet to be published, but even though the cardiovascular end points are defined differently in the studies, a

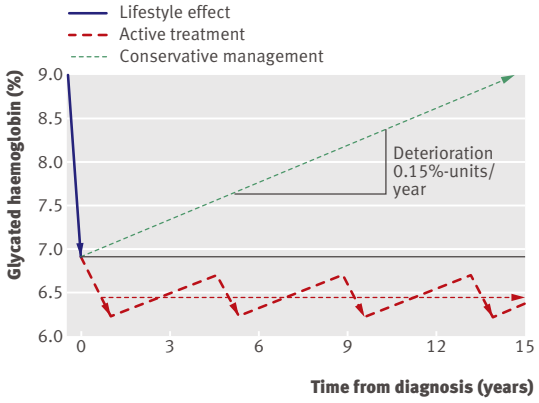
meta-analysis of these studies would clearly show a statistically significant result, especially if UKPDS (in original or extended form) and PROactive (Prospective Pioglitazone Clinical Trial in Macrovascular Events) were included.

However, some concern surrounds the results from ACCORD. This study was stopped because of increased all cause mortality in people whose glucose was extremely tightly controlled with insulin and multiple oral agents.[6] However, the risk cannot necessarily be attributed to the treatment because it was found by repeated statistical testing performed by safety monitoring committees as the study progressed; only mortality showed an adverse trend and it was inconsistent with other outcomes. Inspection of the time to event curves suggests that chance is a likely explanation, but a real effect for ill understood reasons cannot be excluded. The study should probably not have been stopped.

Another finding from these studies is important to clinical practice. An iconic graph from the UKPDS studies showed that glucose control deteriorated over time in people in the lifestyle and treatment groups, as a result of progressive loss of islet β cell function.[9] ACCORD and ADVANCE found no such deterioration up to six years.[6 7] This suggests that if titration of glucose lowering treatments continues, even in non-intensive conditions, glycated haemoglobin can be maintained to target for at least 16 years from diagnosis. Because the average deterioration in glycated haemoglobin in UKPDS is 0.15% units each year,[2] the potential gain in control over lifestyle alone averaged over 20 years would be ~2.0% units (box; figure). Using the risk reductions seen in the trials this translates to a 20-30% reduction in risk of cardiovascular disease from glucose lowering treatments, in addition to a similar effect from lifestyle change.

The evidence so far has several clinical implications. The conventional glycated haemoglobin target of 6.5% should stand,[10] except where this requires combined intensive treatment with insulin and an oral agent and where life expectancy is less than five years (not to be confused with old age). To achieve the stability of glucose control seen in ACCORD and ADVANCE and avoid the deterioration seen in UKPDS, treatment will probably need to be titrated continuously and new treatments added frequently over the patient's lifetime.[10] Diabetes should be diagnosed early, so that cardiovascular damage can be minimised. Currently it is often cardiovascular disease that precipitates the diagnosis.

Lastly, although lowering glucose over time now seems to be as efficacious as lowering lipids and blood pressure or using antithrombotic drugs, evidence shows that all three approaches must be used together. In the multifactorial risk reduction Steno 2 study in high risk people with diabetes, the numbers needed to treat were between 3.5 and 7 for death, cardiovascular events, and microvascular protection[11]; the intervention was also highly cost effective.[12]



Calculation of the average improvement in glycated haemoglobin to be achieved by drug treatment in the 20 years from diagnosis

Improvements in glycated haemoglobin

After lifestyle management reduced glycated haemoglobin by ~2.0% to 7.0% in the UK Prospective Diabetes Study (UKPDS), conservative management was associated with a deterioration of about 0.15% each year.[2] This would suggest that at 20 years glycated haemoglobin would be 10.0%, giving an average deterioration over the 20 years above 7.0% of 1.5% ((10.0%–7.0%)/2). In addition, a treatment effect of 0.8% was found, but because the target control value is 6.5% and because glycated haemoglobin values will seesaw around this as treatment is intensified, the average gain will be ~0.5% units (7.0%–6.5%). The total gain from treatment, averaged over the 20 years will then be 1.5%+0.5% or ~2.0% units. These are estimated average effects for a UKPDS based population—individuals and other populations will differ, some will benefit more than others.

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The *Global Health Watch 2* report

Holding the social and economic causes of health inequities to account

JIM DANDY/GETTY IMAGES

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Global Health Watch 2, the second of the self claimed alternative world health reports, is published today.[1] Like its 2005 predecessor, it is an approachable overview of why health inequities persist and what can be done to reduce them. The strength of this report is that it is a product of several civil society organisations and networks, and its inherent activism is strongly evidence based and carefully reasoned.

The report is divided into major sections on health systems, determinants of health, and accountability, and it includes essays on alternative development and on the politics of resistance to unhealthy policies, politics, and economics. A key argument is that our present approach to development divides the world's three most important imperatives—to reduce poverty, improve health, and sustain the environment—into unattainable incoherence. For example, poverty reduction in low income countries, which is assumed to improve health, is driven by growth that is led by exports. These exports are consumed by people in high income countries at a level of consumption that is environmentally unsustainable. In an alternative paradigm, economic growth would be based on supporting production by poorer people in low income countries of goods and services needed by the poor.

The section of the report on health systems may be most appealing to practitioners, although it has no chapters on specific diseases. It accepts that some benefit derives from a disease focus, but it is critical of the dominating global model of targeted initiatives, technology driven interventions, and the proliferating array of public and private donor programmes. Instead, its emphasis is on the political and economic contexts of care and prevention, notably how the collapse of public sector services and increased market driven care has led to an "over servicing" of some people and an "under serving" of others.

The principles for reform are simple—progressive financing and risk pooling (collective insurance) based on the principle of cross subsidisation (where the healthy subsidise the ill and the rich subsidise the poor), and ensuring access on the basis of people's needs and rights to counterbalance creeping commercialisation. This point needs constant repetition because the World Bank, with support from the Gates Foundation, continues to promote entrepreneurial medicine even for the poorest countries in Africa. The report is critical that some of these countries still spend little on their public systems, but also that those countries that do wish to increase their public provision face spending ceilings imposed by the World Bank and the International Monetary Fund.

A strong case is made against the globalisation of many Western mental health constructs—they simply don't fit the cultural and linguistic concepts of many of the world's peoples. Unreflective forms of external aid for mental health problems risk doing more harm than good. This finding also has bearing in high income countries, as more people move around the world more rapidly. Intercultural understanding is no longer optional in health systems, wherever they may be.

Remedying the inequities in the patchwork of health rights for asylum seekers—which are variously inadequate, unknown, unenforced, or ignored—remains urgent. Several of these threads reconnect in the appalling health conditions in most prisons. Half the prison population worldwide is thought to be subject to mental illness, and conditions (overcrowding and abuse) in most prisons worsen the health of inmates. *Global Health Watch 2* reminds us that "prisoners are sent to prison as punishment, not for punishment."

The report's analyses of health determinants include many familiar topics (urbanisation, globalisation and nutrition, water and sanitation, aid, and education) but also some new ones. The obsession with carbon trading as a solution to climate change shows how market based systems generate inequities but fail to reduce emissions. An important commentary on the contentious and politicised construction of "terror" is overshadowed by the fact that more people are being killed from the indirect effects of conflict (loss of water, food, shelter, and livelihood and the subsequent risk of disease) than from violence itself.

Global Health Watch 2 equivocates on the activist dilemma of whether to support violent forms of social change that carry short term negative health effects to overcome persistent and exploitative social systems that damage health. The examples offered of non-violent social mobilisations and transformations (India and South Africa), however, were preceded by violence, arguably rendering the dilemma more a matter of when we should support such moves rather than whether we should support them.

Importantly, the report does not shy away from assessing how well or poorly the world's major health organisations are doing in improving global health (see box on bmj.com).

The report's focus on accountability is driven by its concern with the increasing role played by private organisations and donors in health aid (now about 25% of all such aid) and consequent reform of health systems.

Global Health Watch 2 has some omissions. The chapter on water, although noting that the poor pay proportionately more for water, does not discuss imposing escalating water tariffs to discourage overconsumption while financing a free "lifeline" supply. It does not mention the stresses posed by ongoing population growth, a subject that health professionals, activist or otherwise, seem to shy away from—perhaps as a result of the bad politics of past population policies. Such gaps are forgivable in a short text with almost encyclopaedic scope and ambition.

The closing essay on the politics of resistance begins to deal with how that ambition might be realised. Although much of the report is on the important health role played by governments and institutions, it locates the levers of

change in the active resistance of poorer groups and their globally wealthier sympathisers. Citing several recent examples (the Peoples' Health Movement's Right to Health campaign, the Zapatista's ongoing mobilisations in defence of indigenous peoples in southern Mexico, opposition to mega-dams in India, and the successful legal challenge against prepaid water meters in South Africa) the chapter importantly reminds us that oppressed peoples in the world are not passive. They do resist, and in that resistance lies hope.

But if resistance creates the demand for change, there is a troubling lack of effective leadership at a global level to implement it. WHO is called upon (again) to reassert its moral leadership for global health. The rest of us are urged to support the growing network of national and global civil society organisations working to ensure that such leadership is exercised, and exercised in the interests of global health equity.

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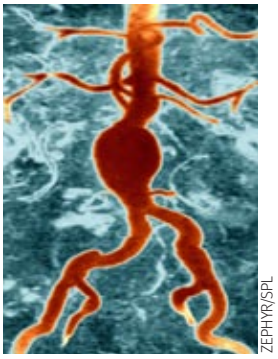
Abdominal aortic aneurysm in postmenopausal women

Smoking remains the main culprit



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Smoking is the dominant risk factor for abdominal aortic aneurysm in both men and women. In the linked cohort study from the Women's Health Initiative, Lederle and colleagues assess the potential risk factors for clinically relevant abdominal aortic aneurysm in 161 808 postmenopausal women. They show that current smokers have a four times greater risk of abdominal aortic aneurysm events and all those who have smoked more than 100 cigarettes have a twofold increase in risk, even if they have given up smoking.[1]

Smoking increases the relative risk of abdominal aortic aneurysm four times in both men and women, and the risk for ischaemic heart disease or peripheral arterial disease is increased twofold.[2] Previous studies have associated both early onset of smoking and total duration of smoking with heightened risk of abdominal aortic aneurysm, although in many studies these associations were based on aortic diameter rather than clinical events. The effect of passive smoking has not been reported. In addition, the benefits of stopping smoking are apparent more quickly with regard to ischaemic heart disease than abdominal aortic aneurysm.[3]

Recent studies in Europe show that although the number of male smokers is decreasing, the number of female smokers continues to increase and has not yet peaked.[4] The epidemiology of abdominal aortic aneurysms raises several questions. If abdominal aortic aneurysm follows a lifetime of smoking, is its incidence in women less than in men because, in the past, fewer women than men have smoked, and smoking became popular in women about three decades after it became popular in men? Or, do oestrogens slow changes in aortic disease, so that women are relatively protected from abdominal aortic aneurysm until after the menopause and develop aneurysms later than men? The role of the sex hormones (oestrogens, progestogens, and androgens) has yet to be clarified.

Lederle and colleagues' current study is one of the first to look at the effect of hormone replacement therapy on the development of clinically relevant abdominal aortic aneurysms in women.[1] The apparent protection from abdominal aortic aneurysm for women taking hormone replacement therapy merits further investigation, even though previous smaller studies from the Women's Health Initiative indicated that therapy with oestrogen alone may increase the risk of abdominal aortic aneurysm.[5] Experimental studies have indicated that oestrogens decrease the risk of aortic aneurysm by reducing aortic matrix metalloproteinase expression and other mechanisms,[6] and that androgens may increase the risk by angiotensin receptor dependent mechanisms.[7]

Intriguingly, Lederle and colleagues confirmed that the negative association between diabetes and abdominal aortic aneurysm seen in men is also present in women.[1] However, this association may be less useful for improving the management of abdominal aortic aneurysm than the association seen with sex.

Although abdominal aortic aneurysm is less common in women, the standardised mortality ratio after elective repair of abdominal aortic aneurysm is higher in women than in men, and age standardised mortality is increasing faster in women than in men.[8 9] In addition, abdominal aortic aneurysm has a worse prognosis in women than in men.[6 10] In women, aneurysms rupture at smaller diameters, the rate of intervention is lower, and mortality after intervention may be higher.

So, what are the implications of the results on clinical practice and policy? Getting women to stop smoking is a public health priority. The problem of high mortality from abdominal aortic aneurysm in men is being tackled by population screening programmes focused on men.[11] In the United States screening is in place for women with a strong family history of abdominal aortic aneurysm, but if the incidence of this disorder in women continues to rise, population screening for women who have smoked or continue to smoke might need to be considered.

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All references are on bmj.com