



Manual for investigators describing how to apply optimised medical treatment in ECST-2

Introduction

The key concept behind optimised medical treatment (OMT) is to improve on the best medical treatment (BMT) used in previous trials. An analysis of our last trial, ICSS, showed that during follow-up more than 50% of patients had blood pressure readings above European guideline levels. In ECST-2, we want to take a more active approach to management of risk factors with the aim of getting as many patients as possible within target values. Instead of OMT, we could easily have named our treatment plan TMT, targeted medical treatment. The protocol specifies that investigators should choose individualised targets for their patients in line with UK and European guidelines. This is so that we will not be asking doctors to prescribe treatments or reach targets which are not consistent with standard practice. However, we do want investigators to take a proactive role and involve the patient and the GP or family doctor in achieving the set targets.

Patient diaries

In ECST-2 we are trialling the use of patient diaries as a way of recording blood pressure, cholesterol, medications consumed and visits to health professionals throughout the duration of the trial. Please give each patient a patient diary to fill out between clinic appointments. When patients measure their blood pressure at home or attend their GP to have their blood pressure or cholesterol checked, they should be asked to provide results in the diary for analysis in the central office. The diaries will help to investigate patient compliance with optimised medical therapy and can be used to adjust medications where necessary.

Target blood pressure

Every patient should be set a target for blood pressure (BP) at the time of randomisation. Treatment should aim to lower average BP readings to below the target. As part of involving patients in the trial, please encourage them to buy or borrow a blood pressure measurement machine and use it at home. Please explain to the patient that, if they measure their BP at home, they will be more relaxed and therefore their target blood pressure for home readings will be lower than the clinic target. At the time of randomisation, you should specify target clinic and home BPs for each patient in line with the guideline below. You will need to enter this target clinic value on the baseline medication form. Although we expect most patients to have a target blood pressure as listed below, we want the target to be individualised. For example, if it is known that a patient is unable to tolerate such blood pressures for some reason or another, the investigator can set a higher BP target. In some cases it may be appropriate to set a lower target e.g. if the patient has symptomatic carotid stenosis and already has BP at or below target, or if the patient has diabetes (see page 6). You should also take age into account when setting the target. The following targets are those recommended by the UK NICE (National Institute for Health and Clinical Excellence):

Target aged <80 years:

BP measured in the clinic: 140/90

BP measured at home (or ambulatory recordings): 135/85

Target aged 80 years or older:

BP measured in the clinic: 150/90

BP measured at home (or ambulatory recordings): 145/85

Targets for patients with diabetes: See page 6.

Please enter both target blood pressure values (clinic and home) in the patient's logbook and inform the GP of the targets and ask the GP or family doctor to adjust medication as required to achieve this target.

Measuring and recording blood pressure readings

When measuring BP in the clinic or at home, standardise the environment and provide a relaxed, quiet setting with the patient seated and their arm outstretched and supported during the measurement of the BP.

When measuring BP for the first time in a patient in ECST-2, please measure the BP in both arms. If the difference in readings between the two arms is more than 20mmHg, repeat the measurements. If the difference in readings between the arms remains more than 20mmHg on the second measurement, please record this and measure subsequent BPs in the arm with the higher reading.

If the first BP measured in the clinic (or on the ward) is at or above target, take a second measurement. If the second measurement is substantially different from the first, take a third measurement. Record the lower of the last two measurements as the clinic BP.

It is important to use the correct size of cuff. Ideally, use a BP monitor that is capable of diagnosing atrial fibrillation since these patients will need anticoagulation rather than antiplatelet prophylaxis. If the patient has an irregular pulse, e.g. from atrial fibrillation, BP should then be measured manually using direct auscultation over the brachial artery, rather than using an automated device.

The patient should be advised to measure their BP at home in between ECST-2 visits if they have a home monitor or are willing to purchase one (suitable machines can be bought from a pharmacy for a few tens of pounds or euros). Alternatively, they may visit their GP or family doctor or nurse-led clinic in between ECST-2 visits. If the patient's BP readings are above the target, these measurements should take place at least once monthly but, once targets have been reached, the frequency can be reduced. Measurements made in between visits should be recorded in the patient diary. They will need to be reminded that they must ask their GP or their nurse to write down the figures for them. Tell the patients to ask if they can increase their medication if the reading is above the target value

When using home BP measurements, advise the patient to take two consecutive measurements at least one minute apart, seated, twice daily during their usual waking hours. The patient should repeat the twice daily measurements on at least four separate days between clinic visits. The average of all these readings should be used as the home BP reading.

When recording BP during follow-ups, please record the source of the BP reading (on the ward, in the research/outpatient clinic, at home, or in the nurse/GP/family doctor's clinic). Where more than one measurement has been made in between visits, use the average of the most recent readings up to a maximum of eight recent measurements. If the patient measures their BP at home, use these readings in preference to other measurements when recording BP on the case report forms. If these are not available, use those made in the GP/family doctor's surgery in preference to readings made when they attend the ECST-2 follow up clinic.

Recommended treatment to lower blood pressure

The following is a reminder of the NICE guidelines. However, it is the responsibility of a medically licenced investigator to prescribe or recommend the medication most suitable for the individual patient, bearing in mind the aim of achieving a BP below target values.

Step 1

Patients under the age of 55 should receive first line treatment with an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin II receptor blocked (ARB). NB: ACE-inhibitors cause a dry cough in 10% of men and 20% of women. An ACE inhibitor should not be combined with an ARB.

Patients over the age of 55, and black people of African or Caribbean origin or those from Asia, should be prescribed a calcium channel blocker (CCB) as first line or, if not tolerated, a thiazide-like diuretic, e.g. chlortalidone or indapamide, in preference to a conventional thiazide (bendroflumethazide or hydrochlorthiazide).

Step 2

If BP is not controlled by Step 1 treatment, use a combination of a CCB with an ACE inhibitor or an ARB. If a CCB is not suitable because of intolerance, offer a thiazide-like diuretic. In the presence of heart failure, use a loop diuretic in combination with an ACE-inhibitor or ARB. For black people of African or Caribbean origin, consider an ARB in combination with a CCB.

Step 3

If the patient's BP is still not below target with two medications, check the patient is taking the maximally tolerated doses of each medication before considering treatment with three drugs. If treatment with three drugs is required, use a combination of an ACE inhibitor or ARB with a CCB and thiazide-like diuretic.

Step 4

If BP is still not controlled to target, consider investigating the patient for secondary causes of hypertension and adding a fourth antihypertensive drug, or refer to a hypertension expert.

Target for serum cholesterol

The target in ECST for total serum cholesterol is 4.0mmol/l with an LDL cholesterol level of <2.0mmol/l. Treatment should be adjusted to achieve cholesterol measurements so that both are below this target. If the patient's serum cholesterol levels are above target, they should have treatment to lower cholesterol started or increased. Arrangements should be made for them to have their fasting lipids checked six weeks after starting or changing dosage or type of medication, and an appointment made for timely review of the results.

All patients should be advised about a low fat diet and referred to a dietician if necessary. We recommend starting treatment with a statin, e.g. simvastatin 40mg nocte or atorvastatin 20mg nocte. (Note: certain CCBs, e.g. amlodipine, interact with simvastatin in which case atorvastatin may be preferred.) The dose should then be increased at six weekly intervals until the patient reaches target, to a maximum of simvastatin 40 mg nocte or atorvastatin 80 mg. Alternative statins may be used if required. Specialist advice should be obtained from a lipid expert or clinic if additional

medication is required or if the patient has familial hypercholesterolaemia or raised triglycerides.

Targets for patients with Diabetes mellitus

Please monitor the adequacy of control of diabetes using a target of HbA1c of 6.5%. Patients should be advised to attend a specialist diabetic clinic and keep in contact with their diabetic nurse if there are difficulties achieving the target.

Recommendations for target BP in patients with diabetes are generally lower than those recommended for individuals without diabetes. The Nice Guideline for the management of type 2 diabetes makes the following recommendations:

Clinic Target BP for patients *without* prior stroke or TIA or other risk factors*: <140/80

Clinic Target BP for patients *with* prior stroke or TIA or other risk factors*: <130/80

*other risk factors = raised albumin excretion rate (AER) (microalbuminuria or worse), eGFR <60 ml/min/1.73 m², retinopathy.

Antiplatelet and anticoagulant therapy

All patients should receive antiplatelet therapy unless they develop a contraindication (e.g. life threatening bleeding) or require anticoagulation (e.g. if they have or develop atrial fibrillation). Clopidogrel 75mg daily should be used as first line therapy in ECST-2, but the combination of aspirin and dipyridamole may be used as an alternative. Aspirin alone should only be used if the patient is unable to tolerate clopidogrel and is also unable to tolerate dipyridamole, or in the first 2 weeks after ischaemic stroke if that is the local policy for treatment of acute ischaemic stroke. The combination of aspirin and clopidogrel should be prescribed as follows:

- For 3 months after transient ischaemic attack and minor stroke (if adopted locally in line with the recent CHANCE study)
- Prior to carotid endarterectomy if this is local policy
- Prior to carotid stenting and for up to 6 weeks after stenting according to local policy

If the patient requires anticoagulation for any reason, the patient should be treated with an appropriate anticoagulant (rather than antiplatelet therapy), e.g. full dose heparin, warfarin or a novel oral anticoagulant according to the practice at the centre. Any antiplatelet therapy should be stopped when anticoagulation is initiated. However, low-dose heparin e.g. as prophylaxis for deep vein thrombosis or given as a bolus during revascularisation procedures, can be combined with antiplatelet therapy.

Lifestyle interventions

Smoking cessation

All patients who currently smoke should be referred to a smoking cessation clinic. In the UK, you can do this directly or via their GP. There are many available online resources also or apps for iPhone and android smart phones that may help the patient quit smoking.

Weight loss and fitness

You will need to document the patient's weight and height on the case report forms so that their BMI can be calculated. If a patient has a BMI >25 they should be advised to seek help regarding diet and weight loss, and fitness and exercise. Offer appropriate guidance and written or audio-visual materials to promote lifestyle changes. They should be referred to a dietician if not already seeing one.

Alcohol consumption

Ascertain people's alcohol consumption and encourage a reduced intake if they drink excessively, because this can reduce BP and has broader health benefits. Alcohol targets are: men <21 units per week, women <14 units per week.

Salt intake

Patients should reduce salt intake through avoiding adding salt to cooking and at the table.

Saturated fat intake

Patients should reduce saturated fat intake through reducing red meat and dairy products, and using low-fat milk.

On-line Sources of further information

BP management:

<http://www.nice.org.uk/guidance/CG127/Guidance>

<http://www.nice.org.uk/guidance/CG127/QuickRefGuide>

Lipid modification:

<http://www.nice.org.uk/CG67/FullGuideline>

Type 2 diabetes mellitus:

<http://guidance.nice.org.uk/CG66>

<http://guidance.nice.org.uk/CG66/Guidance/pdf/English>

Antiplatelet therapy:

<http://guidance.nice.org.uk/TA210/Guidance/pdf/English>

Wang J, Wang Y, Zhao X et al. Clopidogrel with aspirin in acute minor stroke or transient ischaemic attack. *N Engl J Med* 2013;369:11-19

Smoking cessation

<http://smokefree.nhs.uk/quit-tools/quit-kit/>

<http://www.nhs.uk/livewell/smoking/Pages/stopsmokingnewhome.aspx>

Obesity

<http://guidance.nice.org.uk/CG43/NICEGuidance/pdf/English>

Royal College of Physicians National Clinical Guidelines for Stroke

<http://www.rcplondon.ac.uk/resources/stroke-guidelines>

(see Section 5.0 Secondary prevention)