Number needed to sacrifice: statistical taboo or decision-making tool?

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Summary
The percentage that benefit from medical preventive measures is small but all are exposed to the risk of side effects so most of those harmed would never benefit from their use. There is no expression or acronym to describe the ratio of harm to benefit nor discussion of what level of harm is acceptable for what benefit. Here we describe the harm to benefit ratio (HBR) expressed as number harmed (H) for 100 to benefit (B) and calculated for commonly used medical interventions. For post TIA carotid endarterectomy the HBR is 25 (25 postoperative strokes or deaths are caused for 100 to be stroke free at 5 years); warfarin in atrial fibrillation in patients aged under 65 results in 400 intracerebral haemorrhages for every 100 saved from a thromboembolic event; fibrinolytic treatment for stroke causes 44 symptomatic intracranial haemorrhages for every 100 that have minimal disability at 3 months; aspirin in high risk patients causes 33 major bleeds for every 100 occlusive vascular events prevented; routine inpatient thromboprophylaxis causes 133 additional bleeds for every 100 pulmonary emboli prevented; breast cancer screening causes 1000 unnecessary cancer treatments for 100 cancer deaths to be prevented.

Conclusion: The HBR or number needed to sacrifice is larger than most imagine. Its wider use would allow us better to recognise the number harmed, allow better informed consent, compare different preventive strategies and understand the risks as well as benefits of preventive treatments.

Introduction
All preventive measures carry risk. For some, such as compulsory wearing of seat belts or childhood vaccination, the risk is small but for others such as aspirin in the prevention of cardiovascular disease or warfarin in atrial fibrillation (AF) the side-effects are significant and measurable and seen every day in emergency departments and admission units. Because preventive measures advantage only a small percentage of those treated, most harmed would never have benefited from their use. We know the percentage (but not the individuals) that will be harmed, and to adopt an intervention we must tacitly agree that the number harmed is an acceptable trade-off for the population’s gain. Without loss there can be no gain. Wittingly or unwittingly we accept that individuals must be sacrificed if the population is to benefit. Outcomes of preventive strategies are expressed as numbers needed to treat (NNT) or harm (NNH) but there is no easy expression or acronym to describe the ratio of harm to benefit nor discussion of what level of harm is acceptable for what benefit. The harm to benefit ratio (HBR) is an important statistic which could
affect our use of preventive strategies and the patient’s wish to receive them. Examples from commonly used preventive strategies are presented below.

**Methods**

Data from the Cochrane Library and recent meta-analyses were used to analyse seven commonly used and highly promoted preventive strategies. For each, the ratio of NNT to NNH was expressed as the HBR calculated as the number harmed for 100 to benefit.

**Carotid endarterectomy for treatment of carotid stenosis in patients with transient ischaemic attack**

A total of 6079 cases of carotid endarterectomy were performed in the UK in 2009/2010. The median delay from symptoms to surgery was 21 days which extrapolating from American NASCET and European ECST figures should result in an absolute risk reduction (ARR) of ipsilateral stroke at five years of 17.6% when compared with medical treatment.

The benefits are clear: but how many lose and for what gain? The UK audit reports a postoperative death or stroke rate of 3%, myocardial infarction 0.8%, postoperative bleeding 4% and cranial nerve injury 4%. Controlled trial data from 13 years earlier showed similar rates with the number harmed independent of time to surgery or severity of initial stroke. The NASCET data, which allow the risk of surgery to be isolated from the background risk, show a net increase in surgical risk at 30 days of 4.3% for any stroke or death, and 1.4% for disabling stroke or death.

Extrapolating this to UK data suggests that an excess of 261 patients will have a stroke or will die because of surgery for the benefit of 1070 patients saved from an ipsilateral stroke at five years.

It is a close call. Twenty-five will have a stroke or die in the immediate postoperative period for every 100 that are prevented from having a stroke at five years (see Table 1). Furthermore, if the affected patient had declined surgery there is a 70% chance that they would be still be alive and stroke-free five years later and as the five-year mortality is the same in those treated medically and surgically (27.6% versus 26.6% at mean of 6.1 years) the sacrifice of those with complications or death following surgery, although of benefit to the population’s five-year stroke risk, does not lead to increased longevity in the operated group. Improvements in surgical technique and better selection may in time alter the gearing of individual loss to population gain but it will never be zero and there is little evidence of improvement in the past 10 years. The ratio of loss to gain is an uncomfortable statistic, seldom voiced. Many are surprised at how close loss is to gain.

**Fibrinolytic therapy for acute stroke**

In the NIND study, the use of recombitant tissueplasminogen activator (rt-PA) up to three hours postpresentation resulted in a 13% absolute increase in the rate of full recovery (39% in the treatment group versus 26% in the placebo group, by dichotomized modified Rankin scale). But the 13% benefit came at a price of 5.8% increase in symptomatic intracranial haemorrhage (ICH) in the rt-PA group within 36 h of treatment. There was no difference in mortality between the two groups at one year but there was an excess mortality from ICH at 36 h of 2.6% in the treatment group. Forty-four suffer a symptomatic ICH within 36 h of treatment and 20 die acutely for every 100 that make a complete recovery and there is a 20–38% chance (depending on the score used) that the patient who died would have otherwise made a complete recovery had they not had rt-PA.

**Aspirin in high-risk cardiac patients**

Rodríguez’s study on discontinuation of aspirin in high-risk patients showed for secondary prevention of cardiovascular outcomes that for every 1000 patient years there were four extra cases of non-fatal myocardial infarction (MI) among patients who discontinued low dose aspirin compared with those who continued but no difference in mortality. An accompanying leader advises patients not to stop aspirin. But what of the harm? The Antithrombotic Trialists’ (ATT) study showed antiplatelet therapy, of
which aspirin was the most commonly used, increased the risk of major gastrointestinal and extra cranial bleeds by one bleed per 1000 patient years. Combining the data suggests 25 patients will bleed for every 100 prevented from having a non-fatal MI and the patient who bleeds would have a less than one in a 100 chance of an MI in the coming year. We accept their loss for the small reduction of MIs in the community. The ATT data also showed 20% mortality in patients who bled on antiplatelet therapy suggesting four die from antiplatelet therapy for every 100 prevented from having a non-fatal MI.

For total vascular risk, the ATT study showed the 2.5% ARR of vascular events in patients on antiplatelet therapy (10.7% versus 13.2%: antiplatelet versus control) was associated with an increased risk of major extracerebral bleeding of 0.42% (1.13% versus 0.71%) and ICH of 0.11% (0.65% versus 0.54%) making a total increase in major bleeding of 0.53%. Twenty-one bleed for 100 patients to avoid a vascular event. For fatal bleeds the difference was 0.05% (0.20 versus 0.15) balanced by a favourable reduction of fatal vascular events of 1.08% (8.52 versus 7.44). Five die from aspirin-induced bleeding for every 100 vascular deaths prevented. Had the person who died declined aspirin there would be a greater than 85% chance that they would still be alive without any further vascular events two years later. We might improve the ratio of bleeds to vascular events by treating Helicobacter pylori, stopping non-steroidal anti-inflammatory drugs or prescribing a proton pump inhibitor but patients will still bleed and die on aspirin. Their death is inextricably linked to the reduction we wish to

| Intervention | Harm to the individual | Gain to the population | Harm to benefit ratio |
|--------------|------------------------|------------------------|----------------------|
| Carotid endarterectomy for TIA | Death | Stroke free at five years | 7/100 |
| Warfarin age <65 in AF Age 65–74 CHADS2 score 4–6 | Postoperative stroke or death | Stroke free at five years | 25/100 |
| Fibrinolytic therapy for acute stroke | Intracerebral haemorrhage | Prevention of TE | 400/100 |
| | Intracerebral haemorrhage | Prevention of TE | 54/100 |
| | Death | Prevention of TE | 19/100 |
| | Death in first 36 h | Minimal or no disability at 3 months | 44/100 |
| Continuing aspirin in high-risk patients | Major extracranial bleed | Prevention of non-fatal MI | 25/100 |
| | Death | Prevention of non-fatal MI | 4/100 |
| | Major bleeding | Prevention of any vascular event | 33/100 |
| Statins (all trials) | Death from bleeding | Prevention of vascular death | 5/100 |
| | All adverse effects | Prevention of cardiovascular event | 24/100 |
| Development of diabetes | Minor or no disability at 3 months | Prevention of cardiovascular event | 4/100 |
| | Major bleeding | Prevention of non-fatal MI | 25/100 |
| Venous TE prophylaxis in hospital patients | Prevention of pulmonary embolism | Major bleeding | 133/100 |
| Colorectal cancer screening | Side-effects from colonoscopy | Prevention of colorectal cancer death | 10/100 |
| Breast cancer screening | Unnecessary cancer treatment | Prevention of breast cancer death | 1000/100 |
| | Psychological distress because of false diagnoses | Prevention of breast cancer death | 20,000/100 |

TIA, transient ischaemic attack; TE, thromboembolic events; AF, atrial fibrillation
see in the numbers of vascular events in the community. The numbers of aspirin-related complications are small but so also are the number of vascular events prevented. Taking an aspirin tablet is a gamble (Figure 1). Will this be the tablet that prevents me from having a heart attack; or will this be the tablet that causes me to bleed? The chances are overwhelmingly that it will do neither, and although the odds are in favour of benefit the patient who bleeds may regret having taken that gamble.

**Warfarin treatment of non-valvular atrial fibrillation**

Meta-analysis of 66,000 person-years of follow-up showed an overall reduction in thromboembolic events (TEs) of 1.04 per 100 patient years in patients in atrial fibrillation on warfarin compared with placebo (2.29 versus 1.25) but an increased rate of ICH of 0.24 per 100 patient years. Overall 23 ICHs are caused to prevent 100 TEs. Taking all patients under age 75, the reduction in risk of TEs of 0.27 per 100 patient years on warfarin (1.12 control risk versus 0.85 warfarin risk) was exactly matched by the increased rate of ICH of 0.28. A total of 104 patients suffer an ICH for every 100 TEs prevented. Subgroup analysis tells us the ratio of harm to benefit is less for women, for those with prior stroke, diabetes or congestive cardiac failure and those over 85, but even in those with the highest CHADS2 score where the benefits of warfarin are greatest (3 TEs prevented per 100 patient years on warfarin) 19 ICHs are the price we pay to prevent 100 TEs, and as in our other examples had the patient
who suffered an ICH not taken warfarin there is a 97% chance that they would not have had a TE in the coming year.\textsuperscript{10}

\section*{Statins}

Even statins with their wide use and proven safety record lead to adverse effects which must be accepted if their benefits are to be realized. Two meta-analyses have shown that, compared with placebo, 24 extra patients suffered an adverse effect taking statins for every 100 cardiovascular events prevented\textsuperscript{11} and 11 developed diabetes.\textsuperscript{12}

\section*{Prophylaxis against venous thromboembolism in hospital inpatients.}

Meta-analysis of 36,000 patients showed a borderline statistically significant reduction in mortality (relative risk, 0.93, confidence interval 0.56–1.00) in those receiving heparin and a small reduction in pulmonary embolism (3 per 1000 treated) but no reduction in deep venous thrombosis.\textsuperscript{13} However the benefit is at the expense of an increase in bleeding of nine per 1000 and major bleeding in four per thousand. For every 100 patients prevented from having a pulmonary embolus 133 patients have a major bleed. The American College of Physicians warn strongly against universal prophylaxis with heparin.\textsuperscript{13}

\section*{Cancer screening}

Outcome studies from the UK faecal occult blood bowel cancer screening programme show complications occurred as a result of colonoscopy in 275 of 2,269,983 subjects screened and these were serious in 94.\textsuperscript{14} The chance of an individual benefitting from colorectal cancer screening (CRC) screening is estimated at one in 862\textsuperscript{15} so of the total screened 2623 are likely to benefit but at the expense of 275 harmed. Ten will be harmed (4 seriously) for 100 to benefit.

For breast cancer screening the 2011 Cochrane review\textsuperscript{16} concluded that screening is likely to result in an absolute reduction in breast cancer mortality of 0.05% in those screened, but at the expense of an absolute increase of 0.5% in overtreatment. For every 100 cancer deaths prevented in women invited for screening 1000 healthy women will be treated unnecessarily and 20,000 women will experience important psychological distress for many months because of false-positive findings. It is these startling figures which have prompted a review of breast cancer screening in the UK.

\section*{Discussion}

The use of the HBR allows us to question the level of harm that is acceptable in routine practice. Thus treating all patients with AF under age 65 with warfarin must surely be unacceptable (see Table 1). But what of fibrinolytic therapy for acute stroke; are 44 ICHs with 20 deaths in 36 h acceptable for 100 patients free of deficit at three months? Is any death acceptable for an intervention that does not prevent death (such as continuing aspirin in high-risk cardiac patients)? Is the harm caused by breast cancer screening offset by its benefit? And how would the patient who bleeds on heparin view the pressure in UK trusts for all in-patients to be considered for heparin prophylaxis? The HBR is subject to the same statistical insecurity as NNT and NNH and its interpretation by patient and doctor will depend on the weight placed on the seriousness of the side-effects but its use allows better focus on the quality of the intervention, better informed consent and better comparison between preventive strategies such as colon and breast cancer screening than either measure alone.

Buyx \textit{et al.}\textsuperscript{17} believed funding should be withheld if interventions did not reach a predefined threshold of effectiveness in terms of increased length or quality of life. Incorporation of HBR would allow further discrimination on ethical as well as financial grounds for preventive and cancer drugs, but also for procedures such as bariatric surgery and radiological interventions including CT scans. For example a 30-year-old patient having a single CT scan of the abdomen has an increased lifetime attributable cancer mortality risk of 0.06%.\textsuperscript{18} Even if a cancer death is prevented for every 1000 scans carried out, 60 will die from iatrogenic cancer for every 100 cancer deaths saved.

The Aztecs believed that they must give strength to the sun god Uitzilopochtli with human blood and thereby benefit the population
by postponing the end of the world.19 The numbers sacrificed were considerable but if, as they believed, the whole population would benefit the gearing of sacrifice to gain was more favorable for their victims than that which we accept in modern clinical practice.

Today many dismiss the harm we do to patients as necessary opportunity costs for the benefit of the population. The Aztecs would look on those harmed as a necessary sacrifice for the greater good. To the harmed individual the end result is the same. Those injured or killed are the foot-soldiers in medicine’s battle to reduce illness and disability in the population. They lose so others gain. The use of the HBR allows us to better recognize their number and better understand the risks as well as the benefits of preventive medicine.

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