Asymptomatic Carotid Surgery Trial-2
ACST – 2

A large, simple randomised trial to compare carotid endarterectomy with carotid artery stenting to prevent stroke

If a patient needs treatment for asymptomatic carotid stenosis, there may be substantial uncertainty shared by the doctor and patient about whether to opt for carotid endarterectomy (CEA) or carotid artery stenting (CAS). ACST-2 seeks to randomise such individuals between CEA and CAS to compare both the immediate hazards of the two procedures within the first few weeks and the long-term stroke rates over the next 5 to 10 years.

ACST-2 can succeed only if many thousands of patients are randomised. This is made possible by streamlining the procedures and minimising the workload for collaborators so that the study can be integrated easily into routine health care:-

- **Eligibility:** Patient has asymptomatic carotid artery stenosis that is thought to need some procedural intervention, but both the doctor and patient are substantially uncertain whether CEA or CAS is preferable.
- **Randomisation:** Following patient consent, obtain a blood spot, complete the 1 page Randomisation Notepad and call 24-hour randomisation number +44(0)1865 765615 to obtain the treatment allocation (CEA or CAS) and ACST-2 patient identification number, this call only takes only about 5 minutes.
- **1 month follow-up:** Review the patient 1 month after the planned procedure and complete a single-sided form to describe any peri-procedural events.
- **Long-term follow-up:** Annual follow-up will be conducted by the ACST-2 office for at least 5 years and will determine whether the patient has remained free of stroke.

As the study is so easy, many hundreds of doctors and many thousands of patients can take part, and uniquely reliable evidence will then emerge comparing the immediate and the long-term safety of CEA and CAS. If a few thousand patients are randomised the results will be useful; if several thousand are randomised the results will be more useful; and if really large numbers are randomised then the results could affect the treatment of millions of patients in future decades.

**Asymptomatic carotid artery stenosis?**

**Uncertain whether to treat with carotid endarterectomy or carotid artery stenting?**

**CONSIDER FOR ACST-2**

ACST-2 protocol: Version 2.0, July 2006. ISRCTN21144362
HOW TO JOIN ACST-2

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To RANDOMISE a patient telephone
24-hour randomisation service
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at the Clinical Trial Service Unit
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**Background**

Stroke is responsible for more than 10% of all deaths and much severe disability in developed countries\(^1\). Atherosclerotic narrowing of the carotid arteries is a well-recognised cause of stroke, about 100,000 people in the UK and at least one million people in Europe alone have severe narrowing or stenosis in one or both of their carotid arteries\(^2\).

**Treatments for patients with carotid artery stenosis:**

**Medical treatment**

Appropriate medical treatment for symptomatic and asymptomatic patients, with for example aspirin and cholesterol-lowering medicines is standard to prevent both heart attack and stroke. However, if surgery is used to remove the carotid stenosis this will reduce patient stroke risk further.

**Carotid endarterectomy (CEA)**

In 1991 two large trials of CEA to remove carotid artery stenosis in symptomatic patients (who had a stroke or stroke-like symptoms <6 months previously) showed that CEA is more effective than medical treatment alone in reducing the risk of future stroke (ECST and NASCET\(^3&4\)). CEA has now become an effective, well-recognised treatment for stroke prevention in symptomatic patients.

The Asymptomatic Carotid Surgery Trial (ACST)\(^5\) and the smaller Asymptomatic Carotid Atherosclerosis Study\(^6\) then investigated the role of CEA in almost 5000 patients with similar carotid stenoses, but with no stroke or stroke-like symptoms within the previous 6 months. In ACST more than 3000 patients were randomised between medical treatment only or medical treatment and 'immediate' surgery. CEA involved a small (~3%) but definite peri-procedural risk of stroke or death, a substantial (~3% vs ~12%) reduction in the subsequent stroke rate over the next 5 years and a net 5-year gain of ~6% vs ~12% in the overall risk of stroke or peri-procedural death. ACST's clear 5-year findings are already changing surgical practice, and long-term follow-up of stroke rates continues\(^7\).

**Carotid stenting (CAS) and the need for large-scale randomised clinical trials of CEA vs CAS**

CAS is a newer method of treating carotid stenosis whereby a catheter is inserted through a tiny groin incision into the femoral artery, up the aorta into the narrowed carotid artery, and finally guided into the narrowed area. A wire mesh stent is passed up the catheter and placed across the narrowed portion of the artery. A balloon may then be inflated inside the stent to open it permanently keeping the artery open. The catheter and balloon are then removed. During stent placement it is possible that some of the diseased portion of artery may crumble blocking the blood supply to the brain and cause a stroke. Compared with CEA, CAS avoids surgical wound discomfort, is usually performed under local anaesthetic, could shorten hospital stay and might reduce the risk of peri-procedural heart attacks or strokes and may be more acceptable to the patient than surgery. However there is substantial uncertainty about the immediate hazards and long-term reliability of CAS compared to CEA.

A Cochrane meta-analysis of CEA vs CAS trials (mainly in symptomatic patients) stated that 'the current evidence does not support a widespread change in clinical practice away from recommending CEA as the treatment of choice for suitable carotid artery stenosis. There is a strong case to continue recruitment in the current randomised trials comparing carotid stenting with endarterectomy\(^8\). Multicentre trials, undertaken in mainly symptomatic patients (e.g. ICSS, SPACE, EVA-3S, CREST & SAPPHIRE\(^9\-13\)) have not yet resolved uncertainty. Much larger trials particularly in asymptomatic patients are now needed. The European Stroke Initiative Recommendations for Stroke Management support this and propose that 'carotid angioplasty (balloon dilatation), with or without stenting, is not routinely recommended for patients with asymptomatic carotid stenosis. It may be considered in the context of randomised clinical trials\(^14\).

**ACST-2: Design and objectives**

ACST-2 is a large, simple, randomised trial of CEA versus CAS for stroke prevention and is designed to maximise recruitment by minimising the workload per patient so that it can be integrated easily in routine health care. Minimal data are required at randomisation and at the 1-month follow-up after the patient has undergone the procedure (CEA or CAS), after which annual follow-up will be organised by the ACST-2 coordinating office. The Randomisation Notepad and the 1-month follow-up form are the ONLY forms that routinely need to be completed by the doctor.
The trial will be conducted internationally and will randomise at least 5000 patients with asymptomatic carotid artery stenosis in whom prompt physical intervention is thought to be needed, but where there is substantial uncertainty shared by patient and doctor about whether CEA or CAS is the most appropriate choice. Half of the patients will be randomised to CEA and half to CAS on an intention-to-treat basis, and patients will then be followed up for at least 5 years. Basing eligibility on uncertainty should ensure large-scale randomised recruitment of an appropriately heterogeneous group. This increases the medical value of the study, making it possible to determine whether the net effects of CEA/CAS are influenced by certain patient characteristics recorded at entry. The two principal objectives are to compare:-

**Primary objectives:** To compare 1) the peri-procedural risks (myocardial infarction (MI), stroke and death) ≤30 days of undertaking CEA or CAS, and 2) The long-term (up to 5 years) prevention of stroke, and of disabling or fatal stroke, during the years after CEA or CAS.

**Secondary objectives:** Depending on the numbers eventually randomised, the data may permit the identification of sub-groups of patients in which one or other procedure is clearly preferable. Comparisons of health-related quality of life will be assessed as part of the health economic evaluation.

**Starting the trial in your centre**

Ethical approval is required in each centre before the study can proceed, using this protocol (version 2.0). A centre can be organised between colleagues in neighbouring hospitals. Each centre should have a neurologist or stroke physician, a vascular surgeon and a stenting interventionalist. They will be jointly responsible for patient recruitment, treatment and follow-up. Each collaborator must send a summary of their experience with either CEA or CAS, as appropriate, in the form of a “Track Record” to the ACST-2 office which needs to be validated by the local stroke physician or neurologist. The information required in a “Track record” will include:-

Depending upon experience, details of the last 25, 50 or 100 CEAs and/or CAS’ (as appropriate): dates when undertaken, number of symptomatic/ asymptomatic patients, number of strokes (fatal/ non-fatal) and non-stroke deaths within 30 days of surgery.

Collaborators should be have ≤8% stroke and death risk for symptomatic patients and ≤4% stroke and death risk for asymptomatic patients as per accepted trial guidelines.

Once ethical approval has been obtained and the Track Record has been approved centrally, patients can be enrolled into the study by following the simple steps described on the following pages. The patient procedures must be undertaken by the collaborator whose Track Record has been approved, and it is the responsibility of the collaborator to use techniques and equipment which are approved for routine clinical practice (e.g. centres in Europe must use CE marked devices). Please note that the use of cerebral protection devices should be considered.

**Identifying eligible patients**

- Carotid artery stenosis, confirmed by duplex ultrasound and with no ipsilateral carotid territory symptoms for ≥6 months
- Other stroke risk factors appropriately treated
- Doctor and patient both substantially uncertain about whether to treat with CEA or CAS
- Patient fit and willing for follow-up in person (at 1 month) and by letter (for at least 5 years).

Reasons for not entering patients are specified by the responsible doctor, not by the protocol but might include:

- Previous CEA or CAS in artery to be randomised
- Small likelihood of worthwhile benefit e.g. a very low risk of stroke (e.g. very minor stenosis) or a major life-threatening disease (e.g. advanced cancer)
- High risk of adverse events of trial treatment e.g. inaccessible stenosis (e.g. at carotid siphon).
- Unable or unwilling to give informed consent.
Obtain written informed consent and blood spot

- Discuss the trial with the patient and give them the Patient Information Sheet (Appendix 1). The patient may wish to take the information sheet away to consider whether or not to join the study.
- If the patient decides to join the study, written informed consent will be needed and the patient should understand that they will be contacted annually for at least 5 years.
- Upon consent the patient must include contact details of 2 close relatives and/or friends and their family doctor who may be contacted if we are unable to trace the patient (Appendix 2).
- At the time of consent a blood spot should be obtained from the patient (either from a routine sample or by a separate finger prick and put into the plastic fastening envelope on the consent leaflet.
- When obtaining the blood spot, do not press the patient's finger onto the sample paper. The blood should be dropped in to all of the sample circles.
- The date of collection, patient’s initials and their date of birth should be written on the blood spot patch in the space provided.
- The blood sample will provide direct biochemical information on the patient’s cardiovascular risk at the time of joining the study. Analyses will include, for example, profiles of the different components of blood lipids and the extent of any diabetic disease. The remainder of the sample will be stored securely and may be used for further analyses during the study. The information gained will be used for medical research purposes only and will remain strictly confidential.

Randomising a patient

- Complete the 1-sided Randomisation Notepad (Appendix 3).
- Telephone the 24-hour randomisation service on +44(0)1865 765615.
- You will be asked to give the answers to the numbered questions on the Randomisation Notepad. You will then be given the Patient Identification Number and treatment allocation. Write these down on the Randomisation Notepad.

Send the original copy of the Randomisation Notepad and the consent form with the blood spot in the FREEPOST envelope to: CTSU, Richard Doll Building, Roosevelt Drive, Oxford, OX3 7LF, England.

The patient is now in ACST-2.
Arrange the allocated treatment as soon as possible.

Treatment

- Undertake CEA or CAS as soon as possible using the routine techniques for your centre.
- If allocated treatment NOT given, the reasons why should be stated on the 1-month follow-up form.
- Before discharge:
  - Patient should be assessed by a neurologist/stroke physician.
  - Measure troponin-T 8 –24 hours after the procedure before discharge.
  - Record simple procedure details and troponin-T levels (for use on 1 month follow up form).
  - Schedule duplex ultrasound and 1-month clinical follow-up visit.
- If myocardial infarction (MI) or stroke occur within the first month, ensure patient is appropriately assessed (stroke and TIA must be assessed by a neurologist/stroke physician). If MI, stroke or death occur, complete Major Event Form (Appendix 4) and return to ACST-2 office.

All other aspects of care remain the responsibility of the patient’s doctor. Other than the 1 month follow up, patients do not need to undergo any tests or examinations beyond those which are given as part of their routine care.

1-month follow-up

- Neurologist or stroke physician to examine patient.
- Ensure post-procedural duplex ultrasound has been done.
- Single sided 1- month follow-up form (Appendix 5) should be completed by the randomising doctor and sent to ACST-2 office even if the patient does not have the allocated treatment.
- If patient has a myocardial infarction, stroke or dies during the first month, complete the 1–month follow-up (include the normal troponin-T range in your centre) and Major Event Forms.
• Quality of life information will also be collected on a representative sample of patients using the EuroQOL questionnaire – see below, Economic Evaluation (page 8).

Long-term annual follow-up – organised by ACST-2 office

• Patients will be contacted annually for at least 5 years by letter from the ACST-2 office asking if they remain well (Appendix 6). This letter (and the EuroQOL questionnaire where relevant - see below for the economic evaluation) will be in the patient’s native language with a FREEPOST envelope for return to the ACST-2 office.
• If the patient replies that they have had a stroke the appropriate doctor will be contacted to provide details of the stroke.
• If the patient does not reply, a similar letter will be sent to the friend/relative/family doctor whose contact details were given when the patient joined the study.
• If the patient is too disabled to complete the questionnaire him/herself, the patient’s carer is allowed to complete it with answers provided by the patient, or the carer can complete the questionnaire based on their own assessment of the patient.
• In the small number of patients who do not reply to requests for follow-up information, the collaborator or country collaborator office will help trace the patient. UK patients will be flagged with the Office for National Statistics upon entry into the trial and, where available, national data repositories in other countries will be used to facilitate data collection during the study.

(Although long-term follow-up will be organised by the ACST-2 office, if you know the patient has had a stroke or has died, it would be helpful if you could complete the Major Event Form and return to the ACST-2 office).

Major Events

Reporting on myocardial infarction (MI), stroke and death

• MI
It is only necessary to report MI if this occurs during the peri-procedural (1 month) period (if more than one MI occurs in this period, each event should be reported). A positive diagnosis of MI can be made if 2 of the criteria listed below are fulfilled:-
  1. Symptoms consistent with MI.
  2. Positive enzyme or biomarker (e.g. troponin-T) changes consistent with MI.
  3. ECG changes consistent with MI.

• Stroke
Stroke will be classified using the Modified Rankin scale

  0  No symptoms at all.
  1  No significant disability despite symptoms: able to carry out usual duties and activities.
  2  Slight disability: unable to carry out all previous activities but able to look after own affairs without assistance.
  3  Moderate disability: requiring some help, but able to walk without assistance.
  4  Moderate severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance.
  5  Severe disability: bedridden, incontinent and requiring constant nursing care and attention.

Information from the Rankin Scale will be enhanced by the information that we will obtain by using an established measure of Quality of Life (EuroQOL).

• Death
The only information that is required on the death of a patient is the date of death and whether or not the cause of death is related to stroke.
Economic Evaluation

Resource use data will be collected from the two simple trial forms (randomisation and 1-month follow-up) for every trial participant and health-related quality of life data for a representative sample of trial participants. This will permit the development of an economic analysis relevant to a range of countries represented in the trial. The effect of the trial interventions on health-related quality of life and resource use will be evaluated. Health-related quality of life will be assessed using the EuroQol (EQ-5D) questionnaire at the 1-month follow-up assessment and thereafter at the 1st, 3rd and 5th-year follow-ups. The aim is that all patients (or their carers) who have experienced a non-fatal major event (MI within a month or stroke), along with a representative sample of those who have not, will complete the questionnaire at 1 month, and a representative sample of the surviving trial participants will complete the questionnaire at the 1 year, 3 year and 5 year follow-up assessments. Official versions of the questionnaire are available in all languages likely to be represented in the trial (http://gs1.q4matics.com/EuroqolPublishWeb/).

Resource use during the treatment and follow-up periods will be calculated. The main components will be (a) the initial intervention costs; (b) further short-term re-treatment costs (i.e. repeat or further procedures within 30 days); (c) the costs of MI within 30 days from intervention and any stroke costs (for both strokes caused by the trial intervention and those considered not to be caused by the intervention). The length of stay in hospital will be collected for these events. Annual follow-up questionnaires sent by the trial office to the patient will collect data on the level of care required for a particular patient (modified Rankin score), as well as information on whether the patient has had to have nursing home care.

Economic analyses will evaluate short-term impact of interventions on resource use and health-related quality of life at 30 days following the trial procedures as well as longer-term outcomes and costs.

Patient withdrawal from the trial

As it is so difficult to measure small advantages or disadvantages, the ACST-2 study will invite several thousand patients world-wide to join this trial. A few of those who originally agreed to join the study may later change their minds and withdraw but this should not affect the scientific integrity of the study. If, after agreeing to join, the patient subsequently changes his or her mind, (s)he is free to do so without this adversely affecting his/her medical care. Similarly, the patient’s doctor is free to give any other treatment that is considered to be in the patient’s best interest.

Trial organisation

The study will be managed on a day-to-day basis by the ACST-2 office based at St George’s, University of London. All enquiries about the study should be directed to the ACST-2 office. Randomisation will be through the Clinical Trial Service Unit, Oxford. The trial will be managed by a Trial Steering Committee (TSC) and a Technical Management Sub-Committee of the TSC will be responsible for approving interventionalists/surgeons wishing to participate by reviewing their surgical/interventional track record. Any equipment used by the participating collaborators must be approved by the relevant countries regulatory authorities. An independent Data Monitoring Committee (DMC) will undertake interim analyses of trial data, and an Endpoint Committee will classify major events when adequate information (including quality of life information using the modified Rankin score at 6 months post stroke) is available.

Sample size, Data analysis and Safety monitoring

The main outcomes will be MI, stroke or death 1 month after CEA/CAS, and long-term (up to 5 years) stroke rates, supplemented by appropriate analyses of resource use, health-related quality of life and cost-effectiveness. With 5000 randomised, a decrease of about 60% in the peri-procedural (clinical and troponin-T detected) myocardial infarction rate with stenting versus surgery (e.g. 2% CEA vs. 0.8% CAS) and an increase of about 60% in the 5-year stroke rate (e.g. 3% CEA vs. 5% CAS) could both be detected at P<0.001 with 80% probability (i.e. statistical power), or at 2P<0.05 with 95% power. The exact magnitude of any effect is currently not known, hence the need for the trial, but, taking into account existing information from other trials of CAS vs. CEA, effects of this size would be realistic, meaningful and worthwhile.

The results will be analysed using Kaplan-Meier life table analyses, the established method of analysing trial data. Logrank analyses will compare event rates between those allocated CEA and those allocated CAS at specific time periods. All patients will be followed up whether treatment is carried out or not since the trial analysis will be on an ‘intention to treat’ basis. By the end of the recruitment period, data will be available to consider the peri-procedural outcomes, and – with (by then) about 2 years follow-up on average – analyses will...
be possible of the effects of CEA vs CAS on stroke prevention/stroke mortality/non-stroke mortality. Continued follow-up will allow a more powerful analysis of these longer term outcomes.

Subgroup analyses will be undertaken, where appropriate, to assess the relevance of particular factors. In ACST-1, the 5-year risk of non-peri-operative carotid territory ischaemic stroke was analysed in a number of categories, including: stroke severity; the relevance of age/sex/prerandomisation cholesterol/prerandomisation blood pressure; ipsilateral carotid artery diameter reduction – i.e. degree of stenosis; ipsilateral plaque echolucency; ipsilateral and contralateral carotid territory status at entry; vascular problems as recorded at entry. Similar analyses are planned in ACST-2.

During the study, interim analyses of major events will be supplied to an independent Data Monitoring Committee (DMC). The DMC will advise the TSC whether there is an unacceptably high morbidity associated with surgery or stenting (either overall or in particular centres), or if there is clear evidence that for all or some particular types of patient, there is proof beyond reasonable doubt that one or the other procedure is preferable. Until then, the TSC and collaborators will otherwise remain ignorant of interim results. (Appropriate criteria of proof beyond reasonable doubt cannot be specified precisely, but a difference of at least 3 standard deviations in an interim analysis of a major endpoint may be needed to justify halting or modifying such a study prematurely. If this criterion were to be adopted, it would have the practical advantage that the exact number of interim analyses would be of little importance, so no fixed schedule is proposed.) At any point, anyone associated with the study may write through the ACST-2 office to the ACST-2 DMC Chairman drawing attention to any concerns they may have about the possibility of particular side-effects, or of particular categories of patient requiring special study, or indeed about any other matters thought relevant.

**Modifications to the protocol**

No part of this protocol should be modified. If your centre needs to make any modifications to this protocol so that it complies with national or local regulations this must be discussed in advance with the ACST-2 office.

**Publication of results**

Results of the study will be prepared by a writing committee and circulated to all collaborators prior to publication for comments. Results will be published in the name of the collaborative group. The chief acknowledgement will go to the patients who participated in the study.
References

APPENDICES

Appendix 1 - Patient Information Sheet
Appendix 2 - Patient Consent Form
Appendix 3 - Randomisation Notepad
Appendix 4 - Major Event Form
Appendix 5 - 1-month Follow-up Form
Appendix 6 - Patient Annual Follow-up Letter
Appendix 7 - Annual Follow-up Letter to Family Doctor/Friend/Relative
TRIAL ORGANISATION and COMMITTEES for ACST-2

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Dr Alan Young, Head of Systems Development, CTSU, Oxford, UK

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Professor Richard Gray, University of Birmingham Clinical Trials Unit, Birmingham, UK
Professor Cliff Shearman, University of Southampton, UK

Technical Management Sub Committee
Will be responsible for reviewing track records of interventionalists and surgeons seeking to participate and validating centres.
Dr Marc Bosiers, Dr Sumaira McDonald, Mr. Michael Gough, Professor Piergiorgio Cao

Endpoint Committee
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Mr. Peter Leopold, Frimley Park Hospital, Surrey, UK
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Project Management Group (PMG)
Miss Alison Halliday (Principal Investigator)
Rachael Scott (ACST-2 Trial Co-ordinator)
Steven Robertson (ACST-1 Trial Co-ordinator)
Elizabeth Hayter (Assistant Trial Co-ordinator)
and project staff at the CTSU Data Coordinating Centre and at St George’s University of London.
The PMG will be responsible for the day to day running of the trial, coordination of data collection and analysis.

ACST-2 protocol: Version 2.0, July 2006. ISRCTN21144362
Asymptomatic Carotid Stenosis Trial-2 (ACST-2)
SUMMARY PROTOCOL

ELIGIBILITY
• All patients, high or low risk, with asymptomatic carotid stenosis & other stroke risk factors appropriately treated
• Doctor & patient **substantially uncertain** about whether Carotid Endarterectomy (CEA) or Carotid Artery Stenting (CAS) is the best option
• No definite indications for or contraindications to either procedure
• Patient fit & willing for 5-year follow-up

ENTRY
• Obtain written patient consent to take part in ACST-2 & Blood Spot - place Blood Spot patch in plastic envelope on Consent Form
• Complete one-sided Randomisation Notepad
• Ring 24-hour randomisation service: +44(0)1865 765615 for treatment allocation (CEA or CAS) & patient identification number
• Send Consent Form, Blood Spot & Randomisation Notepad to CTSU in FREEPOST envelope

PROCEDURE & FOLLOW-UP
• Carry out allocated treatment (CEA or CAS) as soon as possible
• Measure Troponin-T 8-24 hrs after procedure
• Arrange (a) post-procedure duplex ultrasound to check carotid artery patency & (b) 1-month clinical follow-up
• Major Events (myocardial infarction, stroke, death) sent to ACST-2 office

Long-term annual follow-up organised by ACST-2 office directly with patient

24-hour randomisation telephone:+44 (0) 1865 765615
ACST-2 office telephone:+44 (0) 20 8725 3746
Fax:+44 (0) 20 8725 3782 Email: acst@sgul.ac.uk
Website:www.acst.org.uk/

Not eligible if contralateral carotid artery has been randomised in ACST-2 or if ipsilateral artery has already had CEA or CAS.
Other reasons for not entering patients into ACST-2 specified not by the protocol but by the responsible doctor, might include:
- either only a small likelihood of worthwhile benefit
• Very low risk of stroke (e.g. very minor stenosis)
• Some major life-threatening disease (e.g. advanced cancer)
- or a high risk of adverse events of trial treatment:
• inaccessible stenosis (e.g. at carotid siphon)
• unfit for surgery (e.g. severe heart failure)