

## Review Article

# The problem of chronic refractory angina

## Report from the ESC Joint Study Group on the Treatment of Refractory Angina

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### Introduction

It has been recognized<sup>[1–5]</sup> that there is a group of patients with severe disabling angina and coronary artery disease who are refractory to conventional forms of treatment. Although this issue has already been debated at the level of the National Societies, we felt that it was appropriate to also tackle it at the European level. This is particularly important in view of the rapid pace of growth of this problem and the lack of a standardized approach. This has encouraged the development of a variety of treatments that vary considerably in terms of cost-effectiveness and safety and require proper validation procedures. The aim of this paper is to draw attention to the problem and start a process that will lead to improvement and harmonization of the care of patients with refractory angina.

### Background

The majority of patients suffering from ischaemic heart disease can be adequately treated by drug

therapy and revascularization procedures, i.e. coronary artery bypass grafting (CABG) and percutaneous transluminal coronary angioplasty (PTCA). Improved drug therapy and refinement and the development of invasive therapy modalities have greatly increased the life expectancy of patients with ischaemic heart disease in the last few decades. However, there are patients who remain severely disabled by angina pectoris.

As a result of the improvements in cardiovascular care this patient group is rapidly growing. This means that we will be faced with a large number of angina patients who are not accessible to further revascularization procedures and who receive optimum medical treatment. This condition has been assigned several different names, such as intractable angina pectoris, end-stage coronary artery disease and refractory angina pectoris. The terms end-stage coronary artery disease and intractable angina pectoris are less suitable as they imply a condition that is not accessible to further treatment. Despite this being considered a therapy-resistant condition, refractory angina is a more appropriate term as a number of therapeutic methods, which will be described below, are available. The present report aims at describing the clinical issue of refractory angina pectoris, outlining assessment and optimization of conventional treatment and presenting a number of additional treatment possibilities that have been developed and applied in recent years. In addition, the authors will try to give some recommendations for the future.

**Key Words:** Refractory angina pectoris.

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**Table 1** *The most common reasons why further revascularization procedure is not possible*

- Unsuitable anatomy, such as diffuse coronary sclerosis, often with well-preserved left ventricular function. Sometimes called end-stage angina.
- One or several previous CABGs and/or PTCA's which exclude further benefit or possibility of further revascularization.
- Lack of graft material.
- Impaired left ventricular function in patients with previous CABG and/or PTCA.
- Extracardiac diseases which increase perioperative/postoperative morbidity or mortality, such as general arteriosclerotic disease, renal insufficiency, carotid stenosis and pulmonary disease.
- Age — often in combination with the above mentioned factors.

## Definition

For the definition of angina pectoris we refer to the definition in the guidelines 'Management of Stable Angina Pectoris', published in the European Heart Journal (1997). Angina pectoris is a condition characterized by chest discomfort due to myocardial ischaemia associated with coronary artery disease<sup>[2]</sup>. The guidelines of the ACC/AHA 1999, for the management of patients with chronic stable angina, are also intended to apply to patients with stable chest pain syndrome and known or suspected ischaemic heart disease<sup>[6]</sup>. It is important to underline that angina pectoris is a clinical diagnosis.

The Joint Study Group has agreed on the following definition of refractory angina pectoris: *Refractory angina pectoris is a chronic condition characterized by the presence of angina caused by coronary insufficiency in the presence of coronary artery disease which cannot be controlled by a combination of medical therapy, angioplasty and coronary bypass surgery. The presence of reversible myocardial ischaemia should be clinically established to be the cause of the symptoms. Chronic is defined as a duration of more than 3 months.*

The most common reasons why further revascularization procedures are not possible are listed in Table 1.

## Epidemiology

Data from the national registry of cardiovascular diseases in Sweden show that both the incidence and rate of admission for myocardial infarction are declining. No data are available for the corresponding rates of angina pectoris, but for this diagnosis the admission rates are increasing. Whether this is a direct effect of more efficient treatment of patients with acute coronary syndromes, or reflects a change in the natural history of coronary heart disease is not clear. As 5–10% of patients with unstable angina develop myocardial infarction or refractory angina in the hospital<sup>[7]</sup>, it seems likely that the number of patients presenting with refractory angina pectoris will increase. We have no accurate figures on the occurrence and frequency of refractory angina, nor is the prevalence of angina pectoris known in most communities. A recent report on a Spanish population aged 45 to 74 years and comprising 10 248 subjects gave

overall angina prevalence figures of 7.3% and 7.7%, in men and women, respectively<sup>[8]</sup>. The figures are likely to be higher in northern Europe. The proportion of these patients who will develop refractory angina is unknown, but a guessed estimate could be in the order of 5–10% of those with the diagnosis, or 3–7 per thousand in these age groups. There is a need for systematic registration recording to assess the burden of this disease, so as to obtain more accurate figures for the prevalence and eventually incidence data.

A Swedish survey of patients referred for coronary angiography because of stable angina pectoris performed by the Swedish Council of Technology Assessment in Health Care in 1994–1995<sup>[9]</sup>, showed that 9.6% of the patients referred were rejected for revascularization despite severe symptoms. Another Swedish investigation made in 1998 in the form of an inventory of patients referred for coronary angiography to the national cardiothoracic centre showed that 5–15% of patients referred for coronary angiography probably have refractory angina<sup>[10]</sup>. In absolute numbers, this would mean approximately 2000 patients/year in Sweden and 30–50 000 patients/year in Europe. A majority of these patients will probably fulfil the diagnostic criteria of refractory angina pectoris.

## Pathophysiological considerations

Up to 70% of episodes of myocardial ischaemia in patients with coronary artery disease may be asymptomatic; for acute myocardial infarction, the incidence of painless events is estimated to be 30%<sup>[11–15]</sup>.

Silent ischaemia often co-exists with painful ischaemia in the same patient, and the evidence suggests that there is no correlation between the degree of pain and the severity of the ischaemia<sup>[16]</sup>.

The higher incidence in diabetics implicates peripheral neuropathy in the process; differences in autonomic nerve function have also been described in non-diabetic patients with silent myocardial ischaemia<sup>[17,18]</sup>. Conversely, silent ischaemia can be shown in many non-diabetics with no evidence of neuropathy.

There is no pathophysiological hypothesis to fully explain these findings. Such an hypothesis should take into account two interrelated phenomena. Firstly, the

development of ischaemia is a dynamic process in which the determinants of the imbalance between oxygen supply and demand are not fixed, but can be modulated by a number of factors<sup>[19]</sup>. Secondly, the sensation of angina pectoris is the result of activity in neural circuits with potential for modulation of the message at all levels of the process<sup>[20]</sup>.

For the sake of clarity we shall consider in turn the peripheral and central mechanisms, but we should remember that the system acts as a fully integrated whole.

## Transduction mechanisms

An adequate peripheral stimulus will lead to the release of numerous pain neurotransmitters; adenosine<sup>[21]</sup> and substance P<sup>[22]</sup> have been shown to be particularly important in this respect. There is disagreement as to whether these ligands activate receptors on specific nociceptors (specificity theory), or whether particularly intense stimulation of receptors for other modalities, such as proprioception, will constitute a nociceptive signal (intensity theory)<sup>[23]</sup>.

It is axiomatic that we do not label this signal 'painful'. Pain is a conscious experience triggered by activity in the peripheral nervous system. Prior to the peripheral signal being processed in the brain, it is perhaps best thought of as 'ischaemia-induced afferent activity'<sup>[19]</sup>.

This afferent activity occurs in anatomically sympathetic fibres, which have their primary synapses in the dorsal horn of the spinal cord<sup>[24,25]</sup>, and vagal fibres, which synapse firstly in the nucleus of the solitary tract<sup>[26]</sup>.

At these synapses, there is potential for modulation of the message. Other sensory input to the spinal cord, descending control mechanisms from the brain and mechanisms integral to the spinal cord will act together to either amplify or diminish ongoing afferent activity<sup>[27]</sup>. After the primary synapse, second order neurones ascend in multiple pathways, including the spinothalamic tract, the spinoamygdaloid pathway and the spinohypothalamic pathway<sup>[28]</sup>.

## Central pathways

The pain experience is multidimensional, composed of a sensory–discriminative component (represented by the ability to identify the stimulus within spatiotemporal and intensive domains) and a hedonic component (through which the intrusive and unpleasant qualities of pain are experienced). Additionally, a cognitive component reflects the ability to evaluate the pain in terms of the threat that it represents to well-being or survival. A great deal of information on central processing of visceral pain and angina has been derived from animals, and the following summarizes this work.

The sensory–discriminative component of the experience is expressed through the S-1 and S-2 somatosensory cortex and the posterior cingulate gyrus. These areas receive input from third-order neurones from the ventroposterior lateral thalamus. Arousal, fear and autonomic activation are expressed through activity in the reticular formation, the amygdala and the hypothalamus. The latter two areas receive third-order projection fibres from the parabrachial nuclei of the pons.

Cognitive appraisal occurs in the parietal cortex and the anterior cingulate cortex. Such appraisal will assess the situation as intrusive and threatening, and there will be appropriate affective sequelae of difficulty, apprehension and fear for the future mediated by increased activity in the pre-frontal cortex and limbic system. These areas receive diffuse projections via third-order neurones from medial thalamic nuclei<sup>[28]</sup>.

This operational separation of the components of pain helps us understand the experience, but we must be aware that these are semantic constructs. The experience of angina is a dynamic, integrated, subjective phenomenon, which is unique to the individual. Recently, positron emission tomography has been used to trace the central pathways mediating angina in humans<sup>[29]</sup>. Positron emission tomography permits non-invasive assessment of regional cerebral blood flow, which is a reliable indicator of regional cerebral neuronal activity. Positron emission tomography was used to assess regional cerebral blood flow in patients with stable angina pectoris and angiographically proven coronary artery disease during dobutamine stress.

Compared to the resting state, angina was associated with increased regional cerebral blood flow in the hypothalamus, periaqueductal gray, bilaterally in the thalamus and lateral prefrontal cortex and left inferior anterocaudal cingulate cortex. In contrast, regional cerebral blood flow was reduced bilaterally in the mid-rostrorocaudal cingulate cortex, fusiform gyrus and right posterior cingulate and left parietal cortices. Thalamic activity could be detected several minutes after stopping dobutamine infusion and after the disappearance of anginal pain and ECG changes. Therefore, it is proposed that the activated central structures constitute the pathways which map the experience of anginal pain and that the thalamus acts as a gate to nociceptive information, with activation of many other areas of the brain being necessary before angina is experienced.

The same positron emission tomography methodology has been used to study patients with silent myocardial ischaemia<sup>[30]</sup>. In this study a difference in the pattern of cerebral cortical activation was observed when symptomatic patients were compared to those with silent myocardial ischaemia. However, the flow pattern in the thalamus was similar when the groups were compared. It was concluded that since bilateral activation of the thalamus can be shown in both angina and silent ischaemia, peripheral nerve dysfunction cannot serve as a full explanation of silent ischaemia. In addition, activity in the frontal cortex appears necessary for the sensation of anginal pain.

**Table 2** *Diagnosis*

- I. Requires a cardiological and cardiothoracic surgical assessment that the patient has angina of ischaemic origin and that revascularization is unfeasible. Regular angiographic review is recommended to exclude the development of a 'new' disease that can be treated with revascularization.
- II. Assessment of the presence of current reversible myocardial ischaemia and its correlation to symptoms. Methods used will depend on local tradition and availability.
- III. Outpatient assessment to include: review of pain history, drug history and a physical examination. It is essential to ensure that the patient has failed to respond to maximum tolerable medication. Poor compliance should be considered and the need for compliance explained. Simplification of the drug regimen is recommended.
- IV. Exclude non-cardiac causes, for example, costochondritis, intercostal neuralgia, anaemia, thyrotoxicosis, reflux oesophagitis (consider proton pump inhibitors).
- V. Multidisciplinary cognitive behavioural pain management programme. *If appropriate, based on established psychological assessment methods, for example the Hospital Anxiety and Depression score. A formal psychological assessment may be of value especially in determining whether formal psychotherapy may be beneficial.*  
It is important to consider the possibility that anxiety or depressive illness may be a significant component in the total pain experience. The HADS (Hospital Anxiety and Depression Score) questionnaire is a simple screening tool that may help identify patients who might benefit from psychiatric or psychological assessment.
- VI. Provide a comprehensive rehabilitation programme including secondary prevention through active risk factor management, physical reactivation, stress management and psychosocial support.

**Table 3** *Steps in optimizing medication and treatment in chronic refractory angina*

1. Checking evidence of diagnosis of angina, ruling out possibilities of PTCA or CABG
2. Aspirin (or warfarin in cases of atrial fibrillation or reduced left ventricular function)
3. Beta-blocking agents: resting heart rate  $<60 \text{ beats} \cdot \text{min}^{-1}$
4. Nitrates: transdermal from 20.00h until 11.00h and high dose of oral nitrates (and preventive sublingual)
5. Molsidomine or nicorandil can be tried instead of long-acting nitrates or added to bridge the recommended 6–8 h nitrate-free period
6. Slow-release calcium-blocking agents in the evening
7. Combination with one of the new long-acting dihydropyridine Ca antagonists such as amlodipine or felodipine
8. Correct anaemia, atrial fibrillation with rapid heart rates, hypertension or thyroid dysfunction
9. Patient and family education including counselling on the disease
10. Adequate risk factor management: smoking cessation, dietary counselling, weight reduction
11. Hormonal replacement therapy in women without contraindication should be considered according to the guidelines from the European Society of Cardiology
12. Aggressive cholesterol-lowering therapy
13. Diagnosis and treatment of anxiety or depression (HADS)
14. Physical training (i.e. cardiac rehabilitation).

### Assessment of the patient with refractory angina

To establish the diagnosis of refractory angina pectoris, a standardized procedure is recommended: to determine whether the patient is inaccessible for a further revascularization procedure, a team of invasive cardiologists and cardiac surgeons should make this decision on the basis of a recent angiogram. It is also necessary to reevaluate the patient's medical therapy in order to be sure that the treatment regime is optimal. Furthermore, it is of the utmost importance to ensure that the patients really have current myocardial ischaemia and that other causes of chest pain such as musculoskeletal pain, oesophageal pain, oesophageal reflux and gastrointestinal disorders are excluded. If no current ischaemia can be demonstrated, restriction of further antiischaemic therapeutic measures are strongly recommended, even in the case of known coronary artery disease and typical anginal pain. In addition, it is crucial to determine whether psychosocial factors are the major symptomatic pain determinants. If this is the case, restriction is

recommended at least until the patient is in an optimum physiological condition after intervention in order to avoid therapeutic failure.

The algorithm for assessment proposed by the Joint Study group is presented in Table 2. This algorithm is based on discussions at the topical seminar on refractory angina pectoris held at the ESC conference in Vienna 1998 and on the proposal from the U.K. Guidelines for Refractory Angina Group<sup>[31,32]</sup>. This approach to the patient has also been outlined by Schoebel *et al.*<sup>[4]</sup> (Table 3).

### Optimizing medical treatment in refractory angina pectoris

The first step is a critical reevaluation of the antianginal drug regimen. Studies in patients with seemingly refractory unstable angina<sup>[33]</sup> or severe chronic angina<sup>[34]</sup> have shown that a considerable proportion of patients improve after the dosage of antianginal drugs has been increased and/or their combinations optimized. The



more aggressive regimen rendered 83% of 65 patients with unstable angina pain-free and 44% of 117 patients referred for transmural laser revascularization could be improved by conventional medical therapy before the intervention<sup>[34]</sup>. The dosage of beta-blockers should be increased to reduce resting heart rates to 55–60 beats  $\cdot$  min<sup>-1</sup>. By combining beta-blockers with one of the long-acting dihydropyridine Ca antagonists such as amlodipine<sup>[35]</sup> or felodipine<sup>[36,37]</sup>, a significantly better therapeutic response can be achieved. The timing of drug administration may also play a critical role. A recent trial by Frishman *et al.* (1999) demonstrated that administration of a controlled-release verapamil preparation at bedtime was more successful in reducing the early morning episodes of chest pain than the combination of amlodipine and atenolol given in the morning<sup>[38]</sup>. In view of the well-known circadian variation of ischaemic episodes, with the highest frequency of events in the early morning, appropriately timed administration of long-acting nitrates, for example transdermal nitroglycerin from 20.00h to 11.00–12.00h with a nitrate-free period during the second part of the day, may also have an effect on symptoms.

The calcium inhibitor bepridil has also been suggested as an alternative drug for symptom relief in severe angina, despite a rather unfavourable side-effect profile<sup>[39–41]</sup>.

The use of nitrates may be limited by tolerance development. Molsidomine or nicorandil can be tried instead of long-acting nitrates or added to bridge the recommended 6–8 h nitrate-free period<sup>[42]</sup>. Amiodarone is also a potentially useful antianginal drug. In a study by Meyer and Amann (1993), the amount of ST-segment depression was reduced and the total exercise duration increased in patients with limiting angina pectoris who were already receiving double or triple therapy with conventional antianginal drugs<sup>[43]</sup>. However, data are limited.

In trying to optimize antianginal therapy in patients with severe symptoms, co-existing aggravating factors, such as anaemia, atrial fibrillation with rapid heart rates, hypertension or thyroid dysfunction, should be corrected.

Among the measures to reduce the incidence and severity of chest pain, aggressive cholesterol-lowering therapy may be successful in the long-term. Several studies have demonstrated that cholesterol reduction improves ischaemic symptoms and STT changes on the ECG when added to conventional antianginal therapy<sup>[44,45]</sup>. However, whether the spectacular effects of marked cholesterol-lowering therapy in stable angina, as recently described in the AVERT Study<sup>[46]</sup>, also improves the results in patients with refractory angina remains to be studied.

In addition, several studies have implied that a reduction in LDL cholesterol has an antiischaemic effect that is attributable to improved endothelial function at the level of the epicardial conductance vessels<sup>[47–51]</sup>.

If the measures mentioned above remain unsuccessful and patients still suffer from frequent episodes of angina,

long-term intermittent therapy with urokinase may be a therapeutic option<sup>[4,52]</sup>. Urokinase at a dose of 500 000 IU intravenously 3 times/week over a period of 12 weeks could reduce antianginal episodes by 70% and the need for nitrate capsules by 84%. At the end of a 12-week treatment period improved myocardial perfusion could also be shown by scintigraphy. With this treatment, fibrinogen levels decreased by 35%. The authors propose that the therapeutic effectiveness of urokinase is at least in part mediated by the improved rheological properties of the blood with consequent increases in blood flow in the myocardial microcirculation. In addition, long-term intermittent thrombolytic therapy could also reduce thrombus formation on atherosclerotic plaques in stenotic vessels. However, despite the promising results reported by Leschke and Schöbel no other centres have published clinical results from intermittent fibrinolytic treatment.

Despite all the therapeutic measures discussed above many patients will remain severely incapacitated by their chest pain. In such cases, other therapeutic options, such as transcutaneous electric nerve stimulation (TENS), spinal cord stimulation (SCS), left stellate ganglion blockade (LSGB), endoscopic thoracoscopic sympathectomy (ETS), transmural laser revascularization (TMR) and angiogenesis have to be considered.

It is recommended that all patients receive treatment with acetylsalicylic acid if there are no contraindications.

Opioid treatment in non-malignant pain conditions is widely discussed and slightly controversial. However, recent recommendations from experts in pain medicine advocate the use in non-malignant pain on strict indications and in certain conditions<sup>[53]</sup>. Opioids can be used in refractory angina in selected cases where other therapies fail. In these cases, it is important to follow guidelines for opioid treatment in chronic non-malignant pain and select patients carefully. However, specialists in pain medicine agree that the risk of developing drug addiction is small in socially well adapted patients without a previous history of drug abuse.

In contrast to other European countries, opioids are quite commonly used in severe angina pectoris in Denmark as a result of a local therapeutic tradition.

Hormone replacement therapy should be considered in post-menopausal women who have hyperlipidaemia with poor control by lipid-lowering drugs without contraindication for hormone replacement therapy, as recently advised by the European Society of Cardiology<sup>[54]</sup>.

## The role of cardiac rehabilitation in refractory angina pectoris

The quality of life of patients with refractory angina pectoris is often poor as many patients suffer from anxiety and depression due to their recurrent pain attacks. They may lose their capacity to maintain

'activities of daily living', become physically inactive, socially isolated and increasingly dependent on their relatives or health personnel. For these patients the aim of cardiac rehabilitation is to provide comprehensive care including secondary prevention through active risk factor management, physical reactivation and psychosocial support<sup>[55]</sup>. Several recent guidelines on cardiac rehabilitation are available in the literature<sup>[56–59]</sup>, but no specific guidelines exist for patients with refractory angina. For this reason, we have chosen to review briefly the general recommendations for patients with angina pectoris with the emphasis on points of particular importance for patients with refractory angina. The main areas of intervention are education and counselling targeted at smoking, overweight reduction and a sedentary lifestyle.

Stress management through relaxation might be helpful in controlling and reducing pain in individual patients<sup>[60]</sup>.

Smoking lowers the angina threshold: increased blood levels of carbon dioxide reduce the oxygen carrying capacity, which affects the myocardial oxygen supply. Smoking may even provoke coronary vasospasm. Smoking cessation is a highly cost-effective intervention; support and education of the patient and family, repeated follow-up by a trained nurse is advised and the use of nicotine replacement therapy or bupropion may be very helpful<sup>[61–63]</sup>.

Obesity results in an increase in the myocardial oxygen demand and further deterioration of refractory angina pectoris. A body mass index  $>28 \text{ kg} \cdot \text{m}^2$  or a waist-to-hip ratio  $>0.95$  for men and  $>0.85$  for women is considered to be the limit above which weight reduction is needed.

Physical training and a physically active lifestyle reduces cardiac mortality<sup>[64]</sup>, affects the progress of the atherosclerotic disease<sup>[65]</sup>, and improves myocardial perfusion<sup>[66]</sup>. Patients with exercise-induced ischaemia can obtain similar but less marked training effects as patients without ischaemia after an exercise training programme, i.e. an increase in maximum workload and maximum oxygen uptake<sup>[67]</sup>. The primary aim of the programme should be recovery of the capacity to perform the activities of daily life. A low-intensity endurance training programme will be feasible, but the programme must be tailored to the needs of the individual patient. Activities of daily living include moments of static labour, thus the physiotherapist may include static exercise training in the programme. Activities of daily living counselling by an occupational therapist may be needed, especially for the elderly angina patient for whom the use of energy-saving techniques can be particularly helpful. The patients should be instructed in the prophylactic use of nitroglycerin before commencing strenuous activities. The importance of warm-up and cool-down periods before and after exercise must be stressed. Each period of physical exertion is associated with a transient increase in risk. This is outweighed by the long-term protective effect of a physically active lifestyle<sup>[68,69]</sup>.

A dietician will best perform nutritional counselling with specific focus on the metabolic aspects of coronary artery disease. Information to groups of patients including spouses, practical cooking demonstrations and long-term follow-up of food habits are recommended; the use of a diet rich in omega-3 fatty acids (the 'Mediterranean diet') can improve the long-term prognosis of patients with coronary artery disease<sup>[70]</sup>.

Education of the refractory angina patient is the cornerstone of individualized cardiac rehabilitation. Psychological support should be provided, if needed combined with the use of antidepressive drug treatment and a structured pain management programme<sup>[71]</sup>. Thus, a comprehensive cardiac rehabilitation programme for patients with refractory angina can be recommended and may result in an alleviation of symptoms, an improvement of the long-term prognosis and a better quality of life<sup>[72,73]</sup>.

Depression and anxiety disorders must be ruled out as primary pain determinants. The Hospital Anxiety and Depression Scale (HADS) can be used for this purpose<sup>[74]</sup>.

The steps for optimizing medication and treatment in chronic refractory angina are outlined in Table 3.

## Review of current treatment possibilities in refractory angina pectoris

When evaluating methods of treatment for refractory angina the following considerations are important: clinical efficacy, scientific documentation, feasibility (i.e. accessibility, costs, need of compliance and follow-up) and adverse reactions. These methods are presented below and in Table 4.

### *Neuromodulation techniques — transcutaneous electric nerve stimulation and spinal cord stimulation*

#### *Background*

Treatment with neuromodulation techniques in angina pectoris was introduced in the early 1980s. Although initially met with great scepticism, transcutaneous electric nerve stimulation and later spinal cord stimulation have gained acceptance as therapeutic possibilities in therapy-resistant angina where conventional management strategies have been exhausted<sup>[3]</sup>.

## Methods

### *Transcutaneous electric nerve stimulation*

Transcutaneous electric nerve stimulation is a neuromodulation technique that is comparable to needle

**Table 4** Summary of treatment options in refractory angina pectoris

Therapy	Documented effect		Strength of evidence	Approximate number of patients treated
	Symptoms	Ischaemia		
TENS	+	+	B	4000
SCS	+	+	A	2000
TEDA	+	+	C	300
ETS	+	?	C	80
TMR	+	?	A	8000
PMR	+	?	B	2000
LSGB	+	?	C	100

The amount of scientific documentation is assessed as strength of evidence : A, B, C.

A=strength of evidence provided by well-designed, well-conducted, controlled trials (randomized and non-randomized) with statistically significant results that consistently support the recommendations).

B=scientific evidence provided by observational studies or by controlled trials with less consistent results to support the guideline recommendations.

C=expert opinion that supports the guideline recommendation because the available scientific evidence did not present consistent results, or controlled trials were lacking.

TENS=transcutaneous electrical nerve stimulation; SCS=spinal cord stimulation; TEDA=thoracic epidural anaesthesia; ETS=endoscopic thoracic sympathectomy; TMR=transmyocardial laser revascularization; PLR=percutaneous laser revascularization; LSGB=left stellate ganglion blockade.

acupuncture. However, instead of needles, standard electrodes of silicone-conducting rubber are applied over the painful area of the chest wall. The device can easily be used by the patient at home after instruction.

When an anginal attack occurs or is anticipated the patient applies stimulation for 1–3 min. It is essential to place the electrodes so that the stimulation paresthesiae cover the area of anginal pain, as this is the only way to ensure that the proper spinal segment is activated, i.e. the segment that supplies the heart with nerves.

Transcutaneous electric nerve stimulation was the afferent stimulation technique first used in the treatment of patients with refractory angina in the late 1970s. This was found to be a safe method and the antianginal effect appeared to be secondary to reduced myocardial ischaemia<sup>[75–79]</sup>.

Skin irritation develops in a large number of patients, making it difficult to continue with this form of therapy. This side effect is a disadvantage in long-term treatment. Thus, if long-term neuromodulation treatment is needed, as in angina, spinal cord stimulation is a preferable treatment modality. Clinical observations also suggest that spinal cord stimulation may be more effective than transcutaneous electric nerve stimulation.

Today, transcutaneous electric nerve stimulation is primarily used as a test method for planned implantation, to determine whether myocardial ischaemia is really the cause of the patient's pain and to evaluate whether the patient shows good enough compliance to handle a spinal cord stimulator. According to clinical experience, chest pain after provocation that disappears totally after 30–60 s of high-intensity stimulation, is a strong indicator of ischaemic origin. In contrast to other pain conditions, the effect in ischaemic pain such as angina pectoris is immediate and total.

Another indication where transcutaneous electric nerve stimulation is being used with promising results is in the treatment of unstable angina in patients who cannot be pharmacologically stabilized pending revascularization<sup>[80]</sup>.

### *Spinal cord stimulation — method*

Implantation of the spinal cord system is performed under local anaesthesia. The electrode is positioned epidurally so that paraesthesiae is produced in the region of anginal pain radiation. The patient carries the pulse generator in a subcutaneous pouch below the left costal arch. The pulse generator is connected to the epidural lead with a subcutaneous connection wire. The system is similar to a pacemaker with the electrode placed in the epidural space instead of the heart.

### *Scientific results*

#### *Safety aspects*

Since 1982, numerous studies have been published of the short-term effects of transcutaneous electric nerve stimulation and spinal cord stimulation on myocardial ischaemia and anginal pain. Irrespective of the methods used to stress the heart, for example bicycle ergometer or treadmill tests, pharmacological stress tests and atrial pacing, the relationship between anginal pain and myocardial ischaemia is not significantly affected by stimulation<sup>[75–78,81–86]</sup>. It also seems evident that myocardial ischaemia during treatment gives rise to anginal pain. Thus, the treatment does not seem to deprive the patient of a warning signal. Furthermore, pain relief

with spinal cord stimulation does not appear to conceal myocardial infarction<sup>[87]</sup>. Several studies using Holter monitoring have shown an absence of arrhythmia and a decrease in ischaemic burden<sup>[85,88]</sup>.

#### *Mechanisms of action*

As described above, a number of experimental studies have shown that the symptom relief obtained with stimulation therapy in angina pectoris is secondary to a decrease in myocardial ischaemia. The antiischaemic effect is probably dependent on a decrease in myocardial oxygen consumption at a comparable level of cardiac work<sup>[76,89]</sup>. It also seems evident that myocardial ischaemia during treatment gives rise to anginal pain. Thus, as earlier stated, the treatment does not deprive the patient of a warning signal. Other studies have indicated an amelioration of cardiac blood flow in terms of redistribution from non-ischaemic to ischaemic areas<sup>[90–92]</sup>. The antiischaemic effect may be caused by a decrease in sympathetic tone or a change in the cardiac metabolism of beta-endorphine<sup>[93–95]</sup>.

In summary, the antiischaemic effect is probably complex in nature. It involves a decrease in myocardial oxygen consumption, a probable amelioration of coronary blood flow and neurohormonal mechanisms.

#### *Clinical efficacy studies (Table 4)*

In a number of clinical long-term studies, transcutaneous electrical nerve stimulation and spinal cord stimulation have been proven to provide long-lasting symptom relief with a decrease in anginal Canadian Cardiovascular Society class, improvement in daily life activities and social activities and a reduction in the consumption of short-acting nitroglycerin<sup>[96–98]</sup>. In addition, unstable angina and myocardial infarction during stimulation therapy will give rise to typical symptoms<sup>[87]</sup>. In a retrospective registry study, spinal cord stimulation did not have any negative influence on mortality and morbidity when compared to matched groups<sup>[99]</sup>.

In order to compare spinal cord stimulation to CABG in patients with symptomatic indication only for bypass surgery and with an increased risk of complications, a randomized study was carried out<sup>[100]</sup>. One-hundred and four patients were included (spinal cord stimulation 53, CABG 51; mean age  $63 \pm 9$  years). Both groups had a highly significant reduction in anginal attacks and consumption of short-acting nitroglycerin without any difference between the groups. The CABG group had signs of improved myocardial perfusion during exercise which could not be observed in the spinal cord stimulation group. However, the spinal cord stimulation patients did not have active treatment during exercise. Eight deaths occurred during the follow-up period, seven of which were in the CABG group. On an intention-to-treat basis, mortality and cerebrovascular morbidity were lower in the spinal cord stimulation group. The results of this study implied that CABG and spinal cord stimulation

provide equal symptom relief in this group of patients. Recent data from this study shows that the quality of life is significantly increased in both groups after 6 months and this beneficial effect is unchanged after 3 years. There is no difference in mortality between the CABG and spinal cord stimulation groups after 3 and 5 years, respectively<sup>[101]</sup>.

#### *Clinical results*

Today, about 2000 patients have been implanted with spinal cord stimulation globally. The number of patients treated with transcutaneous electric nerve stimulation for refractory angina is not known but estimated to be approximately 4000 patients worldwide<sup>[102]</sup>.

Clinical long-term follow-up shows that about 80% of the patients enjoy lasting symptom relief in terms of reduced frequency of attacks and reduced consumption of short-acting nitroglycerin, as well as increased physical activity and improved quality of life<sup>[1,103]</sup>. This high success rate is dependent on proper patient selection, careful follow-up and that the patients are treated at units specialized in this kind of treatment. In patients who respond inadequately to treatment, psychological factors are often a major contributor to the development of the chest pain, or the chest pain cannot be correlated to ongoing myocardial ischaemia.

#### *Conclusion*

Neuromodulation techniques (transcutaneous electric nerve stimulation, spinal cord stimulation) are safe and effective methods of treating refractory angina pectoris. The scientific documentation is extensive compared to most other treatment methods used in this patient group.

### **Thoracic epidural anaesthesia**

#### *Background*

Epidural anaesthesia is a well-known and well-established method of local anaesthesia and is widely used in a variety of conditions, such as obstetric analgesia, postoperative analgesia, treatment of malignant pain and other pain conditions. It was introduced for the treatment of unstable angina pectoris by Blomberg, Ricksten *et al.* in the middle of the 1980s<sup>[104,105]</sup>.

#### *Methods*

A conventional epidural catheter is inserted at the level corresponding to the cardiac segments, i.e. C<sub>7</sub>–T<sub>4</sub>. Bupivacaine is infused either continuously with an infusion pump or by intermittent injection. In this way



complete anaesthesia of the corresponding spinal roots and sympathetic trunks is achieved bilaterally. The clinical effect is tested by pin-prick stimulation of the affected dermatomes and when complete anaesthesia of these dermatomes is achieved the transthoracic epidural anaesthesia is considered to be successful.

### *Scientific results*

There is ample scientific documentation of this method in unstable angina pectoris and acute myocardial ischaemia. In animal studies, transthoracic epidural anaesthesia induced a decrease in ischaemic complications after coronary ligation<sup>[106]</sup>. In studies on humans, transthoracic epidural anaesthesia has been shown to have favourable effects on central haemodynamics<sup>[105]</sup> and to induce good symptom relief and a reduction in myocardial ischaemia in unstable angina<sup>[104,107]</sup>. Furthermore, stress-induced myocardial ischaemia and left ventricular function have both been shown to be favourably influenced by transthoracic epidural anaesthesia treatment<sup>[104,108]</sup>. Gramling-Babb *et al.* used transthoracic epidural anaesthesia for continuous treatment of ten patients with severe coronary artery disease and chronic stable angina pectoris during 1 year. They reported good symptom relief but the method was hampered by complications, mainly infections, epidural fibrosis and paraspinal muscle spasms<sup>[109]</sup>.

### *Clinical results*

Transthoracic epidural anaesthesia has been used for a decade for the treatment of patients with severe angina pectoris, mainly unstable angina pectoris. Several hundred patients have been subjected to the treatment. The experience in unstable angina pectoris is excellent and transthoracic epidural anaesthesia is an accepted method for the treatment of patients with unstable angina where conventional strategies are insufficient. It is not well documented in chronic stable angina pectoris and seems less attractive for chronic use, mainly due to the rate of complications and practical disadvantages for the patients, such as carrying an infusion pump, administering injections and so forth. In addition, the scientific documentation in chronic stable angina pectoris is sparse.

### *Endoscopic thoracic sympathectomy*

The sympathetic innervation of the heart originates predominantly in the lower cervicle and superior thoracic parts of the sympathetic trunk. Cardiac pain transmission is carried in C fibres which are transported in the same peripheral nerves as the afferent sympathetic nerves. The rationale for sympathectomy/

sympathectomy as treatment in angina pectoris is to achieve a permanent afferent sympathetic blockade to the heart as well as an analgesic effect through discontinuance of afferent pathways. Different ways of modulating the sympathetic nervous system in order to treat refractory angina pectoris have been explored since the 1920s.

### *Methods*

Open surgical sympathectomy of parts of the thoracic sympathetic trunk for the treatment of angina was introduced in the 1890s<sup>[110]</sup>. During the period 1920–1940, several clinical observational reports were published<sup>[111,112]</sup>. The rate of severe complications, death excluded, was approximately 10%. However, symptom relief was obtained in 70–80% of patients. Open sympathectomy was abolished in favour of other surgical methods for the treatment of angina pectoris, mainly coronary artery bypass surgery.

High thoracic sympathectomy includes extirpation of the lower part of the stellate ganglion and the following four or five thoracic ganglia. Such a procedure is considered to produce adequate cardiac sympathetic denervation<sup>[113]</sup>. Endoscopic transthoracic sympathectomy was developed by Göran Claes in the mid 1980s<sup>[114]</sup>. Initially it was used to treat palmar hyperhidrosis. In the late 1980s, Claes, Wettervik *et al.* started to use high transthoracic endoscopic sympathectomy to treat refractory angina pectoris.

The procedure is performed under general anaesthesia. The pleural cavity is entered through the second or third intercostal space anteriorly. Carbon dioxide is then insufflated and the lung collapsed. Sympathetic ganglia are electrocoagulated using an electroresectoscope. Transsection of the thoracic ganglia T<sub>1</sub>–T<sub>5</sub> is usually performed. The procedure is normally performed on the left side. If the effect is unsatisfactory the operation is done bilaterally. Note that the procedure should not be performed on the right side only as this carries a risk of inducing ventricular arrhythmia.

### *Scientific results*

The scientific documentation in endoscopic transthoracic sympathectomy is rather limited. In two studies (24 and 43 patients, respectively) anginal attacks decreased, exercise capacity increased and the degree of ST segment depression at maximum comparable workload decreased<sup>[115,116]</sup>. In a study on 57 patients using long-term Holter recording and analysis of heart rate variability, the heart rate variability spectrum was influenced in a way that was considered favourable<sup>[117]</sup>.

### *Clinical results*

To date, approximately 80 patients have been subjected to endoscopic transthoracic sympathectomy. The vast

majority of these procedures has been performed at Borås Hospital, Sweden. A reduction in anginal symptoms and consumption of short-acting nitroglycerin has been reported. However, the frequency of complications, including perioperative and postoperative death, myocardial infarction, autonomic disturbances and sensory disturbances, is not negligible.

Endoscopic transthoracic sympathectomy is still to be considered as an experimental therapy modality with an unfavourable profile of mortality, morbidity and complications. The scientific basis is still rather weak.

Endoscopic transthoracic sympathectomy is not suitable as a primary alternative for the treatment of refractory angina pectoris. It has one great advantage, namely the complete absence of need for compliance. Furthermore, in contrast to transcutaneous electric nerve stimulation and spinal cord stimulation, it has a favourable effect on chest pain of other origin. It can therefore be considered for patients for whom compliance problems can be expected, but only after careful assessment of the risks involved.

### Left stellate ganglion blockade

Sympathetic ablation by paravertebral injection of alcohol was used to treat angina in patients before surgery until the 1950s. The technique was not without complications and with the development of antianginal medication it lost its attractiveness as a treatment for angina. However, it was later modified and a local anaesthetic was used instead. In 1966, Wiener *et al.* studied ten male patients with angina and assessed the changes that bilateral stellate ganglion blockade produced on post-exercise ECG, both before and after treatment with xylocaine or isotonic saline<sup>[118]</sup>. Nine out of ten patients had relief from the angina following the xylocaine block, as compared to three out of nine who had the sham block. Left stellate ganglion blockade is presently being studied as a treatment for chronic refractory angina pectoris in the U.K.<sup>[119]</sup>. The method is not without complications and mortality has been reported<sup>[118,120–127]</sup>. Performed by a skilled physician under optimum conditions, this method seems attractive as it is cheap, readily accessible and, according to clinical experience from one centre in the U.K., effective<sup>[128, 129]</sup>. The treatment needs to be repeated at regular intervals. The method needs thorough evaluation, especially concerning the safety aspects before being considered for inclusion in the therapeutic arsenal in refractory angina.

### Laser revascularization

#### *Background*

The original concept of direct myocardial revascularization was to carry blood from the ventricular cavity into the myocardium and therefore into the coronary

circulation. It encompasses drilling of channels in the wall of the left ventricle by myocardial acupuncture with a needle<sup>[130]</sup> or with a laser beam<sup>[131]</sup> in order to mimic the naturally occurring channels of reptile hearts.

### Transmyocardial laser revascularization

#### *Methods*

##### *Surgical technique*

The left pleural space is entered through a limited left anterior or anterolateral thoracotomy, usually through the fifth intercostal space. After opening the pericardium, the procedure is performed on a beating heart and without the use of cardiopulmonary bypass. The handpiece of the laser arm of a laser (mostly CO<sub>2</sub> or holmium: yttrium-aluminium-garnet [YAG] laser) is aimed at the epicardium in the area of reversible ischaemia, which has been assessed before the procedure, while at the same time care is taken to avoid visible epicardial vessels. The laser is triggered to fire on the R wave of the electrocardiogram when the ventricle is in diastole, maximally distended and electrically quiescent. Synchronization of the very brief laser pulse to the R wave of the electrocardiogram reduces the risk of arrhythmia. The laser energy penetrates from the epicardium to the endocardium with minimum damage to the surrounding tissue. The channels are approximately 1 mm in diameter and distributed approximately one per square centimeter in the area of reversible ischaemia.

Possible perioperative and postoperative complications encompass myocardial infarction, low output syndrome, ventricular arrhythmias, atrial fibrillation, sudden development of mitral regurgitation as a result of laser injury to the chordae tendineae, bleeding, and other usual postoperative complications, such as wound infection or pneumonia<sup>[132–134]</sup>.

#### *Scientific and clinical results*

Transmyocardial laser revascularization is used in selected patient groups with chronic angina pectoris, good or only slightly depressed left ventricular function and inoperable coronary artery disease refractory to maximum medical therapy. Patients with poor left ventricular ejection fraction are not good candidates for laser therapy. There is no evidence of effectiveness in acute myocardial ischaemia. It is a therapy that may reduce symptomatic angina pectoris in some patients with rapid early relief of symptoms but with a trend towards worsening over time. There is no improvement of dyspnoea and generally no improvement in the left ventricular ejection fraction and myocardial perfusion. Unfortunately, it is not possible to predict the duration of the angina-free period. The mortality rates range

from 5–20% and the perioperative morbidity has been between 32 and 68% in different studies<sup>[135]</sup>. Although some animal studies have suggested patency of the lasered channels, most recent studies and autopsy reports<sup>[136,137]</sup> do not support this. Another possibility is that laser-induced myocardial injury stimulates angiogenesis and subsequent collateralization, resulting in improved perfusion.

Six multicentre, randomized controlled trials have compared transmyocardial revascularization with medical therapy in patients with severe angina not suitable for further revascularization procedures<sup>[138–143]</sup>. In all six trials there was an improvement in the frequency and severity of angina although the extent of the improvement varied. Myocardial perfusion was assessed in five of six trials. In four of these five trials perfusion did not improve and in the fifth, the magnitude of the symptom improvement was disproportionate to the improvement in perfusion<sup>[139–143]</sup>. Although it has been suggested that neovascularization caused by angiogenesis may improve perfusion after laser revascularization, there is no evidence that the procedure will alter global or regional left ventricular performance, which is often the result of clinically significantly improved perfusion<sup>[144]</sup>. Furthermore, in animal studies, transmyocardial revascularization has been shown to destroy cardiac nerve fibres<sup>[145]</sup>. For this reason, the symptom relief seemed to be largely dependent on placebo mechanisms but denervation and angiogenesis may be of importance. However, reports are inconsistent.

### *Percutaneous laser revascularization*

A less traumatic approach to laser revascularization has been used in recent years.

A catheter laser fiberoptic system is introduced through the femoral artery and through the aortic valve into the left ventricle. The laser-made channels in the myocardium are created from the endocardium towards the epicardium guided by fluoroscopy and simultaneous transoesophageal echocardiographic monitoring. Injury to the epicardial coronary artery, chordae tendineae, bleeding into the pericardial sac and neurological complications are possible as well as other complications that accompany ventriculography.

This technique may be promising but there is still very little scientific data. In a feasibility report, results from Frankfurt, Germany, on 30 patients subjected to the treatment have been reported<sup>[146]</sup>. The goal of this study was to establish the feasibility and safety of percutaneous laser revascularization treatment. The feasibility was easy to demonstrate. Major complications were limited to one incident of pericardial tamponade. Symptomatic relief was reported to be at least two angina classes in these patients.

One small study of eight patients showed improved perfusion in the treated area<sup>[147]</sup>. The results with percutaneous laser revascularization are similar to TMR in some studies: there is an improvement in angina

class and exercise capacity with minimum or no change in nuclear perfusion scans<sup>[147–149]</sup>. In a larger trial (the Pacific Trial) 220 patients were randomized to percutaneous laser revascularization or conventional medical therapy. Randomized placebo-controlled trials are underway. The data available at present seem to indicate that the result is similar to TMR, i.e. a decrease in angina, an increase in exercise tolerance and no evidence of increased myocardial perfusion. The mortality rate is estimated to 1%. Further scientific data are needed before the role of percutaneous laser revascularization in the therapeutic arsenal can be determined.

## **Other methods**

### *Angiogenesis, growth factors and gene therapy in the treatment of refractory angina*

Another new treatment option for patients with refractory angina is improving myocardial perfusion by new blood vessel formation. This can be achieved either by the formation of new capillaries from pre-existing ones (angiogenesis) or by the enlargement and functional recruitment of pre-existing collateral vessels (arteriogenesis)<sup>[150]</sup>. Next to these processes, *vasculogenesis*, as defined by the process involving the differentiation of precursor cells (angioblasts) into endothelial cells, and thereafter assembling into premordial blood vessels has recently been described as also occurring in post-natal life<sup>[151]</sup>. During *angiogenesis* endothelial cells respond to angiogenic stimuli by initiating the formation of new vessels. In this process endothelial cells produce metalloproteinases to digest the basement membrane. They can then break loose from the basement membrane, migrate, proliferate and form a network of endothelial tubes. In order to become functionally important these vessels need to mature<sup>[152]</sup>. During subsequent *arteriogenesis*, vessels become extensively covered by a muscular coat, thereby endowing blood vessels with visco-elastic and vasomotor properties<sup>[153]</sup>.

Stimulation of angiogenesis with vascular endothelial growth factor gene therapy is until now the most extensively investigated form of gene therapy. For this purpose direct intramyocardial injection of naked DNA encoding for vascular endothelial growth factor as well as adenoviral transfection with vascular endothelial growth factor have been explored. Experimental data show remarkable improvement of flow to ischaemic areas in peripheral arteries as well as in the heart<sup>[154]</sup>. Preliminary clinical results so far are encouraging but need to be further validated in placebo-controlled trials<sup>[155,156]</sup>.

In summary, stimulation of new blood vessel formation by gene therapy with angiogenic growth factors is a recent development. Validation and optimization of these strategies are warranted.

### *Enhanced external counterpulsation*

Enhanced external counterpulsation is a technique that increases arterial blood pressure and retrograde aortic blood flow during diastolic augmentation. Cuffs are wrapped around the patient's legs and compressed. Sequential pressure is applied from the lower legs to the lower and upper thighs in early diastole to propel blood back to the heart. Enhanced external counterpulsation has been shown to give rise to a decrease in anginal episodes and in some studies observations suggesting a reduction in myocardial ischaemia have been made<sup>[157,158]</sup>. The mechanism of the benefits of enhanced external counterpulsation is unclear. This method has been used in the United States but the experience in Europe is limited.

### *Heart transplantation*

Heart transplantation has been used in selected patients with refractory angina pectoris at some centres. However, at most centres it is not considered to be a therapeutic alternative in refractory angina pectoris.

## **Summary and recommendations**

Refractory angina pectoris is a clinical problem that has not been fully recognized until recently. With improving cardiovascular care, this patient group is large and rapidly growing. Several different definitions and approaches to therapy have been used. The therapy modality used depends on local tradition. This means that the patient with refractory angina may receive very different assessments and treatments depending on where he/she lives or is subjected to evaluation and treatment. This is a situation that needs to be remedied. It is of great importance to reach a consensus on the definition of refractory angina and to create a diagnostic algorithm that will be generally applicable. A large number of further therapeutic possibilities has emerged. There is an urgent need to define a more standardized approach to this therapeutic arsenal and to make recommendations on which methods should be used in which patients. The choice will be largely dependent on feasibility and local traditions. The patients should be evaluated in a stepwise manner as outlined previously in the text and in [Table 2](#). It is of the utmost importance that all patients who are considered for these therapeutic measures are first subjected to careful optimization of medical treatment, optimum cardiac rehabilitation and evaluation concerning psychosocial pain determinants.

Scientific documentation and complication rates with the different methods must be considered when making this decision. The methods have not been compared in proper randomized trials. However, such trials are underway.

All physicians treating patients with angina should be aware of the syndrome of refractory angina and be able

to detect such a patient. The diagnosis should be established by cardiologists and cardiothoracic surgeons on the basis of a recent coronary angiogram. The assessment and choice of treatment method should be carried out at specialized centres where experience can be gathered and proper investigations performed.

The Joint Study Group proposes the following recommendation:

Therapeutic alternative 1: Transcutaneous electrical stimulation, spinal cord stimulation.

These are comparatively well documented methods used in several centres with positive effects on symptoms and ischaemia and a favourable side-effect profile. The choice of method will largely depend on local resources and, thus, practical feasibility.

Therapeutic alternative 2: Left stellate ganglion blockade, which is a theoretically promising method that needs further evaluation.

Therapeutic alternative 3: Thoracic epidural anaesthesia, endoscopic thoracic sympathectomy, transmyocardial laser revascularization, percutaneous laser revascularization.

These therapies are less well documented and/or have unfavourable documentation with conflicting results or serious adverse effects. They have therefore limited feasibility. In a stepwise approach to the patient, as outlined in this manuscript, these therapies should be avoided until more documented and/or less destructive methods have been tried.

Research in this field must also be encouraged. The epidemiology of refractory angina is unclear and descriptive epidemiological studies are urgently needed. Such studies should preferably be undertaken on an international basis as a multicentre effort. In addition, comparative studies between the different treatment modalities used in refractory angina have to be performed.

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