Treating Individuals 3

From subgroups to individuals: general principles and the example of carotid endarterectomy

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Clinicians often have to make treatment decisions based on the likelihood that an individual patient will benefit. In this article we consider the relevance of relative and absolute risk reductions, and draw attention to the importance of expressing the results of trials and subgroup analyses in terms of absolute risk. We describe the limitations of univariate subgroup analysis in situations in which there are several determinants of treatment effect, and review the potential for targeting treatments with risk models, especially when benefit is probably going to be dependent on the absolute risk of adverse outcomes with or without treatment. The ability to systematically take into account the characteristics of an individual patient and their interactions, to consider the risks and benefits of interventions separately if needed, and to provide patients with personalised estimates of their likelihood of benefit is shown using the example of endarterectomy for symptomatic carotid stenosis.

Introduction

> "The most important thing about a treatment is that it is effective, not merely that it ought to be effective".
>
> Richard Asher, 1961[1]

Asher was referring to treatments that ought to be effective on the basis of untested medical theories and was arguing for randomised controlled trials (RCTs). That argument has since been won, but his aphorism is equally relevant to how the results of RCTs are applied in routine practice. The most important thing about a treatment is that it is effective in the individual who is being treated, not merely that it ought to be effective on the basis of the overall result of an RCT or a systematic review. Clinicians have a responsibility both to try to provide the most appropriate treatment for each individual patient and to use limited health-care resources efficiently.[2] Both of these aims need treatments to be targeted at those individuals who are likely to benefit and avoided in those with little chance of benefit or in whom the risks of treatment are too great.

Many treatments, such as blood pressure lowering in uncontrolled hypertension, are indicated in most patients. However, a targeted approach is useful for treatments with modest benefits (eg, lipid lowering in primary prevention of vascular disease),[3] for costly treatments with moderate overall benefits (eg, interferon beta in multiple sclerosis),[4] if the availability of treatment is limited (eg, organ transplantation),[5] in developing countries with very small health care budgets, and most importantly, for treatments which, although of overall benefit in large trials, are associated with a substantial

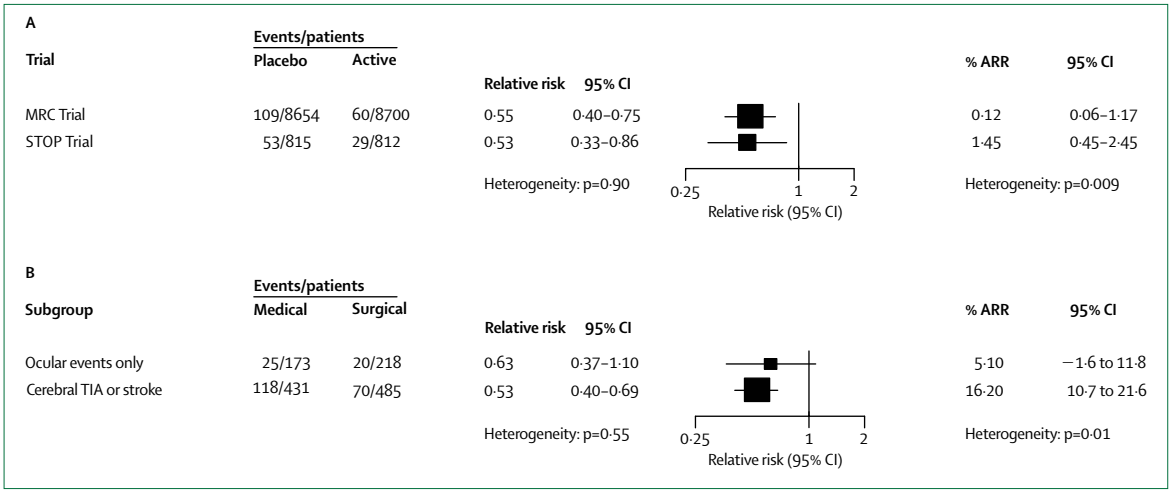

Figure 1: **Comparison of relative and absolute reductions in risk of stroke with treatment**
A: two trials of blood pressure lowering in primary prevention;[10,11] B: two subgroups of patients in randomised comparison of effect of carotid endarterectomy for ⩾70% symptomatic stenosis (patients presenting with ocular ischaemic events versus cerebral hemispheric events).[12] TIA=transient ischaemic attack. ARR=absolute risk reduction.

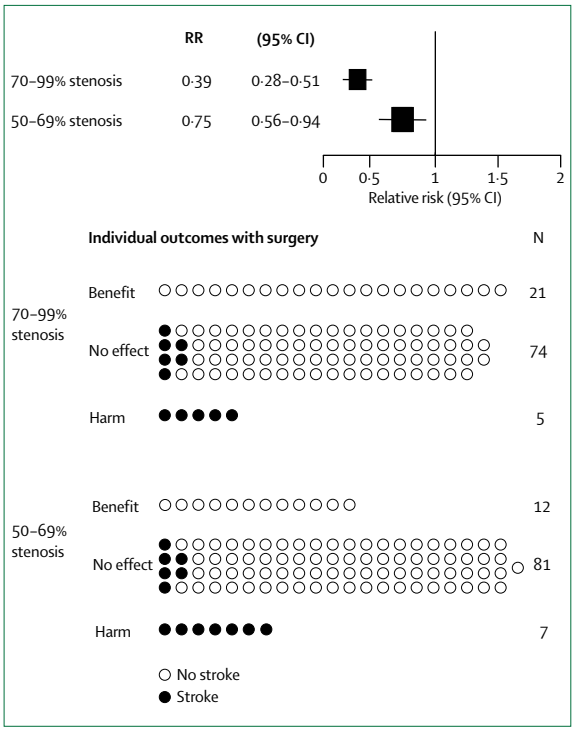

Figure 2: **Effect of carotid endarterectomy for ⩾70% and 50–69% symptomatic stenosis on 5-year risk of stroke and operative death**
Data taken from RCTs of endarterectomy versus medical treatment alone.[7] Relative risk reductions are shown in standard format (upper). Effect of endarterectomy on individual patients is depicted below. Plots show actual outcomes after endarterectomy in 100 individuals with 70–99% stenosis and 100 individuals with 50–69% stenosis. Calculation of outcomes is based on first stroke during follow-up, and assumes that risk of stroke on medical treatment and operative risk with surgical treatment are independent, and that strokes that occur after postoperative period would have occurred had the patient not had surgery. Absolute risk reduction = $N_{benefit} - N_{harm}$; relative risk= $(N_{no\ effect\ strokes} + N_{harm}) / (N_{no\ effect\ strokes} + N_{benefit})$.

risk of harm.[6,7] The dilemma is how to use data from large pragmatic RCTs, which provide the most reliable estimates of the average effects of treatment, to determine the probable effect of treatment in an individual. The first article in this series discussed the extent to which the methods, setting, and participants in an RCT affect the relevance of the result to patients in routine clinical practice (ie, external validity). The second article discussed the need for reliable data about the effects of treatment in subgroups. In this article we will consider the possible approaches to predicting the probable effect of treatment in individuals, continuing with the example of endarterectomy for symptomatic carotid stenosis.

Absolute risk reductions and individual outcome

When considering the overall result of an RCT or systematic review the result must be understood in terms of outcomes for individual patients. The first step is to calculate the absolute risk reduction with treatment in the relevant RCT or the number needed to treat to prevent an adverse event.[8,9] An absolute risk reduction tells us what chance an individual has of benefiting from treatment—ie, an absolute risk reduction of 25% suggests that there is a 1-in-4 chance of benefit (number needed to treat=4). By contrast, a specific relative risk reduction gives absolutely no information about the likelihood of individual benefit. For example, the relative reductions in the risk of stroke were virtually identical in the STOP (0·53, 0·33–0·86)[10] and the MRC (0·55, 0·25–0·60)[11] trials of blood pressure lowering in primary prevention, but there was a 12-fold difference in absolute risk reduction (figure 1A). All other things being equal, 830 of the young hypertensives in the MRC trial would have to be treated for 1 year to prevent one stroke compared with 69 of the elderly hypertensives in STOP.

The overall absolute risk reduction in a trial can, however, be less generalisable to routine clinical practice than the relative risk reduction, partly because patients enrolled in RCTs tend to have a better outlook than patients in routine clinical practice.[13–16] For example, 30-day mortality in one trial in patients with acute myocardial infarction was 6% in randomised patients compared with 18% in eligible non-randomised patients.[15] Moreover, as discussed in the first article in this series,[17] the differences between eligible and non-eligible patients can be even greater. Consequently, overall absolute treatment effects measured in trials often underestimate the absolute benefits of treatment in routine clinical practice. Nevertheless, absolute risk reductions in large pragmatic RCTs are still the best guide to the probable effects of treatment of individuals in routine practice.

Consideration of individual outcomes is more complex for treatments, such as carotid endarterectomy, that have associated risks and benefits. For an individual there are only two possible outcomes (stroke or no stroke), but surgery can have four possible effects: (1) harm—ie, an operative stroke in a patient who would not otherwise have had a stroke; (2) benefit—ie, prevention of a stroke that would have occurred if the patient had not had surgery; (3) no stroke but no benefit—ie, the patient did not have a stroke but would not have had a stroke without surgery anyway; and (4) stroke but no harm—ie, the patient had a stroke but would also have had a stroke without surgery. Figure 2 shows the relative risks of stroke with endarterectomy for patients with 50–69% stenosis and 70–99% stenosis and the distribution of individuals across these four different outcomes. The difficulty for clinicians is that only a small proportion of individuals benefit from surgery because most patients are destined to remain stroke-free without surgery. Most patients face the anxiety and discomfort of surgery without any potential for benefit and a substantial proportion are harmed as a result of the 5–7%

operative risk of stroke. Evidence-based guidelines recommend operating on all patients similar to those who participated in the trials, but clinicians understandably want to operate on only the small subset of patients who will benefit. How can these patients be identified?

Determination of treatment effect in individuals

> "We cannot necessarily, perhaps very rarely, pass from (the overall result of a clinical trial) to stating exactly what effect the treatment will have on a particular patient. But there is, surely, no way and no method of deciding that."
>
> Austin Bradford Hill, 1952[18]

Stating exactly what effect a treatment will have on a specific patient is rarely possible, but it is sometimes possible to predict the probable effect of treatment. The most obvious approach is to try to determine the effect of treatment in those trial patients who are most similar to an individual patient. Similarity can be defined either in terms of measured baseline clinical characteristics or in terms of predicted absolute risk of a poor outcome without treatment.

Individuals with similar characteristics

Subgroup analysis to determine the effect of treatment in patients with specific characteristics in relation to relative treatment effects was reviewed in the previous article in this series.[2] However, to determine the likelihood of individual benefit, subgroup analyses should also be expressed as absolute risk reductions. It is especially important to understand that an absence of a significant difference in relative treatment effect between subgroups does not indicate that there is no difference in absolute risk reduction. Figure 1B shows the effect of carotid endarterectomy for severe symptomatic stenosis in patients presenting with retinal ischaemic events versus cerebral hemispheric events.[12] There is no significant heterogeneity of relative treatment effect (interaction p=0·55) but there is a significant (p=0·01) and clinically important three-fold difference in absolute treatment effect. This inconsistency is inevitable if relative risk reductions are similar in two subgroups but the absolute risks without treatment are sufficiently different.

It cannot even be assumed that any difference in absolute risk reduction between subgroups will be in the same direction as that for the relative risk reduction. For example, in a pooled analysis of data from trials of lipid lowering in prevention of vascular events, the relative treatment effect was significantly lower in patients with hypertension than in those with no hypertension (relative risk reduction=14%, 95% CI 2–24 *vs* 33%, 25–40; interaction p=0·003) but absolute benefit was still

Subgroup	Events/patients: Surgical	Events/patients: Medical	RR	95% CI	% ARR	95% CI
Sex						
Male	92/890	172/784	0·46	0·41–0·51	13·1	9·2 to 16·9
Female	59/436	55/346	0·84	0·63–1·12	2·7	−2·6 to 8·0
Time since last event						
<2 weeks	30/284	80/269	0·35	0·31–0·40	21·0	14·0 to 28·0
2–4 weeks	29/233	41/193	0·57	0·45–0·73	9·7	2·1 to 17·2
4–12 weeks	56/512	76/450	0·63	0·52–0·78	6·8	2·0 to 11·5
>12 weeks	36/297	30/218	0·85	0·58–1·26	2·3	−4·4 to 9·0
Time since last event: males						
<2 weeks	20/178	52/185	0·39	0·33–0·47	18·6	10·0 to 27·2
2–4 weeks	16/139	33/136	0·45	0·35–0·58	14·4	4·9 to 23·9
4–12 weeks	37/365	60/317	0·52	0·43–0·64	9·9	4·1 to 15·7
>12 weeks	19/208	27/146	0·47	0·36–0·61	11·3	2·7 to 19·9
Time since last event: females						
<2 weeks	10/106	28/84	0·28	0·23–0·33	25·8	13·6 to 38·1
2–4 weeks	13/94	8/57	1·00	0·44–2·26	0·0	−11·7 to 11·7
4–12 weeks	19/147	16/133	1·04	0·54–1·99	−0·5	−8·8 to 7·7
>12 weeks	17/89	3/72	4·30	1·48–12·46	−16·0	−26·5 to −5·5
Total	151/1326	227/1130	0·55	0·50–0·62	9·8	6·6 to 12·9

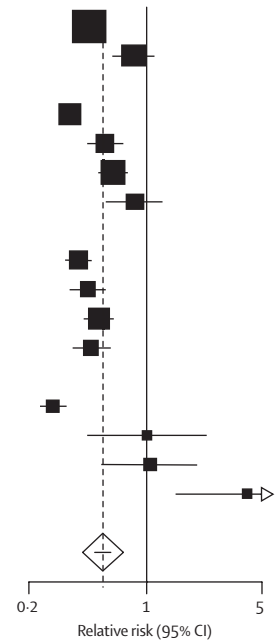

Figure 3: **Interaction between two independent univariate subgroup analyses of effect of carotid endarterectomy for ⩾50% symptomatic stenosis**
Data from Carotid Endarterectomy Trialists' Collaboration showing independent effects of sex and time from last symptomatic ischaemic event to randomisation on the benefit from surgery (upper) and effect of time from last symptomatic ischaemic event to randomisation on benefit from surgery in men and women separately.[12] RR represents the relative risk at 5 years derived from survival tables and will not coincide exactly with the numbers of events/patients given.

greater in the patients with hypertension because of their greater absolute risk without treatment.[19] These considerations are crucial in elderly people, in whom relative treatment effects are sometimes less than in younger patients, often because disease is more advanced, but absolute treatment effects are frequently greater because the absolute risk of a poor outcome without treatment is higher.

Absolute risk reductions in subgroups can be useful in predicting the probable effect of treatment in individuals, but analyses are usually done only in relation to one baseline variable and are of little use if there are several clinical characteristics that might have important effects on the risks or benefits of treatment. Absolute risk reductions for patients with many specific characteristics cannot be derived indirectly from separate univariate subgroup analyses. Even relative risk reductions cannot be derived indirectly—ie, if two clinical characteristics were each associated with a doubling of the relative risk reduction with treatment in univariate subgroup analyses, benefit will not necessarily be four-fold greater in a patient who possesses both characteristics than in a patient who possesses neither. It is possible, however, to do multivariate subgroup analysis to estimate the exact benefit. For example, carotid endarterectomy for symptomatic carotid stenosis is less effective in women than in men (interaction: p=0·007), and benefit is also very closely related to the delay since the presenting transient ischaemic attack or stroke (interaction: p=0·006).[12] Figure 3 shows the effect of surgery in the relevant subgroups in patients with 50–99% stenosis. Although the univariate subgroups are independent (ie, there was no difference in the mean delay in men and women) the subgroup effects are not. The effect of the delay to surgery on benefit is almost confined to women (difference in trend: p<0·001), probably as a result of sex differences in the pathology of symptomatic carotid plaque.[20]

Thus interactions between different subgroup effects can only be determined with multifactorial subgroup analysis, but since statistical power in RCTs is usually insufficient for univariate subgroup analyses, reliable multifactorial subgroup analysis will rarely be possible in practice. Benefit from endarterectomy for symptomatic carotid stenosis depends on age, the type of presenting event, plaque surface morphology, sex, and the time since the last symptomatic event.[12] What would be the probable benefit from surgery in a 78-year-old (increased benefit) female (reduced benefit) with 80% stenosis who presented within 2 weeks (increased benefit) of an ocular ischaemic event (reduced benefit) and had an ulcerated carotid plaque (increased benefit)? On the basis of the clinical characteristics of the patients in the RCTs of endarterectomy, to have an adequate sample of patients (about 2000) with the same characteristics as this patient, a total trial population of about 200 000 would be needed.

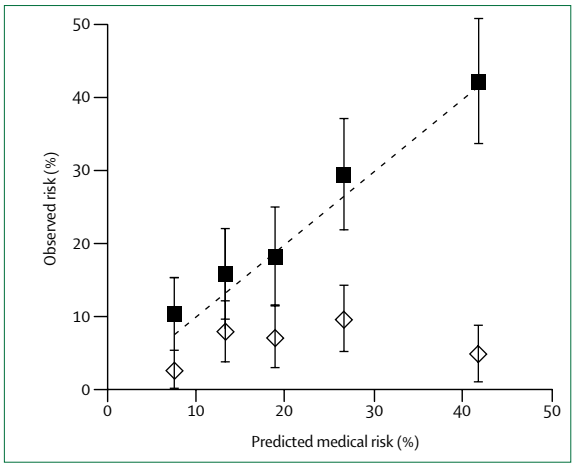

Figure 4: **Reliability of ECST prognostic model for 5 year risk of stroke on medical treatment in patients with 50–99% stenosis in NASCET (squares). Operative risk in patients randomised to surgery in NASCET is also stratified by predicted risk of stroke on medical treatment (diamonds)**
Error bars represent 95% CIs.

Individuals with similar risks

A more realistic approach is to abandon any attempt to determine the effect of treatment in subgroups that are defined by specific characteristics, and to base decisions on the predicted absolute risks of a poor outcome with each treatment option in individual patients. It is usually suggested that the best way to determine the probable effect of treatment in an individual is to simply multiply the overall relative risk reduction from a relevant trial or systematic review by whatever absolute risk of a poor outcome it is estimated that the patient faces without treatment.[21–23] However, as detailed in the previous article in this series,[2] difficulties arise when there is clinically important heterogeneity of relative treatment effect, especially when the relative treatment effect itself depends on the absolute risk of a poor outcome in the control group,[6,24–34] such that the two variables cannot simply be multiplied as if they were independent. Moreover, clinicians are often inaccurate in assessment of risk in their patients,[35] and there is frequently an absence of high quality and up-to-date natural history data on which to base estimates.[36] Less simplistic approaches are needed.

A better approach is to use risk models to predict the absolute risks of a poor outcome with each treatment option in individual patients.[6,37] Validated prognostic models are available for many disorders (although not nearly enough),[38,39] and there are several for prediction of individual risk of coronary heart disease and stroke,[3,6,30,34,39–48] especially in primary care.[46–48] Although trial populations do, on average, have a lower absolute risk of a poor outcome than do patients in routine clinical practice, they usually contain some high-risk patients,[49] and do therefore allow determination of the effect of treatment in individuals with a reasonable range of baseline risk. The usefulness of this approach

in exploring the relations between the effects of treatment in RCTs and the baseline absolute risk of a poor outcome in trials in vascular medicine is shown by the demonstration of qualitative heterogeneity of relative treatment effect in relation to baseline risk for carotid endarterectomy for symptomatic stenosis,[6] anticoagulation in primary prevention of stroke in patients with non-valvular atrial fibrillation,[23] coronary artery bypass grafting,[25] and anti-arrhythmic drugs after myocardial infarction.[34] Clinically important heterogeneity of relative treatment effect by baseline risk has also been shown for blood pressure lowering,[26] aspirin,[27] and lipid lowering[28] in primary prevention, for benefit from treatment with clopidogrel[29] and with enoxaparin[30,31] in patients with acute coronary syndromes, and in treatment of non-cardiovascular disorders.[32,33] Weightings based on patient preferences for different outcomes can be built in,[50–52] and modelling also allows the interactions between the effects of different characteristics, as was shown in figure 3, to be determined and incorporated.

Predicting benefit from carotid endarterectomy

The potential usefulness of a risk modelling approach is shown below with the example of carotid endarterectomy for recently symptomatic carotid stenosis. There are several validated models to predict stroke risk in different situations,[40,42,43,53] but these models were derived in populations with a low prevalence of carotid disease and did not include the degree of carotid stenosis. In view of the importance of this measurement in determining the risk of stroke on medical treatment in patients with recently symptomatic carotid disease,[7] models are needed for use in this specific clinical situation. One such model was derived from the patients randomised in the European Carotid Surgery Trial (ECST).[6]

The ECST risk model could not at first be validated using data from a similar trial because of differences in the method of measuring the degree of carotid stenosis and in the definition of outcome events.[7] However, after remeasurement of the degree of stenosis on the pre-randomisation angiograms and revision of the definition of outcome events, the ECST data were made consistent with data from the North American Symptomatic Carotid Endarterectomy Trial (NASCET),[7,54] and the ECST model was re-derived (table). The potential usefulness of the model is shown in figure 4, which shows the risk of stroke on medical treatment in patients with 50–99% symptomatic carotid stenosis who were randomised to medical treatment in NASCET stratified into quintiles of predicted risk according to the ECST model. There was close agreement between predicted and observed medical risk ($\chi^2_{Heterogeneity}$=43·1, df=4, p<0·0001; Mantel-Haenszel χ^2_{Trend}=41·3, df=1, p<0·0001) and the model reliably distinguished between quintiles with 10% and over 40% risks of ipsilateral ischaemic stroke after 5 years follow-up. Importantly, figure 4 also shows that the operative risk of stroke and death in patients who were randomised to surgery in NASCET was unrelated to the medical risk ($\chi^2_{Heterogeneity}$=7·2, df=4, p=0·13; Mantel-Haenszel χ^2_{Trend}=0·98, df=1, p=0·32). Thus, when the operative risk and the small additional residual risk of stroke following successful endarterectomy were taken into account, benefit from endarterectomy at 5 years varied significantly across the quintiles (p=0·001), with no benefit in patients in the lower three quintiles of predicted medical risk (ARR=0–2%), moderate benefit in the fourth quintile (ARR=10·8%, 95% CI=1·0–20·6), and substantial benefit in the highest quintile (ARR=32·0%, 95% CI=21·9–42·1).

Similar clinically important heterogeneity of both relative and absolute treatment effect has been shown for many other interventions in vascular medicine in this way.[6,24–34] This stratification of trial data using an independently derived model is essential, even if the model has been validated previously in non-trial cohorts, because although trials tend to recruit low risk individuals, the distribution of risks in patients who are considered for treatment in clinical practice may well also be different from that in the non-trial observational cohorts used for derivation and validation of the model. Clinicians also need to be convinced that use of a risk modelling approach does produce clinically useful heterogeneity of treatment effect.

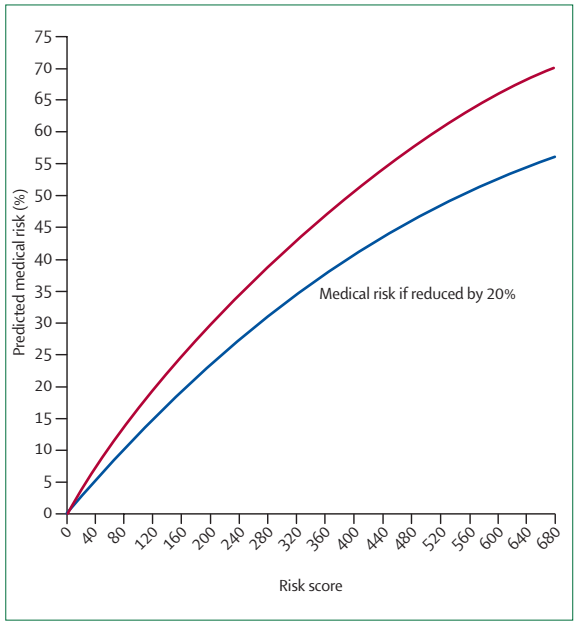

Figure 5: **Plot of total risk score derived from table against 5-year predicted risk of ipsilateral carotid territory ischaemic stroke**
Data derived from full model in the table in patients in ECST (red line). This should be used as a nomogram for conversion of score into prediction of percentage risk. Blue line represents a 20% reduction in risk as might be seen with more intensive medical treatment than was available in ECST in late 1980s and 1990s.

For most treatments, in which the risk of harm from the treatment itself is much lower than the risk of a poor outcome without treatment, it is only necessary to model the risk of a poor outcome without treatment. However, for treatments that have a substantial risk of harm, the risk of a poor outcome with treatment should be considered separately because its determinants may be different.[6,12] For carotid endarterectomy, for example, female sex is associated with a low risk of stroke on medical treatment but a higher operative risk of stroke and death,[12,55] whereas increasing age and a very recent symptomatic ischaemic event are associated with a high risk of stroke on medical treatment but not with an increased operative risk.[12,41,55,56] A modelling process that provides estimates of the probable individual risks with both treatment options is therefore needed.[6] Figure 4 shows that risk modelling is a useful approach to targeting carotid endarterectomy but a more sophisticated model that includes interactions, such as that between sex and the effect of the timing of surgery, and that also takes predicted individual operative risk into account, would be more effective.

Making the results of risk models accessible

Prediction of risk using models needs a computer, a pocket calculator with an exponential function, or internet access to use the model online (the ECST model

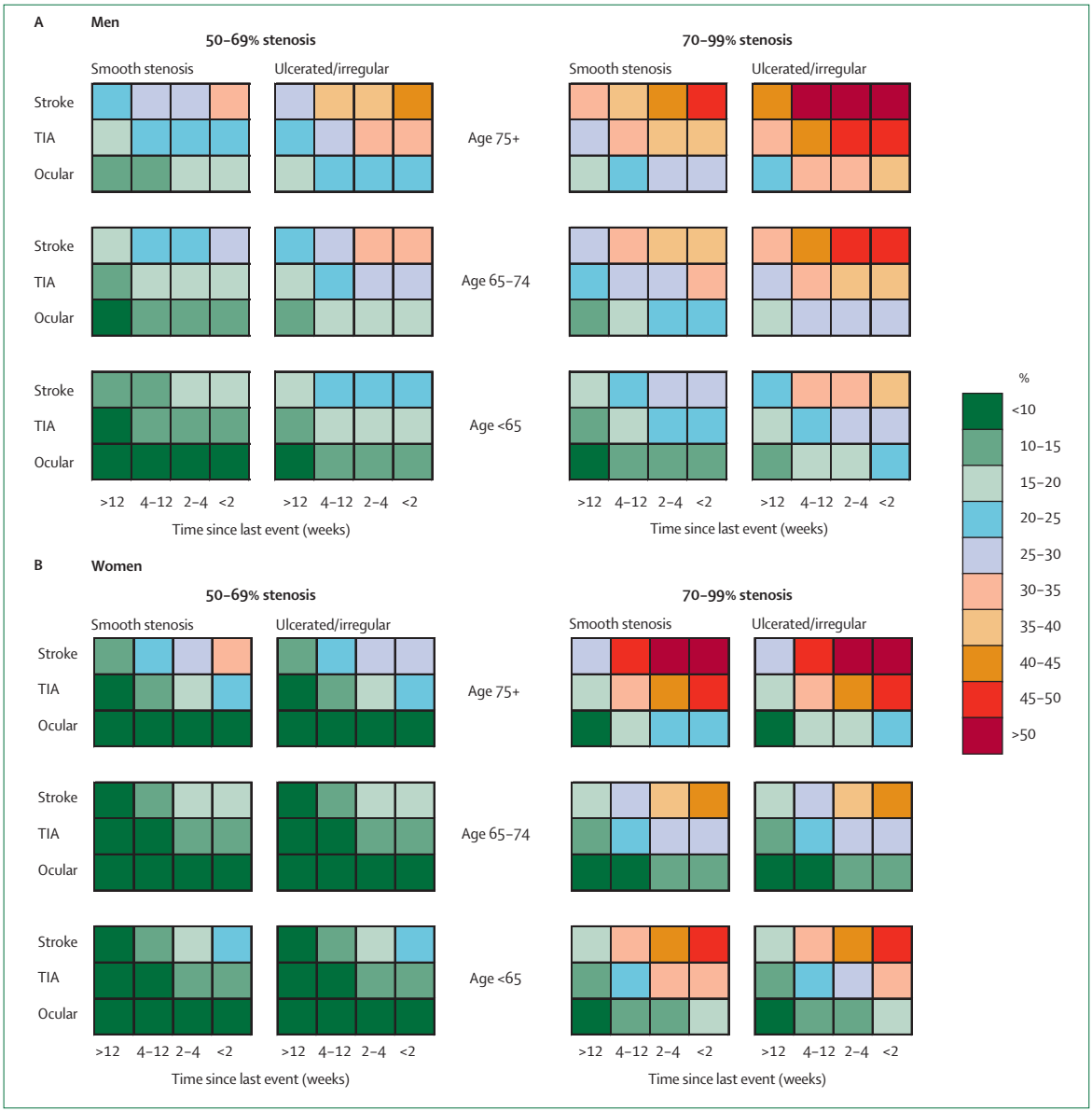

Figure 6: **Table of predicted absolute risk of ipsilateral ischaemic stroke on medical treatment in patients with recently symptomatic carotid stenosis**
Derived from Cox model based on five clinically important patient characteristics in (A) men and (B) women. TIA=transient ischaemic attack. Stroke/TIA/Ocular refers to the most severe symptomatic ipsilateral ischaemic event in the past 6 months: Stroke>Cerebral TIA>Ocular Events only.

Model			Scoring system		
Risk factor	Hazard ratio (95% CI)	p value	Risk factor	Score	Example
Stenosis (per 10%)	1·18 (1·10–1·25)	<0·0001	Stenosis (%)		
			50–59	2·4	2·4
			60–69	2·8	
			70–79	3·3	
			80–89	3·9	
			90–99	4·6	
Near occlusion	0·49 (0·19–1·24)	0·1309	Near occlusion	0·5	No
Male sex	1·19 (0·81–1·75)	0·3687	Male sex	1·2	No
Age (per 10 years)	1·12 (0·89–1·39)	0·3343	Age (years)		
			31–40	1·1	
			41–50	1·2	
			51–60	1·3	
			61–70	1·5	1·5
			71–80	1·6	
			81–90	1·8	
Time since last event (per 7 days)	0·96 (0·93–0·99)	0·0039	Time since last event (days)		
			0–13	8·7	8·7
			14–28	8·0	
			29–89	6·3	
			90–365	2·3	
Presenting event			Presenting event		
Ocular	1·000	0·0067	Ocular	1·0	
Single transient ischaemic attack	1·41 (0·75–2·66)		Single transient ischaemic attack	1·4	
Multiple transient ischaemic attacks	2·05 (1·16–3·60)		Multiple transient ischaemic attacks	2·0	
Minor stroke	1·82 (0·99–3·34)		Minor stroke	1·8	
Major stroke	2·54 (1·48–4·35)		Major stroke	2·5	2·5
Diabetes	1·35 (0·86–2·11)	0·1881	Diabetes	1·4	1·4
Previous myocardial infarction	1·57 (1·01–2·45)	0·0471	Previous myocardial infarction	1·6	No
Peripheral vascular disease	1·18 (0·78–1·77)	0·4368	Peripheral vascular disease	1·2	No
Treated hypertension	1·24 (0·88–1·75)	0·2137	Treated hypertension	1·2	1·2
Irregular/ulcerated plaque	2·03 (1·31–3·14)	0·0015	Irregular/ulcerated plaque	2·0	2·0
			Total risk score		263
			Predicted medical risk using nomogram		37%

TIA=transient ischaemic attack. PVD=peripheral vascular disease. Model differs slightly from one previously published[6] in that degree of stenosis and definition of outcome event are based on those used in NASCET trial.[7] Hazard ratios derived from model are used for scoring system. Score for the 5-year risk of stroke is product of individual scores for each risk factor present. Score is converted into a risk with graphic in figure 5. An example is shown. In cases of near-occlusion, enter degree of stenosis as 85%. Presenting event is coded as most "severe" ipsilateral symptomatic event in the last six months (severity is as ordered above ie, ocular events are least severe and major stroke is most severe). Major stroke is defined as stroke with symptoms persisting for at least 7 days. Treated hypertension includes previously treated or newly diagnosed.

Table: **Cox model for 5-year risk of ipsilateral ischaemic stroke on medical treatment in patients with recently symptomatic carotid stenosis derived from ECST**

is at www.stroke.ox.ac.uk). As an alternative when access to computing or the internet is not possible, a simplified risk score based on the hazard ratios derived from the relevant risk model can be helpful.[57,58] For example, the table also shows a score for the 5-year risk of stroke on medical treatment in patients with recently symptomatic carotid stenosis derived from the ECST model. Clinicians calculate the total risk score as the product of scores for each risk factor. Figure 5 shows a plot of the total risk score against the 5-year predicted risk of ipsilateral carotid territory ischaemic stroke derived from the full model, and is used as a nomogram for the conversion of the score into a prediction of the percentage risk. An example of the use of the risk score is also shown in the table.

To eliminate the need for clinicans to calculate a risk or a score, colour-coded risk tables that indicate the predicted risk in patients with specific characteristics can be derived. This approach is best suited to situations in which there are a small number of important variables to consider and has the major advantage that scores do not have to be calculated by the clinician or patient. Figure 6 shows a risk table indicating the 5-year risk of ipsilateral ischaemic stroke in patients with recently symptomatic carotid stenosis on medical treatment. To limit the number of separate tables necessary, only the six variables that were significant predictors of risk in the ECST model (table) or yielded clinically important univariate subgroup treatment effect interactions in the analysis of pooled data from the relevant trials, or both,[12] are included: sex, age, time since last symptomatic event, type of presenting event(s), carotid plaque surface morphology, and degree of stenosis (each categorised as in the previous subgroup analysis).[12]

Problems with use of individual risk to target treatment

The use of risk models to target treatment is not without difficulties. Models tend to overpredict (ie, to label high-

risk patients as higher risk than they really are and low-risk patients as lower risk) and it is therefore essential that they are externally validated and adjusted if there is over-prediction. Models rarely work as well in independent populations as in the derivation populations and are usually less effective when validated by groups other than those who derived the model.[62,63] Nevertheless, as shown in figure 4, models can still be clinically useful. There are also difficulties with rigid risk cut-off points below which treatment should not be given, which are usually based on short follow-up periods. In primary prevention of vascular disease, for example, it does not necessarily make long-term sense to withhold treatment from young low-risk patients and only start treatment when they have reached an age and an absolute risk that mean that they have already developed serious underlying disease. The relative benefit of long-term early treatment may well be greater than in short-term trials in older age groups.

One of the main arguments against risk modelling to select individual patients with the most to gain from treatment is that even if there is a validated risk score that is able to identify high-risk individuals, most of the clinical events that we want to avoid will still usually occur in the generally much larger number of apparently low and moderate risk individuals, the so-called prevention paradox.[64,65] For example, figure 7 shows the results of RCTs of three antithrombotic treatments for acute coronary syndromes[29–31] stratified by the independently-derived Thrombolysis In Myocardial Infarction (TIMI) risk score.[30] In all three trials, the intervention was of no benefit in low-risk patients but was highly beneficial in high-risk cases. However, figure 7 also shows that in each trial the proportion of patients with low risk scores (no benefit from treatment) and high risk scores (major benefit) was small and most of the patients and events prevented were in the large moderate risk (moderate benefit) groups. However, this demonstration of the prevention paradox is by no means an inevitable result of the risk modelling approach; it is merely a result of the use of poorly predictive models. Admittedly, risk models are sometimes poorly predictive, often because the outcome has few known risk factors or there are insufficient data from high quality cohort studies with which to derive and validate models. However, the validation of the carotid stenosis risk model (figure 4) shows that as many adverse outcomes can potentially be prevented by treating high-risk subsets of patients as by treating all patients.

Finally, if effective new treatments are introduced, models derived in the past may overestimate risks. For example, the ECST medical risk model was derived from data that were obtained before the use of statins was widespread. However, such improvements in treatment pose more problems for interpretation of the overall trial results than for the risk modelling approach. For example, it would take only a modest improvement in the effectiveness of medical treatment to erode the overall benefit of endarterectomy in patients with 50–69% stenosis in figure 2. By contrast, major improvements in medical treatment would be needed to significantly reduce the benefit from surgery in patients in the high predicted risk quintile in figure 4. Thus, the likelihood that ancillary treatments have improved, and are expected to continue to improve, is an argument in favour of a risk-

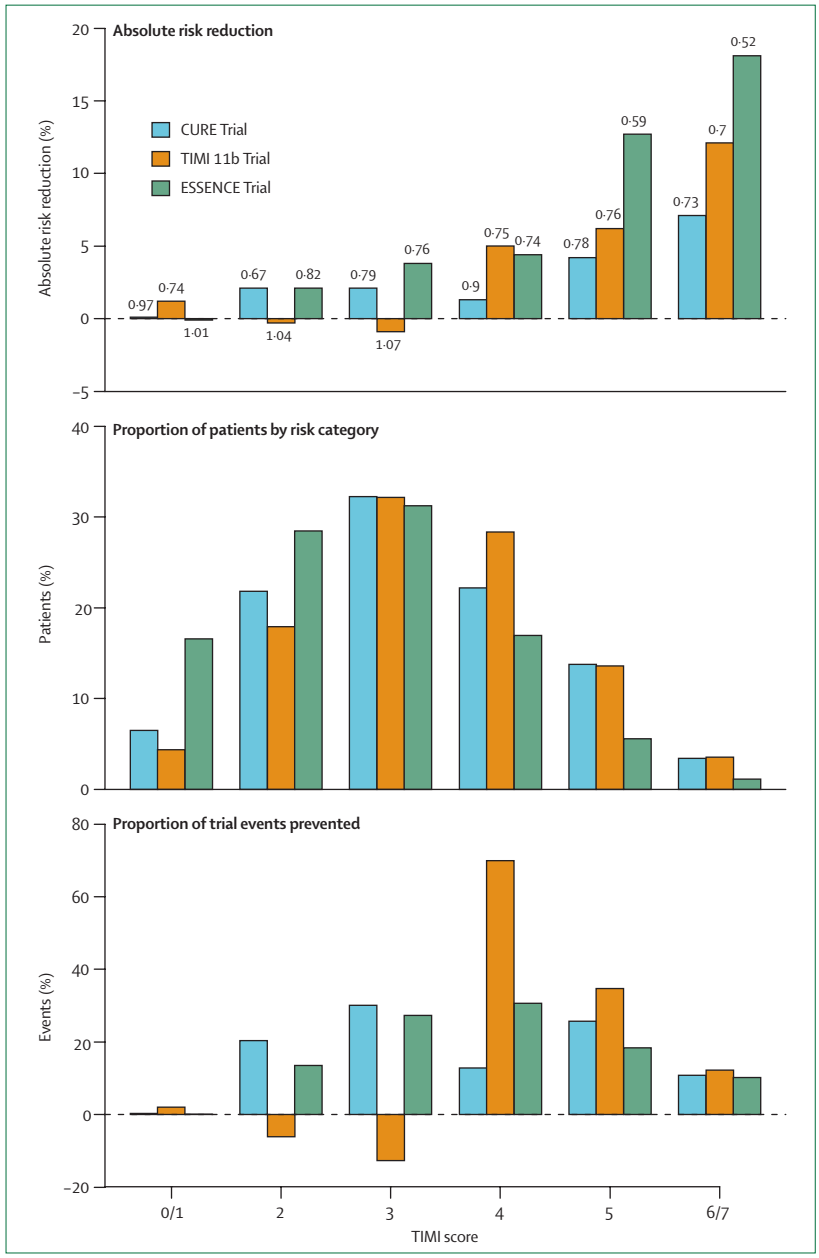

Figure 7: **Results of three randomised trials of treatments for acute coronary syndromes[29–31] stratified by independently-derived TIMI risk score[30]**

For each trial absolute risk reduction with treatment (upper), proportion of patients (middle) and proportion of events prevented (lower) are shown in each risk category. The numbers shown above bars of the graph of absolute risk reductions (upper) are the corresponding relative risks. CURE=Clopidogrel in Unstable angina to prevent Recurrent Events. ESSENCE=Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q wave Coronary Events.

based approach to targeting treatment. In a patient given a statin, it would be reasonable, for example, to reduce the risks derived from the risk models in the table by 20% in relative terms to account for the probable benefit of that treatment. The same approach can be used to account for any reductions in the risks of treatment. The operative risk of stroke and death attributable to endarterectomy was 7% in the large trials,[12] and does not seem to have fallen since, at least in published series,[66] but the risk may be reduced in future or be lower for carotid angioplasty with cerebral protection.[67]

Conclusions

Clinicians often have to make treatment decisions based on the absolute likelihood of benefit for individual patients. Since relative risk reductions are uninformative in this regard, overall results of trials and subgroup analyses should also be expressed as absolute risk reductions. When there are several clinically important subgroup-treatment effect interactions, multifactorial subgroup analysis could in theory provide useful information, but very large trials or meta-analyses of individual patient data from several trials are needed. Alternatively, and especially in clinical disorders or interventions in which benefit is probably going to be very dependent on the absolute risk of adverse outcomes with or without treatment, the effect of baseline risk on benefit from treatment should be determined by stratification of trial populations with independently derived and validated prognostic models. Risk modelling avoids some of the difficulties of subgroup analysis, including chance findings with many post-hoc subgroup comparisons, and is a more powerful instrument for differentiating between patients who are likely to benefit from treatment and those who are not. Risk models allow clinicians to take into account the many characteristics of an individual patient and their interactions in a logical and systematic manner, to consider the risks and benefits of interventions separately if needed, and to provide patients with personalised estimates of their likelihood of benefit.

Conflict of interest statement

We declare that we have no conflict of interest.

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