Who should have carotid surgery or angioplasty?

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Carotid endarterectomy reduces the overall risk of stroke in patients with recently symptomatic stenosis, and to a lesser extent, at least in the short-term, in patients with severe asymptomatic stenosis. Whether angioplasty and stenting is a reasonable alternative will be decided by the results of ongoing RCTs of angioplasty versus endarterectomy. The current policy of operating on all patients with a recently symptomatic severe carotid stenosis will, on average, do more good than harm. However, the number of patients needed to treat to prevent one stroke is still relatively high. The effectiveness of endarterectomy could be improved by selecting patients more rigorously. Subgroup analysis and risk factor modelling are likely to be of some value, but further testing is required before final models can be recommended for routine use in clinical practice. However, it is also likely that predictive models will eventually also take into account information on cerebral microemboli, cerebral perfusion, and genetic characteristics. The development and validation of integrated predictive models, combining these different modalities, will require large prospective clinical studies.

Most strokes are due to cerebral infarction, and the majority of these occur in the territory of the carotid arteries. Significant atherosclerotic narrowing of the origin of the internal carotid artery ipsilateral to the infarct is found in 20–30% of cases, compared with 5–10% of the general population in the same age range. It was suggested at the beginning of the century that carotid atheroma may cause stroke, and this was eventually proven by the observation that endarterectomy of severe atherothrombotic stenosis markedly reduces the risk of subsequent ipsilateral carotid territory ischaemic stroke. This chapter will review the results of the randomised controlled trials (RCTs) of carotid endarterectomy and percutaneous transluminal angioplasty (PTA) for recently symptomatic and asymptomatic carotid stenosis, and consider ways in which those patients with most to gain from these procedures might be selected.
Randomised controlled trials of endarterectomy for symptomatic carotid stenosis

About 150,000 carotid endarterectomies are performed each year in the US, and rates continue to rise in Europe. There have been five RCTs of endarterectomy for symptomatic carotid stenosis. The first two were small, did not produce statistically significant results, and probably no longer reflect current surgical practice. The larger VA trial (VA #309) reported a non-significant trend in favour of surgery, but was stopped early when the two largest trials, the European Carotid Surgery Trial (ECST) and the North American Symptomatic Carotid Endarterectomy Trial (NASCET), reported their preliminary results in 1991. Because patients at high risk of stroke on medical treatment are likely to have the most to gain from surgery, the analyses of these trials were stratified by the degree of stenosis of the symptomatic carotid artery, which is a powerful predictor of stroke risk on medical treatment. However, different methods of measurement of the degree of stenosis on pre-randomisation angiograms were used; the NACSET method underestimating stenosis compared to the ECST method. Stenoses reported to be 70–99% in the NASCET trial were equivalent to 80–99% by the ECST method, and stenoses reported to be 70–99% by the ECST trialists were 50–99% by the NASCET method. The ECST showed that surgery reduced the risk of stroke in patients with ECST 70–99% stenosis. The NASCET trial reported similar results in patients with NASCET 70–99% (ECST 80–99% stenosis). The ECST also reported that surgery was harmful in patients with mild stenosis (ECST 0–29%), in whom the risk of stroke on medical treatment was too low to offset the operative risks. Both trials continued to randomise patients with moderate stenosis, and reported their final results in 1998. The ECST showed that there was no benefit from surgery in patients with either ECST 30–49% stenosis or ECST 50–69% stenosis. Indeed, when the results were stratified by decile of stenosis rather than the predefined stenosis groups, endarterectomy was only significantly beneficial in patients with ECST 80–99% stenosis (NASCET 70–99% stenosis). Only a very small trend in favour of surgery was seen in patients with ECST 70–79% stenosis (NASCET 50–69% stenosis). The absolute reduction in risk of major stroke or death at three years in patients with ECST 80–99% stenosis (NASCET 70–99% stenosis) was 11.6% (P < 0.001). This is consistent with the 10.1% (P < 0.01) reduction in major stroke or death at 2 years reported in NASCET in patients with NASCET 70–99% stenosis. However, NASCET also reported a 6.9% (P = 0.03) absolute reduction in risk of disabling stroke or death in patients with NASCET 50–69% stenosis (ECST 70–80% stenosis), although no benefit was seen in patients with less severe stenosis. ECST did not show benefit...
within the ECST 70–80% stenosis group, but the confidence interval of the estimate of treatment effect was wide. Taking the results of both trials together, it is reasonable to conclude that they have demonstrated some overall benefit from endarterectomy in patients with a recently symptomatic ECST 70–99% stenosis (NASCET 50–99% stenosis). It is necessary to operate on 8–10 patients to prevent one stroke over the next 3 years.

**Randomised controlled trials of endarterectomy for asymptomatic carotid stenosis**

There have been seven RCTs of endarterectomy for asymptomatic carotid stenosis\(^1\), one of which is on-going\(^2\). The initial studies were small and did not produce statistically significant results.\(^1\) The VA study (VA #167) demonstrated a significant reduction in the risk of the combined outcome of stroke and TIA in the endarterectomy group in patients with NASCET 50–99% stenosis, but did not have the power to demonstrate a reduction in the risk of stroke alone\(^3\). In 1995, the Asymptomatic Carotid Artery Study (ACAS)\(^4\) demonstrated a clearly significant reduction in the risk of ipsilateral ischaemic stroke in surgical patients with NASCET 60–99% asymptomatic stenosis (assessed by Doppler ultrasound); a reduction in the 5 year actuarial risk of ipsilateral ischaemic stroke or operative death from 11% to 5.1% \((P < 0.001)\). In other words, 17 operations are required to prevent 1 stroke over the next 5 years or 85 operations per year to prevent 1 stroke per year. This benefit is not regarded by many neurologists as sufficient to justify routine surgery for asymptomatic stenosis. The Asymptomatic Carotid Surgery Trial (ACST) is a large European RCT which is still recruiting and has now randomised in excess of 2000 patients\(^2\). It is expected to publish results sometime after 2002, and will more than double the existing randomised data.

Thus, there is some evidence of benefit from endarterectomy in patients with asymptomatic stenosis. However, the low short-term risk of ipsilateral ischaemic stroke on medical treatment distal to an asymptomatic stenosis (approximately 2% per annum) means that the overall short-term reduction in the absolute risk of stroke following endarterectomy will always be small\(^5\). However, short-term data may not be adequate. A younger patient with a severe asymptomatic stenosis may well survive for 10–20 years. The mean follow-up in the completed RCTs of endarterectomy for asymptomatic stenosis was little over 2 years. There are no detailed data on the long-term risk of stroke distal to different degrees of asymptomatic stenosis, but a preliminary analysis of a large collaborative natural history study has recently suggested that the
10 year stroke risk may be as high as that distal to symptomatic stenosis\textsuperscript{16}. More detailed work is required to confirm or refute this observation. If true, it would have important implications for ongoing RCTs of endarterectomy and PTA, and for the use of endarterectomy in primary prevention of stroke. It is important to bear in mind that the risks of stroke and death due to endarterectomy for asymptomatic stenosis are significantly lower than for symptomatic stenosis\textsuperscript{17}.

**Randomised controlled trials of carotid endarterectomy versus PTA**

The operative risks of stroke and death within 30 days of carotid endarterectomy are not insignificant: 6.8\% (95\% CI = 5.6–8.0) in ECST and 6.7\% (5.3–8.4) in NASCET\textsuperscript{8,9}. These risks are higher than those reported in many surgical case-series\textsuperscript{18}, but these may be undermined by publication bias, and the trial risks are likely to be the most reliable guides to the real risks of the operation in good surgical practice. Angioplasty, with or without stenting, has been suggested as a potentially safer and less costly alternative to endarterectomy in patients with carotid stenosis. The 30 day risks of stroke and death due to PTA, and the rates of early and late restenosis have yet to be defined precisely. The Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS) has now provided useful data on which to base the further evaluation of angioplasty.\textsuperscript{19} The main core of CAVATAS was a randomised comparison of angioplasty and endarterectomy. A total of 560 patients were recruited (504 randomised between angioplasty and endarterectomy). The 30 day risks of stroke and death were 10\% in both treatment groups and there was no clear benefit for either treatment on initial follow-up. The 30 day risks in both groups had wide confidence intervals and were not statistically significantly different from the risks reported in ECST and NASCET. Follow-up continues in CAVATAS in order to determine the restenosis rate. A further small (17 patients) single centre RCT of angioplasty and stenting versus endarterectomy was stopped in 1998 due to an unacceptably high complication rate in the angioplasty group (5 out of 7 patients had strokes following angioplasty)\textsuperscript{20}. Clearly, therefore, there is still uncertainty about the role of angioplasty\textsuperscript{21}, and further RCTs are necessary. A second and larger CAVATAS trial, in which angioplasty will be combined with routine stenting, will shortly begin recruitment. A similar large RCT of angioplasty and stenting versus endarterectomy is about to get underway in the US (CREST). At the present time, carotid angioplasty and stenting should only be performed within well-designed RCTs.
How can we identify the patients who are most likely to benefit from endarterectomy or PTA?

The overall results of RCTs of endarterectomy and PTA are useful, but they only go so far in helping patients and clinicians to make decisions in the clinic. For example, as described above, it has been shown that endarterectomy is beneficial in patients with a recently symptomatic ECST 70-99% stenosis. However, although endarterectomy does indeed reduce the overall risk of ischaemic stroke by about 50% in relative terms over the next 3 years, only about 20% of such patients actually suffer a major stroke on medical treatment alone. Strictly speaking, therefore, the operation is of no value in the other 80% of patients who, despite having a severe symptomatic stenosis, are destined to remain stroke-free without surgery. Indeed, as a group, these patients will be harmed by surgery because of the significant operative risk of morbidity and mortality. Figure 1 illustrates the possible outcomes in patients undergoing endarterectomy for severe symptomatic carotid stenosis. The overall effect of surgery is shown as the point estimate and 95% confidence interval in the traditional meta-analysis format. The actual outcomes in individual patients are depicted by open dots (no stroke) or closed dots (stroke). The majority of patients (groups b and c) did not benefit from surgery, but were not harmed by the operation. Either they did not have an operative stroke, but would not have had a stroke

![Diagram showing possible outcomes in patients undergoing endarterectomy for severe symptomatic carotid stenosis.](image-url)

**Fig. 1** The possible outcomes in patients undergoing endarterectomy for severe symptomatic carotid stenosis. The point estimate for the overall effect of surgery and the 95% confidence interval are shown in the traditional meta-analysis format. The actual outcomes in individual patients are depicted by the circles. See text for explanation.
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anyway had they received medical treatment alone (group b) or they had an operative stroke, but would also have had a stroke if they had received medical treatment only (group c). A few patients (group d) were harmed by surgery, i.e. they had an operative stroke, but would not have had a stroke if they had not been operated. Only a relatively small proportion of patients (group a) actually benefited from surgery. These patients would have had a stroke had they only received medical treatment, but they did not have a stroke following endarterectomy. Clearly, if possible, it would be highly desirable to be able to identify in advance, and operate on, those individual patients who were most likely to fall into group a, and avoid surgery in all other patients. In this way, it would be possible, in theory at least, to prevent more strokes than would be prevented by operating on all patients, but only operate on a fraction of the patients. In practice, this ideal may not be achievable, but it is possible to go some way towards that goal by using as much prognostic information as is available to try to identify those individuals who are most likely to fall into group a, i.e. patients with a high risk of stroke on medical treatment alone, but a relatively low operative risk. Three techniques which might help us to do this are discussed below.

Subgroup analysis of data from RCTs

Subgroup analysis in clinical trials allows the effects of a treatment to be determined in patients with a particular characteristic. This allows clinicians to assess whether a particular patient with or without that characteristic might be more or less likely to benefit from treatment than suggested by the overall trial result. There are, of course, dangers with subgroup analysis. Results are subject to the play of chance, and there have been many examples of misleading subgroup analyses which have led to particular groups of patients being denied treatments, which were subsequently shown to be effective when further trial data became available. Mistakes are particularly likely when multiple subgroup analyses are performed without correction of statistical significance for multiple comparisons. However, given a sufficient sample size and a statistically rigorous approach, subgroup analysis can be of some value. It should be borne in mind that stratification of trial results by severity of carotid stenosis is itself a subgroup analysis. In the final reports of the ECST and NASCET trials, other subgroups were examined in combination with severity of stenosis. In ECST, the benefit derived from endarterectomy in patients with ECST 80–99% stenosis was reported to be greater in men than in women, with clear benefit in women only evident in patients with ECST 90–99% stenosis. In NASCET patients with moderate stenosis, endarterectomy was reported to be most beneficial in
men, in patients with stroke as the qualifying event, and in patients with hemispheric (as opposed to ocular) symptoms. Unfortunately, neither trial was powered to determine these relationships with certainty and the results cannot be relied upon. However, the individual patient data from the ECST, NASCET and VA trials have been combined in a single database in order to allow subgroup analyses with sufficient statistical power to influence clinical practice (The Carotid Endarterectomy Trialists’ Collaboration). The collaboration includes detailed data on over 6000 randomised patients (95% of all patients randomised in RCTs of endarterectomy for symptomatic stenosis). It is proposed to determine the inter-relation between the effect of endarterectomy, the severity of carotid stenosis and each of the following characteristics: age, sex, diabetes, lacunar versus cortical presenting events, ocular versus cerebral presenting events, TIA versus stroke, contralateral carotid occlusion, ipsilateral plaque surface morphology, and post-stenotic collapse of the distal internal carotid artery.

**Risk modelling using data from RCTs**

Formal risk modelling or multivariate prognostic modelling has two main advantages over subgroup analysis. Firstly, it allows clinicians to take the effect of several different baseline characteristics into account, whereas traditional subgroup analysis is limited to one or two characteristics at a time. Individual patients may have several important risk factors each of which interact in a way which cannot be described using univariate subgroup analysis. In order to identify and operate only on those patients at high risk of stroke on medical treatment and a relatively low operative risk, a clinician must take all these characteristics into account. Secondly, as discussed above, single variable subgroup analyses are subject to the play of chance and the problems of multiple *post hoc* comparisons, whereas stratification of trial results using an independently derived prognostic score is a single analysis based on the reasonable hypothesis that treatment effect is likely to vary with the risk of a poor outcome in the different treatment groups.

Previous prognostic models for the risk of stroke on medical treatment in patients with TIA or minor stroke have either been based on relatively small cohorts of patients, or not included the degree of stenosis of the symptomatic carotid artery. No prognostic model has been validated in an independent group of patients and used routinely in clinical practice. However, several clinical and angiographic characteristics, in addition to the severity of carotid stenosis, have been shown to identify patients at high risk of stroke on medical treatment alone. For example, patients with recent cerebral ischaemic events are at higher risk of stroke than patients
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Table 1 The hazard ratios (95% confidence intervals), statistical significance, derived risk points and points allocated in the predictive score for each of the independent predictors of outcome in the following models

Medical model. a Cox’s proportional hazards model for ipsilateral carotid territory major ischaemic stroke (i.e. fatal or lasting longer than 7 days) on medical treatment derived from the 857 patients with 0–69% stenosis who were randomised to no-surgery in the ECST

Surgical model: a multiple logistic regression model for any major stroke (i.e. fatal or lasting longer than 7 days) or death from other causes within 30 days of carotid endarterectomy derived from 1203 patients with 0–69% stenosis who were randomised to surgery in the ECST

<table>
<thead>
<tr>
<th>Prognostic variable</th>
<th>Hazard ratio</th>
<th>(95% CI)</th>
<th>P</th>
<th>Risk points*</th>
<th>Predictive score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebral versus ocular events</td>
<td>2.45</td>
<td>(1.09–3.71)</td>
<td>0.02</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Plaque surface irregularity</td>
<td>2.09</td>
<td>(1.21–3.62)</td>
<td>0.008</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Any events within the last 2 months</td>
<td>1.82</td>
<td>(1.02–3.18)</td>
<td>0.04</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Carotid stenosis (per 10% stenosis)</td>
<td>1.30</td>
<td>(1.10–1.40)</td>
<td>0.001</td>
<td>0–2</td>
<td>0–2</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Surgical model</th>
<th></th>
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</tr>
</thead>
<tbody>
<tr>
<td>Female sex</td>
<td>2.05</td>
<td>(1.29–3.24)</td>
<td>0.002</td>
<td>1</td>
<td>–0.5'</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>2.48</td>
<td>(1.51–4.13)</td>
<td>0.0004</td>
<td>1</td>
<td>–0.5'</td>
</tr>
<tr>
<td>Systolic BP &gt; 180 mmHg</td>
<td>2.21</td>
<td>(1.29–3.79)</td>
<td>0.004</td>
<td>1</td>
<td>–0.5'</td>
</tr>
</tbody>
</table>

The full lists of variables (and definitions) from which these models were derived are reported elsewhere

Risk points were derived by rounding the hazard ratio to the nearest whole number and subtracting one

For application to the 70–99% stenosis group, points were allocated as follows 70–79% (0), 80–89% (1), 90–99% (2)

In the risk factor model which is applied to the 70–99% stenosis group, surgical risk points are subtracted (i.e. become negative) and their weighting is reduced by 50% as detailed in the methods

with ocular events, patients with an irregular carotid plaque are at higher risk than patients with smooth plaques, and there are several risk factors for the operative risk of stroke and death due to endarterectomy.

A preliminary analysis of the ECST, using prognostic models to predict the risk of ipsilateral carotid territory ischaemic stroke on medical treatment and the risk of stroke and death within 30 days of carotid endarterectomy, suggests that benefit from surgery is confined to a subgroup of about 20% of patients with ECST 70–99% stenosis. Using data on the 2060 ECST patients with 0–69% carotid stenosis, two prognostic models were developed; one for the risk of ipsilateral carotid territory major ischaemic stroke (fatal of lasting longer than 7 days) on medical treatment and one for the risk of major stroke and death within 30 days of endarterectomy (Table 1). Using these models, a score was developed to identify patients with a high risk of stroke on medical treatment, but a relatively low operative risk. The utility of the score was tested on the ECST patients with 70–99% carotid stenosis. When the 990 patients with 70–99% stenosis were stratified using the scoring system, based on seven independent prognostic factors, endarterectomy was beneficial in only 162 (16%) patients with risk scores of 4 or more (Fig. 2). The odds of carotid territory ipsilateral major ischaemic stroke or
Fig. 2 The reduction in the 5 year actuarial absolute risk of ipsilateral carotid territory major ischaemic stroke or surgical major stroke or death in the surgery group compared with the medical group in patients with each predictive score. Statistical significance is tested at each score using the log rank test and the number of cases on which the estimate is based is given for each score.

Operative major stroke or death were decreased considerably by surgery in this group (OR = 0.12, 95% CI = 0.05–0.29), but not in the other 828 (84%) patients (OR = 1.00, 95% CI = 0.65–1.54): the resulting 5 year actuarial absolute risk reductions were 33% (log rank = 20.5, $P < 0.00001$) and 1% (log rank = 0.8, $P = 0.7$), respectively. Contrary to the overall results of ECST and NASCET, these data suggest that many patients with recently symptomatic ECST 70–99% carotid stenosis do not benefit from carotid endarterectomy. Further work is required to refine and validate the predictive score on external datasets, but these preliminary results suggest that risk factor modelling might well be useful in identifying patients in whom endarterectomy is particularly beneficial. It may also be possible to use the same approach to identify a subgroup of patients with moderate stenosis in whom surgery is clearly beneficial. This will be pursued by the Carotid Endarterectomy Trialists’ Collaboration. A similar approach is required for the RCTs for endarterectomy for asymptomatic stenosis.

**Ancillary investigations**

There have been several developments in stroke research which were unavailable at the time the when current and previous RCTs of
endarterectomy and PTA were designed. However, these developments may be of value in identifying the individual patients who are most likely to benefit from these interventions. Three of the most promising areas are discussed below.

Detection of cerebral microemboli
It is possible to detect microemboli, made up of platelet emboli or plaque material, in the middle cerebral artery distal to a carotid stenosis using transcranial Doppler ultrasound (TCD; see also Markus elsewhere in this issue). TCD detection of microemboli has been shown to be reproducible and to have pathological validity. Microemboli decrease with time after the last symptomatic ischaemic event, emboli are detected most frequently distal to carotid plaques which are subsequently found to have surface thrombus at endarterectomy, and the frequency of emboli is reduced considerably by surgery. These findings suggest that emboli counting might be useful in identifying patients at particularly high early risk of ischaemic stroke. One recent pilot study has produced encouraging results, but large prospective cohort studies are clearly required in order to determine whether this technique will be clinically useful.

Cerebral perfusion studies
Cerebral infarction may also result from the reduction in cerebral perfusion pressure which occurs distal to a tight carotid stenosis or occlusion. A proportion of patients who have a recently symptomatic severe carotid stenosis or occlusion have significant hypoperfusion of the ipsilateral cerebral hemisphere and a loss of the ability to increase perfusion in response to raised levels of carbon dioxide. This can be demonstrated using TCD, SPECT, $^{133}$Xe radionuclide CT, functional MRI, and PET. It has also been shown, using magnetic resonance spectroscopy, that such patients have metabolic changes in the affected hemisphere which are consistent with chronic ischaemia in the absence of any evidence of cerebral infarction. Both the perfusion deficit and the metabolic changes are reversed following carotid endarterectomy and extracranial-intracranial bypass grafting. It is possible that cerebral hypoperfusion and ischaemic metabolic changes distal to severe carotid stenosis might also be useful in identifying patients at particularly high risk of stroke. Two small studies have recently suggested that hypoperfusion is associated with a high risk of stroke distal to a unilateral carotid occlusion, but no such link has yet been demonstrated in patients with carotid stenosis. It is possible to get indirect measures of cerebral perfusion distal to a carotid stenosis from traditional arterial imaging, and the
presence or absence of angiographically defined collateral vessels and the
degree of collapse of the post-stenotic internal carotid artery have recently
been shown to predict the risk of stroke on medical treatment$^{41,42}$.

**Genetic studies**

Genetic characteristics might be useful in predicting the susceptibility to
ischaemic stroke in individuals. Family history is an important
independent risk factor for ischaemic stroke in man$^{43}$. Twin studies have
yielded proband concordance rates of about 20% for monozygotic twins
and about 4% for dizygotic twins$^{44}$. Work in animal models of stroke has
shown that much of the genetic variation in susceptibility to stroke is
independent of risk factors for vascular disease *per se*$^{45}$, and some
potentially important unrelated polymorphisms have been identified$^{46,47}$. 
Prediction of ischaemic stroke in individual patients with established
cerebrovascular disease is likely to be improved by combining clinical and
genetic risk factors. Thus far, studies have been too small and have,
therefore, produced conflicting results$^{45}$. Moreover, the vast majority have
been case-control studies. What is required are large prospective cohort
studies, detailed enough to take into account the pathological hetero-
geneity of stroke, but large enough to define small relative risks with
precision. There are already several interesting potential genetic risk
factors, and it is highly likely that many other candidates of interest (as
well as single nucleotide polymorphisms) will be identified over the next
few years.

**Key points for clinical practice**

- Carotid endarterectomy reduces the overall risk of stroke in patients with
  ECST 70–99% recently symptomatic stenosis. It is necessary to operate on
  8–10 patients to prevent 1 stroke over the next 3 years

- Carotid endarterectomy reduces the overall risk of stroke in patients with
  severe asymptomatic stenosis. It is necessary to operate on about 17
  patients to prevent 1 stroke over the next 5 years

- Carotid angioplasty and stenting may be a reasonable alternative to
  endarterectomy, but more data are required before it can be used routinely.
  Angioplasty should not currently be used outwith well-organised RCTs

- Carotid endarterectomy should be targeted at individual patients with a
  high risk of stroke on medical treatment alone and a reasonably low
  operative risk. The results of subgroup analyses and risk modelling using
  existing data from RCTs will help clinicians to do this
Optimal prediction of the risk of stroke in individual patients is likely to require a combination of different types of data, probably including clinical data, imaging data, data on the frequency of cerebral microemboli, data on cerebral perfusion, and data on particular genetic characteristics.

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