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Society Guidelines

Management of Patients With Refractory Angina: Canadian Cardiovascular Society/Canadian Pain Society Joint Guidelines

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ABSTRACT

Refractory angina (RFA) is a debilitating disease characterized by cardiac pain resistant to conventional treatments for coronary artery disease including nitrates, calcium-channel and β -adrenoceptor block-

RÉSUMÉ

L'angine de poitrine réfractaire (APR) est une maladie débilitante caractérisée par une douleur cardiaque résistant aux traitements traditionnels de la maladie coronarienne incluant les nitrates, le canal

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See page S36 for disclosure information. The disclosure information of the authors and reviewers is also available from the CCS on the following websites: www.ccs.ca and www.ccsguidelineprograms.ca.

This statement was developed following a thorough consideration of medical literature and the best available evidence and clinical experience. It represents the consensus of a Canadian panel comprised of multidisciplinary experts on this topic with a mandate to formulate disease-specific recommendations. These recommendations are aimed to provide a reasonable and practical approach to care for specialists and allied health professionals obliged with the duty of bestowing optimal care to patients and families, and can be subject to change as scientific knowledge and technology advance and as practice patterns evolve. The statement is not intended to be a substitute for physicians using their individual judgement in managing clinical care in consultation with the patient, with appropriate regard to all the individual circumstances of the patient, diagnostic and treatment options available and available resources. Adherence to these recommendations will not necessarily produce successful outcomes in every case.

ade, vasculoprotective agents, percutaneous coronary interventions, and coronary artery bypass grafting. The mortality rate of patients living with RFA is not known but is thought to be in the range of approximately 3%. These individuals suffer severely impaired healthrelated quality of life with recurrent and sustained pain, poor general health status, psychological distress, impaired role functioning, and activity restriction. Effective care for RFA sufferers in Canada is critically underdeveloped. These guidelines are predicated upon a 2009 Canadian Cardiovascular Society (CCS) Position Statement which identified that underlying the problem of RFA management is the lack of a formalized, coordinated, interprofessional strategy between the cardiovascular and pain science/clinical communities. The guidelines are therefore a joint initiative of the CCS and the Canadian Pain Society (CPS) and make practice recommendations about treatment options for RFA that are based on the best available evidence. Concluding summary recommendations are also made, giving direction to future clinical practice and research on RFA management in Canada.

Refractory angina (RFA) is a debilitating disease characterized by severe, unremitting cardiac pain,^{1,2} resistant to all conventional treatments for coronary artery disease (CAD).^{1,2} The mortality rate of patients living with RFA is not known but is thought to be in the range of approximately 3%.³ These individuals suffer severely impaired health-related quality of life (HRQL), with recurrent and sustained pain, poor general health status, psychological distress, impaired role functioning, activity restriction, and inability to self-manage.⁴⁻⁷ The global prevalence of RFA is increasing;^{1,2,8,9} available estimates suggest that RFA affects between 600,000 and 1.8 million people in the United States² with as many as 50,000 new cases each year, and 30,000-50,000 new cases per year in continental Europe.^{1,2,9} Canadian Community Health Survey (2000-2001) data (www.statcan.gc.ca) suggest that approximately 500,000 Canadians are living with unresolved angina. The proportion of these patients living with true RFA is not known.⁸ The incidence and prevalence of RFA will continue to rise as CADrelated survival rates increase and populations age.⁸⁻¹⁰

Effective care for the growing RFA population in Canada is critical. A number of patients have inadequate pain relief, revisit local hospital emergency departments, and undergo repeated investigations in coronary catheterization units.^{5,11-14} The potential cost implications are considerable. In the UK, direct costs of persistent anginal pain including prescriptions, repeated emergency department and other admissions, outpatient referrals, and procedures account for 1.3% of the total National Health Service expenditure.¹³ A more recent (2008) Ontario-based study conservatively estimated the annualized cost of angina-related disability from a societal perspective including direct, indirect, and system costs, at CAD\$19,209 per patient.¹⁴

These guidelines are predicated upon a 2009 Canadian Cardiovascular Society (CCS) Position Statement which identified that underlying the problem of RFA management is the lack of a formalized, coordinated, interprofessional strategy between the cardiovascular and pain science/clinical communities.¹⁵ The guidelines are therefore a joint initiative of the CCS and the Canadian Pain Society (CPS)¹⁵ and were developed using the

calcique et le blocage des récepteurs *β*-adrénergiques, les agents vasculoprotecteurs, les interventions coronariennes percutanées et le pontage aortocoronarien. Le taux de mortalité des patients vivant avec une APR n'est pas connu, mais est présumé se situer à environ 3 %. Ces individus souffrent sévèrement de leur qualité de vie liée à leur santé déficiente, dont une douleur récurrente et soutenue, un mauvais état de santé général, une détresse psychologique, un déficit de fonctionnement et une restriction d'activité. Au Canada, l'efficacité des soins offerts aux patients souffrant d'une APR est dramatiquement sous-développée. Ces lignes directrices s'appuient sur un énoncé de position de la Société canadienne de cardiologie (SCC) 2009 qui déterminait que le problème sous-jacent de la gestion de l'APR est le manque de stratégies interprofessionnelles, coordonnées et formalisées, entre les communautés clinique et scientifique dans les domaines cardiovasculaire et de la douleur. Les lignes directrices sont par conséquent une initiative conjointe de la SCC et de la Société canadienne de la douleur (SCD) et font des recommandations pratiques sur les options de traitement de l'APR qui sont basées sur les meilleures preuves disponibles. Des recommandations sont aussi faites, donnant une direction à la pratique clinique future et à la recherche sur la gestion de l'APR au Canada.

Grading of Recommendations, Assessment, Development, and Evaluation (GRADE)¹⁶⁻¹⁹ system of evidence evaluation, in order to make practice recommendations about treatment options for RFA that are based on the best available evidence.

Pathophysiology: Production and Persistence of Cardiac Pain

Most events that trigger anginal pain do so by changing myocardial oxygen demand; these triggers may be physical, emotional, or metabolic.²⁰ The beneficial effects of most conventional anti-anginal treatments may be explained through their ability to correct determinants of myocardial oxygen supply and demand. However, by definition, RFA patients are resistant to all conventional treatments for ischemia.¹⁵ In RFA, there is an important link between mechanisms of chronic/recurrent myocardial ischemia and the neuropathophysiology of persistent pain.¹⁵

Cardiac sensory receptors triggered by myocardial ischemia lead to a sympathoexcitatory reflex.²⁰ The biochemical stimuli for RFA pain are multi-factorial and analogous to the pain hypersensitivity seen in other forms of chronic tissue injury. Concentrations of bradykinin, adenosine, lactate, and potassium from ischemic damage to the myocardium are released in the effluent of the coronary sinus,²¹⁻²⁵ activating capsaicinsensitive transient receptor potential cation channel subfamily V member 1 (TRPV1) receptors, which serve as the primary transducer of the ischemic noxious stimulus.²² Neurochemicals, such as the neuropeptides substance P and calcitonin gene-related peptide, are also synthesized and released from the endings of cardiac afferents thereby augmenting adenosineprovoked pain.^{23,24,26,27} Cardiac primary afferents transmitting this noxious input ascend via multiple pathways including the spinothalamic tract and the spinoamygdaloid and spinohypothalamic pathways to neurons in cortical and subcortical areas of the brain that have somatic receptive fields in the chest, neck, and arms.²⁷ Cognitive appraisal of the stimulus occurs in the parietal cortex and anterior cingulate cortex.^{24,26} The noxious stimulus is assessed in these structures as threatening, causing activation of the bilateral prefrontal cortex and limbic system, leading to apprehension of further pain and fear for the future.^{1,24,26,28}

For patient assessment and management, it is important to recognize that there is often no clear relationship between the severity of one's anginal pain and the degree of ischemia,²⁷ as indicated by changes in objective diagnostic indicators such as stress electrocardiogram or serum levels of creatine kinase (CK) and CK-MB. As the 2002 European Society of Cardiology (ESC) Joint Study Group on RFA^1 and others^{24,26,28,29} have argued, RFA, like other types of pain, is not simply the endproduct of the linear transmission of a noxious stimulus. Increasing basic science and clinical evidence points in fact to the variability of cardiac pain, wherein pain may be experienced with minimal to no myocardial ischemia and, conversely, the majority of ischemic episodes are silent.^{24,26-29} Nociceptive processes arising in the periphery are modulated in the central nervous system by mechanisms that actively participate in the selection, abstraction, and synthesis of information from the total peripheral sensory input. The amount, quality, and nature of pain experienced are therefore dynamic and multidimensional products of sensory-discriminative, cognitive-evaluative, and affective-motivational components.³⁰ Recent discoveries related to the plasticity of the nervous system support neuronal modifiability as fundamental to, and chiefly responsible for, the experience of persistent pain.^{31,32}

Definition of RFA

Commensurate with the understanding that both ischemic and persistent pain mechanisms underlie the problem, the 2009 CCS position statement put forth the following definition of RFA, adapted from the 2002 ESC Joint Study Group definition:¹

Refractory angina is a persistent, painful 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/percutaneous interventions, and coronary bypass surgery. While the presence of reversible myocardial ischemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without this ischemia. Chronic is defined as persisting for more than 3 months.

Inclusion Criteria

These guidelines included systematic reviews, single randomized controlled trials (RCTs), and quasi-experimental and pre-post studies. Observational/descriptive, retrospective, and case studies did not meet our criteria for systematic review. We reviewed 3 classes of interventions including invasive, noninvasive, and pharmacologic therapies. Our specific outcomes were patient-centred, including chest pain, nitrate use, HRQL, morbidity (myocardial infarction [MI], heart transplant, cerebrovascular events, other cardiac events, and associated hospitalizations), exercise tolerance, and mortality.

Guidelines Development Process

A detailed description of our development process including search methods, consensus-building procedure, appraisal of methodologic quality, and data synthesis (meta-analysis) is available as a slide kit on the CCS Web site (http://www.ccs.ca/ consensus_conferences/cc_library_e.aspx).

Grading of Evidence and Practice Recommendations

The quality of the evidence that supports each practice recommendation was rated according to GRADE criteria¹⁶⁻¹⁹ as follows:

- **High:** Further research is very unlikely to change our confidence in the estimate of effect.
- **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- Very Low: Any estimate of effect is very uncertain.

Based on these evidence ratings, our practice recommendations made are either 'Strong' or 'Weak', according to the following operational definitions:

- **Strong:** The desirable effects of an intervention clearly outweigh the undesirable effects, or clearly do not.
- **Weak:** The trade-offs are less certain—either because of low-quality evidence or because evidence suggests that desirable and undesirable effects are closely balanced.

We also took into account key influencing factors, as outlined by Guyatt et al.,³³ including the quality of the available evidence, clinical insight into risks vs benefits of treatment options, patient values and preferences, and resource implications.

Establishing a Diagnosis of RFA and Ongoing Evaluation of Symptoms

Consistent with the definition of RFA employed in these guidelines, the presence of myocardial ischemia must first be established.¹⁵ A thorough evaluation of patients' cardiovascular status is required as well as a review of current pharmacotherapy to ensure maximally-tolerated and appropriate medical management; conventional revascularization procedures should also have been exhausted.^{1,25,34,35} In addition to standard CAD assessment, Table 1 lists originating sources of chest pain (as applicable) that should be ruled out to ensure a correct diagnosis of RFA.^{1,36-38}

Table 1. Sources of chest pain to be ruled out in diagnosing RFA

- Aortic dissection
- Aortic stenosis
- Anemia
- Cardiac syndrome X
- Costochondritis
- Dilated cardiomyopathy
- Gallbladder disease
- Hypertrophic cardiomyopathy
- Intercostal neuralgia
- Pancreatitis
- Peptic ulcer
- Pericarditis/pleuritis
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Pulmonary hypertension
- Esophageal spasmReflux esophagitis
- Thyrotoxicosis

RFA, refractory angina.

Review: Transmyocardial laser revascularization versus medical therapy for refractory angina Comparison: 1 Transmyocardial laser revascularization vs. medical treatment Outcome: 1 Angina reduction

Study or subgroup	Favours treatment n/N	Control n/N	Odds Ratio M-H, Fixed, 95% Cl	Weight	Odds Ratio M-H,Fixed,95% Cl
1 CCS score Allen 1999	58/132	45/143		57.0 %	1.71 [1.04, 2.79]
Burkhoff 1999	47/92	8/90		9.3 %	10.71 [4.65, 24.63]
Frazier 1999	44/91	23/101	-	26.5 %	3.17 [1.71, 5.91]
Jones 1999	29/43	0/43	+	0.4 %	177.00 [10.16, 3083.55]
Schofield 1999	18/94	3/94		5.7 %	7.18 [2.04, 25.32]
Subtotal (95% Cl) Total events: 196 (Favou Heterogeneity: Chi ² = 24 Test for overall effect: Z :	452 rs treatment), 79 (Contro .79, df = 4 (P = 0.0000) = 8.67 (P < 0.00001)	471 5); I ² =84%	•	99.0 %	3.95 [2.90, 5.39]
2 NYHA scale Aaberge 2000	19/49	0/49		0.7%	63.30 [3.69, 1086.76]
van der Sloot 2004	11/15	0/15		0.3%	79.22 [3.87, 1622.84]
Subtotal (95% CI) Total events: 30 (Favours Heterogeneity: Chi ² = 0.(Test for overall effect: Z :	64 s treatment), 0 (Control) D1, df = 1 (P = 0.91); I ² = 3.85 (P = 0.00012)	64 =0.0%	-	10%	68.32 [7.95, 587.38]
Total (95% Cl) Total events: 226 (Favou Heterogeneity: Chi ² = 34 Test for overall effect: Z :	516 rs treatment), 79 (Contro .41, df = 6 (P<0.00001) = 10.00 (P < 0.00001)	535)) ; ² =83%	•	100.0 %	4.63 [3.43, 6.25]
		0.0 Favours control	001 0.01 0.1 1 10 100 Favours treatmen	1000 t	

Figure 1. Comparison of transmyocardial laser revascularization vs medical treatment, outcome Canadian Cardiovascular Society (CCS) class. Cl, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel; NYHA, New York Heart Association. Reproduced from Briones et al.⁴⁹ Copyright © 2009 Cochrane Collaboration, reproduced with permission.

Once a baseline diagnosis of RFA is established, ongoing assessment of symptoms and functional ability is needed. This should include re-examination of CCS class,³⁹ as well as comprehensive pain assessment including pain history, intensity, qualities, impact on mood, interference with everyday activities, and effectiveness of current treatments for symptom relief.⁴⁰ Like all other types of pain, cardiac pain arising from RFA is a complex, subjective experience with sensory-discriminative, motivationalaffective, and cognitive-evaluative components. Each of these dimensions, subserved by specialized systems in the brain (ie, spinal, limbic, reticular, neocortical), contribute to the overall patient experience of pain (and related individual response) and should therefore be addressed as part of routine assessment.⁴¹

Invasive Therapies

Transmyocardial laser revascularization

Transmyocardial laser revascularization (TMLR) is a surgical treatment, developed in the 1980s,⁴² aimed at reducing anginal symptoms through the creation of transmural channels via a CO_2 , holmium yttrium-aluminum-garnet (Ho:YAG), or XeCL excimer lasers.⁴³⁻⁴⁸ By way of thoracotomy or sternotomy, laser energy is directed to the epicardial surface of the left ventricle in order create a series of transmural channels in targeted regions of viable myocardium; a variety of protocols have been used that vary with respect to laser system, number of channels created, and levels of energy delivered.

In a recent Cochrane Review, Briones et al.⁴⁹ reviewed the results of 7 RCTs published between 1999 and 2004 including 1137 patients in total; 559 were randomly allocated to the TMLR

group. A CO₂ laser was used in 3 studies, $^{45-47}$ a Ho:YAG laser was used in another 3 studies, 43,50,51 and a single study used a XeCL excimer laser. 52 Operative procedures were similar across trials. 49

This meta-analysis found that TMLR significantly reduced angina by at least 2 CCS classes for 43% of patients treated (n = 240) (odds ratio [OR] = 4.63; 95% confidence interval [CI], 3.43-6.25; P < 0.001) (Fig. 1), representing a clinically meaningful reduction in RFA symptoms.

Impact of TMLR on HRQL was measured using the disease-specific Seattle Angina Questionnaire (SAQ).⁵³ A weighted mean difference of 13.10 (95% CI, 6.82-19.38; P <0.001) for the SAQ-physical limitation subscale was found, suggesting significant improvement in physical limitation for the treatment group (Fig. 2). Despite this improvement in physical limitation, the meta-analysis found no significant improvement in exercise tolerance, however only two studies (n = 129) were amenable to statistical pooling (Fig. 3).

Thirty-day mortality after TMLR was found to be 4% and 3.5% for treatment and control groups respectively, based on intention-to-treat (ITT) analyses.⁴⁹ However, there was almost a 4-fold increase in early postoperative mortality for the treatment group when patients were analyzed as treated, taking into account patient crossovers (OR 3.76; 95% CI, 1.63-8.66) (Fig. 4).⁴⁹ Briones et al.⁴⁹ therefore argued that the clinical benefits of TMLR do not outweigh the potential risks.

Quality of evidence according to GRADE

The Cochrane Review was of high methodological quality, employing comprehensive search methods and risk of bias assessment as well as robust meta-analytic techniques. We rate the quality of the available evidence as high (Table 2).

Study or subgroup	Treatment N	Mean(SD)	Control N	Mean(SD)		Mean IV,Fip	n Difference ced,95% Cl	Weight	Mean Difference IV,Fixed,95% CI
Frazier 1999 van der Sloot 2004	93 14	51 (25) 52.1 (30.4)	99 15	39 (21) 26.7 (29.7)				91.8 %	12.00 [5.45, 18.55] 25.40 [3.50, 47.30]
Total (95% Cl) Heterogeneity: Chi ² = 1.3 Test for overall effect: Z =	107 2, df = 1 (P = 4.09 (P = 0.0	0.25); l² =24% 00043)	114				•	100.0 %	13.10 [6.82, 19.38]
					-50	-25	0 2	5 50	
				Favours treatmen	t		Eavou	's control	

Review: Transmyocardial laser revascularization versus medical therapy for refractory angina Comparison: 1 Transmyocardial laser revascularization vs. medical treatment Outcome: 8 Seattle Angina Questionnaire - physical limitation

Figure 2. Comparison of transmyocardial laser revascularization vs medical treatment, outcome Seattle Angina Questionnaire-physical limitation. CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation. Reproduced from Briones et al.⁴⁹ Copyright © 2009 Cochrane Collaboration, reproduced with permission.

RECOMMENDATION

Despite some observed improvements in pain and physical limitations, TMLR is associated with significant early postoperative mortality risk and is not recommended (Strong Recommendation, High-Quality Evidence).

Values and preferences. This recommendation places a high value on patient safety, recognizing that some patients still undergo TMLR, where available (ie, international centres).

Percutaneous myocardial laser revascularization

Percutaneous myocardial laser revascularization (PMLR) therapy emerged as a treatment option for RFA in the 1990's as an alternative to TMLR.⁵⁴ A major impetus for adopting PMLR was the elimination of the incumbent risks of sternotomy and/or left anterior thoracotomy required for the TMLR procedure.^{52,55,56} PMLR entails the application of Ho:YAG laser energy to the endocardial surface of the left ventricle via a flexible catheter; laser firing is synchronized during systole to create a series of nontransmural channels in targeted regions with reversible ischemia.^{52,55} Proposed mechanisms of action include direct perfusion, ⁵⁷⁻⁵⁹ microvascular angiogenesis, ⁶⁰⁻⁶³ and cardiac afferent denervation, however evidence is contradictory.⁶⁴⁻⁶⁷

Symptom relief, improvements in exercise duration, HRQL, and safety have been reported in several RCTs.^{55,56,68-73} In a recent systemic review,⁶⁰ we meta-analyzed the data from 5 of 7 available RCTs^{55,56,68-73} of PMLR that were published between 2001 and 2006 including 1213 patients in total; 651 were randomly allocated to the PMLR group.⁵⁴ Our analyses⁵⁴ found that PMLR significantly reduced angina by at least 2 CCS classes (pooled OR 2.13; 95% CI, 1.22-3.73; P = 0.008) (Fig. 5), representing a clinically meaningful reduction in RFA symptoms. Impact of PMLR on HROL was measured using the SAQ, and a small difference^{74,75} in the positive impact of PMLR plus maximal medical therapy (ie, treatment) vs maximal medical therapy alone (ie, control) was found (Figs. 6-10).⁵⁴ The clinical significance of these findings is uncertain. Nonetheless, coupled with the improvements found in CCS class, they are encouraging considering the high levels of perceived psychological burden and related disability associated with unrelieved CCS class III-IV angina symptoms.

With respect to exercise performance, extractable data were combined from 3 trials,^{68,70,76} each with different approaches to measurement including the modified Bruce protocol,⁷² the Naughton protocol,⁶⁸ and treadmill or bicycle ergometry. We found that PMLR did not significantly improve exercise performance, perhaps due to inconsistent exercise protocols (Fig. 11).⁵⁴ We also found that PMLR had no significant impact on all-cause mortality (Fig. 12).⁵⁴ The available data seem to suggest that PMLR is as effective as TMLR and that it poses less

Review: Transmyocardial laser revascularization versus medical therapy for refractory angina Comparison: 1 Transmyocardial laser revascularization vs. medical treatment Outcome: 7 Exercise tolerance

Mean Difference Study or subgroup Treatment Control Mean Difference Weight Mean(SD) Mean(SD) IV, Fixed, 95% CI IV, Fixed, 95% CI Aaberge 2000 50 457 (152) 50 444 (191) 80.0% 13.00 [-54.66, 80.66] van der Sloot 2004 14 519 (157) 15 445 (212) 20.0 % 74.00 [-61.18, 209.18] 100.0 % 25.22 [-35.28, 85.72] 65 -200 -100 100 200 Favours treatment Favours control

Figure 3. Comparison of transmyocardial laser revascularization vs medical treatment, outcome exercise tolerance. CI, confidence interval; df, degree of freedom; IV, inverse variance; SD, standard deviation. Reproduced from Briones et al.⁴⁹ Copyright © 2009 Cochrane Collaboration, reproduced with permission.

Review: Transmyocardial laser revascularization versus medical therapy for refractory angina Comparison: 1 Transmyocardial laser revascularization vs. medical treatment Outcome: 6 Early postoperative mortality (as treated)

Study or subgroup	Treatment n/N	Control n/N	Odds Ratio M - H, Fixed, 95% Cl	Weight	Odds Ratio M - H, Fixed, 95% Cl
Aaberge 2000	2/50	0/50		6.2%	5.21 [0.24, 111.24]
Allen 1999	11/178	2/97		31.7 %	3.13 [0.68, 14.41]
Burkhoff 1999	1/92	0/90		6.5 %	2.97 [0.12, 73.80]
Frazier 1999	12/151	2/41		37.8 %	1.68 [0.36, 7.84]
Jones 1999	5/43	0/43		- 5.7 %	12.43 [0.67, 232.14]
Schofield 1999	5/94	0/94		- 6.2 %	11.61 [0.63, 213.09]
van der Sloot 2004	1/15	0/15		5.9 %	3.21 [0.12, 85.20]
Total (95% Cl) Total events: 37 (Treatmer Heterogeneity: Chi ² = 2.3' Test for overall effect: Z =	623 nt), 4 (Control) 9, df = 6 (P = 0.88); I ² = 3.11 (P = 0.0019)	430	•	100.0 %	3.76 [1.63, 8.66]
	F	0.00) avours treatment	2 0.1 1 10 Favours co	500	

Figure 4. Comparison of transmyocardial laser revascularization vs medical treatment, outcome early postoperative mortality (as treated). CI, confidence interval; df, degree of freedom; M-H, Mantel-Haenszel. Reproduced from Briones et al.⁴⁹ Copyright © 2009 Cochrane Collaboration, reproduced with permission.

risk, but this could not be concluded definitively. Lack of detailed reporting on mortality vs adverse events in some trials necessitated an examination of all-cause mortality. The validity of this end point as a proxy for the safety of PMLR is uncertain. The incidence and severity of periprocedural risks (eg, pericardial effusion and hematoma, tamponade, and left ventricular and coronary perforation) during PMLR (vs TMLR) should also be examined for a more comprehensive assessment of safety.

Quality of evidence according to GRADE

The methodological quality of the 5 trials was found to range from moderate^{68,73} to high,^{55,70,71,72} with 5 trials blinding outcome assessors, 4 trials blinding participants, and 3 trials blinding

Table 2. Quality of evidence according to GRADE

PMLR operators and other clinicians involved. Although most trials were of good to excellent methodological quality, variations in laser dose across trials produced inconsistent results. We rate the quality of the available evidence as moderate (see Table 2).

RECOMMENDATION

PMLR may be considered for reduction in the perceived severity of angina pain symptoms (Weak Recommendation, Moderate-Quality Evidence).

PMLR may be considered for improvement in aspects of HRQL (Weak Recommendation, Moderate-Quality Evidence).

	High	Moderate	Low	Very low	Unable to evaluate
TMLR	•				
PMLR		•			
SCS		•			
EECP			•		
SMT		•			
TCS*					•
HTEA*					•
ETS*					•
Allopurinol [†]				•	
Ranolazine [†]		•			
Trimetazidine [†]				•	
Nicorandil [†]				•	
Ivabradine [†]		•			
Intermittent thrombolysis [†]				•	
Shock wave therapy*					•
Coronary sinus reducer*					•
Myocardial cryotherapy*					•

EECP, enhanced external counter-pulsation; ETS, endoscopic transthoracic sympathectomy; GRADE, Grading of Recommendations, Assessment, Development, and Evaluation; HTEA, high thoracic epidual analgesia; PMLR, percutaneous laser revascularization; RFA, refractory angina; SCS, spinal cord stimulation; SMT, self-management training; TCS, temporary cardiac sympathectomy; TMLR, transmyocardial laser revascularization.

* Existing evidence does not meet criteria for inclusion; limited to case reports and observational studies.

[†]Shows promise; more RFA-specific evidence needed.

	Experime	Experimental Control				Odds Ratio	Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Leon 2005 (LD)	47	98	42	102	37.9%	1.32 [0.75, 2.30]	
Salem 2004	14	39	6	40	18.4%	3.17 [1.07, 9.41]	
Whitlow 2003	90	164	51	166	43.7%	2.74 [1.75, 4.30]	
Total (95% Cl)		301		308	100.0%	2.13 [1.22, 3.73]	•
Total events	151		99				
Heterogeneity: Tau ² = 0	0.13; Chi² =	= 4.57, d	lf = 2 (P =				
Test for overall effect: Z = 2.66 (P = 0.008)							Favours control Favours treatment

Figure 5. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Canadian Cardiovascular Society class. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al., ⁵⁴ © 2010, with permission from Dove Medical Press Ltd.

PMLR is not associated with significant increase in allcause mortality compared with medical management up to 1 year post intervention (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations recognize that some patients may choose to pursue PMLR, where available (ie, international centres) and balance improvement in symptoms and aspects of HRQL with procedural risk.

Spinal cord stimulation

Spinal cord stimulation (SCS) is a minimally invasive therapy that involves application of electrical current to the dorsal columns of the spinal cord with the goal of reducing angina.⁷⁶⁻⁷⁸ Electrodes are implanted into the epidural space at the level which induces bilateral paresthesia across the chest, typically between C7 and T4. The electrodes are attached to an implanted pulse generator; treatment may be intermittent or continuous as required using a patient-controlled programmer. Complications reported include lead dislodgement, electrode fracture, and subcutaneous infections. Periprocedural complications are rare as the electrodes are inserted percutaneously.^{77,79} Treatment is not suitable for patients who have diseases of the spinal column or have cognitive impairment precluding safe use of an external programming device. SCS

produces anti-ischemic effects in addition to analgesic effects.^{1,80} Pain is modulated by selective stimulation of the inhibitory afferent fibres in the posterior horns of the spinal cord.⁷⁹ Treatment does not mask myocardial ischemia.⁷⁹

Taylor et al.⁸¹ meta-analyzed the results of 7 RCTs published between 1998 and 2008 including 270 RFA patients in total; 162 were randomly allocated to the SCS group. Key outcomes included angina symptoms, HRQL, ischemic burden, exercise capacity, and adverse events.⁸¹ SCS was compared with no SCS controls,⁸²⁻⁸⁶ coronary artery bypass grafting,⁸⁷ and PMLR.⁸⁸ Follow-up periods ranged from 48 hours⁸⁹ to 5 years.⁹⁰

Taylor et al.⁸¹ reported a pooled standardized mean difference (SMD) of 0.76 (95% CI, 0.07-1.46; P = 0.03) with respect to exercise capacity, indicating a significant improvement for those allocated to SCS (Fig. 13). HRQL, as measured by aggregate scores, was also significantly improved (SMD 0.83; 95% CI, 0.32-1.34; P = 0.001) (Fig. 14). Low complication rates including infection (1%) and lead displacement or fracture (7%) were reported across trials.

Quality of evidence according to GRADE

While the investigators⁸¹ were comprehensive in their search methods, selection of studies, and statistical methods, limited reporting of methodological details across primary trials hampered risk of bias assessment. Some methodological problems included lack of clarity about allocation concealment



Figure 6. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Seattle Angina Questionnaireangina frequency. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al.,⁵⁴ © 2010, with permission from Dove Medical Press Ltd.



Figure 7. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Seattle Angina Questionnairedisease perception. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al.,⁵⁴ © 2010, with permission from Dove Medical Press Ltd.

and lack of blinding. The overall quality of the available evidence is moderate (Table 2).

RECOMMENDATION

SCS may be considered for improving exercise capacity (Weak Recommendation, Moderate-Quality Evidence).

SCS may be considered for improving HRQL (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the results of multiple RCTs and a metaanalysis reporting significant improvements in exercise capacity and HRQL outcomes.

Additional invasive therapies

Three additional invasive therapies, used in some practices, were examined including temporary cardiac sympathectomy, ⁹¹⁻⁹³ high thoracic epidural analgesia, ⁹⁴⁻⁹⁸ and endoscopic transthoracic sympathectomy. ⁹⁹⁻¹⁰² The evidence for these therapies is limited to descriptive studies and case reports and was therefore not evaluated; no practice recommendations can be made at this time (Table 2).

Noninvasive Therapies

Enhanced external counter-pulsation

Enhanced external counter-pulsation (EECP) is a noninvasive therapy that employs the application of compressive cuffs to the calves, lower thighs, and upper thighs. The cuffs are synchronized to inflate in a distal to proximal sequence during

early diastole and to simultaneously deflate at the onset of systole.103,104 The hemodynamic effect of the treatment augments diastolic pressure, presumably resulting in increased coronary perfusion during cuff inflation.105 The rapid cuff deflation immediately before systole decreases systemic vascular resistance and cardiac workload. A typical treatment course consists of 1- to 2-hour sessions over several weeks, for a total of 35 hours of treatment.¹⁰⁵ Proposed mechanisms of action have included increased coronary perfusion resulting in increased collateralization, angiogenesis, and improved endothelial function as a result of treatment-induced shear stress.¹⁰⁶⁻¹¹¹ A more recent study supports that EECP has beneficial effects on peripheral artery flow-mediated dilation and endothelial-derived vasoactive agents.¹¹² EECP is contraindicated for persons with arrhythmias that interfere with the device triggering mechanism, bleeding diathesis, active thrombophlebitis, peripheral vascular disease, aortic aneurysm, or aortic stenosis, uncontrolled hypertension (ie, 180/110), severe lower extremity arterial-occlusive disease, uncontrolled congestive heart failure, and pregnancy.¹⁰⁵

A Cochrane Review by Amin et al.¹¹³ identified 1 RCT of EECP including 139 patients in total (the **Mu**lticenter **St**udy of **E**nhanced External Counterpulsation [MUST-EECP] trial).¹¹⁴ Seventy-two patients were randomized to EECP; controls (n = 72) received 'sham' EECP, consisting of inactive counter-pulsation treatments. Key outcomes included self-reported HRQL, angina frequency, nitrate use, and exercise treadmill test (exercise duration and time to \geq 1-mm ST-segment depression) 1 week post-treatment. Eighty-six percent of participants were male with baseline symptom severity ranging from CCS class I-III.¹¹⁴ An additional 7 pre-post observa-



Figure 8. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Seattle Angina Questionnairephysical limitation. Cl, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al.,⁵⁴ © 2010, with permission from Dove Medical Press Ltd.

	Exp	eriment	ntal Control					Std. Mean Difference	Std. Mean Difference				
Study or Subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI		IV, Rai	ndom, 95	i% Cl	
Leon 2005 (LD)	30.3	30.64	98	26.6	30.15	102	72.0%	0.12 [-0.16, 0.40]			-		
Salem 2004	20	24.27	39	16	23.72	39	28.0%	0.17 [-0.28, 0.61]				-	
Total (95% CI)			137			141	100.0%	0.13 [-0.10, 0.37]			•		
Heterogeneity: Tau ² = 0.00; Chi ² = 0.03, df = 1 (P = 0.87); l ² = 0%									<u> </u>	1			<u> </u>
Test for overall effect: Z = 1.11 (P = 0.27)								Favou	rs cont	rol Favo	ours treat	ment	

Figure 9. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Seattle Angina Questionnaireangina severity. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al.,⁵⁴ © 2010, with permission from Dove Medical Press Ltd.

tional studies,^{103,115-125} including 313 patients in total, were reviewed. Although an EECP registry exists, the International EECP Patient Registry (IEPR), it did not meet our inclusion criteria for scientific rigour.

The MUST-EECP trial¹¹⁴ found that active EECP (compared with sham treatment) significantly improved 3 of 9 parameters of self-reported HRQL. However, response rates were poor (54%) and skewed toward the sham EECP group. ITT analysis found no significant differences between groups with respect to change in angina counts, frequency of nitroglycerine usage, or exercise duration.¹⁰⁵ There was a statistically significant 38-second difference between groups in the change in time to exercise-induced ischemia, favouring the active EECP group.^{105,113} Minor adverse events (eg, skin abrasions, and leg and back pain) related to EECP were reported by 55% of the treatment group, compared with 20% in the sham group.¹¹⁴

We meta-analyzed the additional 7 pre-post observational studies, $^{103,115-120}$ where statistical pooling was possible, by outcome. Sample sizes ranged from 25 to 61. Across studies, follow-up periods varied from immediate post-treatment $^{116-118}$ to 1 year, $^{115,120-122}$ CCS class varied from class I to IV. The pooled proportion of patients experiencing a CCS class change of 1 or more (2 studies, n = 86) 118,123 was found to be 45.5% (95% CI, 31.9-61.6) at 12-month follow-up. A small, significant improvement in anginal stability, as measured by the SAQ (2 studies, n = 87), 115,117 was also found (SMD -0.34; 95% CI, -0.65 to -0.02; P = 0.04) (Fig. 15).

Quality of evidence according to GRADE

The MUST-EECP trial¹¹⁴ is of poor methodological quality, with problems that include incomplete reporting,

significant loss to follow-up, unclear blinding of outcome assessment, and lack of ITT analysis principles.¹¹³ Similar methodological problems were noted among the pre-post studies we reviewed. We rate the overall quality of the evidence as low (Table 2).

RECOMMENDATION

EECP may be considered for improvements in aspects of HRQL (Weak Recommendation, Low-Quality Evidence).

EECP may be considered for improvement in severity of angina symptoms (Weak Recommendation, Low-Quality Evidence).

Values and preferences. These recommendations place a high value on the decision of individual patients to pursue symptom relief and improvements in HRQL outcomes.

Cognitive-behavioural self-management interventions

Cognitive-behavioural self-management interventions are multi-modal treatment packages that employ learning materials and cognitive-behavioural strategies to achieve changes in knowledge and behaviour for effective disease self-management.¹²⁴ They target day-to-day problems that patients encounter such as angina pain, fatigue, decreased mobility and endurance, anxiety, and stress.¹²⁴ Patients are taught several symptom self-management techniques including safe exercise habits, energy conservation, pacing and sleep quality enhancement, and communication and decision-making skills. A sound underpinning in social, cognitive and/or behavioural theories is critical to the success of self-management programs.¹²⁴⁻¹³¹



Figure 10. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome Seattle Angina Questionnairetreatment satisfaction. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al.,⁵⁴ © 2010, with permission from Dove Medical Press Ltd.



Figure 11. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome exercise performance. CI, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al., ⁵⁴ © 2010, with permission from Dove Medical Press Ltd.

A meta-analysis by McGillion et al.¹³² pooled the results of 7 RCTs of self-management programs for chronic angina-including RFA-involving 949 patients in total. Outcomes examined included angina frequency and duration, sublingual (SL) nitroglycerine use, HRQL, and aspects of psychological well-being including anxiety and depression.¹³² Six trials^{125,133-137} tested small-group self-management interventions (6-15 patients); intervention duration, format, and process varied. The authors found that selfmanagement training resulted in approximately 3 fewer angina episodes per week (delta [Δ] = -2.85; 95% CI, -4.04to -1.66) (Fig. 16).¹³² This was accompanied by a decrease in weekly SL nitrate usage ($\Delta = -3.69$; 95% CI, -5.50 to -1.89) (Fig. 17).¹³² Significant HRQL improvements, as measured by the SAQ, were also found (Figs. 18 and 19).¹³² No pooled estimate of the effect on psychological well-being was generated due to heterogeneity of measures.

Quality of evidence according to GRADE

Most trials had small samples and adequacy of random allocation concealment and blinding was varied.¹³² We rate the overall methodological quality of the evidence as moderate (Table 2).

RECOMMENDATION

Self-management training may be considered for reduction in angina pain symptoms and related use of SL nitrates (Weak Recommendation, Moderate-Quality Evidence).

Self-management training may be considered for improvements in HRQL (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on addressing cognitive and behavioural responses to improve symptoms and HRQL outcomes.

Pharmacologic Therapies

Level of access in Canada to pharmacologic therapies reviewed varies (eg, widely available, approved for use in clinical trials, not available). Readers are referred to the Health Canada Drug Product Database (http://www.hc-sc.gc.ca/dhp-mps/ prodpharma/databasdon/index-eng.php) for drug availability status and related information.

	Experimental Control		ol		Odds Ratio	Odds Ratio		
Study or Subgroup	Events	Total	Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	
Leon 2005 (LD)	4	98	5	102	21.0%	0.83 [0.22, 3.17]		
Oesterle 2000	8	92	3	99	20.6%	3.05 [0.78, 11.86]		
Salem 2004	0	39	1	40	3.6%	0.33 [0.01, 8.43]	←	
Whitlow 2003	13	164	11	166	54.7%	1.21 [0.53, 2.79]		
Total (95% CI)		393		407	100.0%	1.29 [0.70, 2.39]	•	
Total events	25		20					
Heterogeneity: Tau ² = 0								
Test for overall effect: 2	Favours control Favours treatment							

Figure 12. Comparison of percutaneous myocardial laser revascularization vs maximal medical therapy, outcome all-cause mortality. Cl, confidence interval; df, degree of freedom; IV, inverse variance; LD, low dose; SD, standard deviation. Reprinted from McGillion et al., ⁵⁴ © 2010, with permission from Dove Medical Press Ltd.



Favours control Favours SCS

Figure 13. Comparison of SCS vs controls, outcome exercise capacity, between-group difference. CABG, coronary artery bypass grafting; CI, confidence interval; df, degree of freedom; ESBY, **E**lectrical **S**timulation vs Coronary Artery **B**ypass Surgery in Severe Angina Pectoris study; IV, inverse variance; PMR, percutaneous myocardial laser revascularization; SCS, spinal cord stimulation; SD, standard deviation; SPiRiT, Spinal Cord Stimulation vs Percutaneous Myocardial Laser Revascularization in Patients With Refractory Angina Pectoris Trial. Reproduced from Taylor et al.⁸¹ with permission granted under BioMed Central's general open access terms. © 2009 Taylor et al; licensee BioMed Central Ltd.

Metabolic agents

Allopurinol. Allopurinol inhibits xanthine oxidase, the enzyme that catalyses the transformation of hypoxanthine into xantine and uric acid. Allopurinol has generated growing interest due to a series of retrospective clinical observations which have suggested that it could improve the mechano-energetic uncoupling of the failing myocardium.¹³⁸ How allopurinol reduces myocardial ischemia is not entirely clear. At least 2 mechanisms of action have been proposed. Xanthine oxidase is a main source of the reactive oxygen species responsible for the oxidative stress occurring in the ischemic myocardium. By inhibiting xanthine oxidase, allopurinol reduces the oxygen wastage caused by the oxidative stress and may therefore increase the molecular oxygen available to transform fatty acids and pyruvate into energy in the ischemic myocytes. The global antioxidant effect of allopurinol could improve the endothelial dysfunction known to compromise the vasore-activity of coronary arteries.¹³⁹ While encouraging, the anti-ischemic effect of allopurinol awaits validation in larger, independent trials. Likewise, whether allopurinol will be efficient for optimally medicated patients with advanced CAD and RFA remains to be seen.

A recent trial by Noman et al. suggested that allopurinol could relieve myocardial ischemia and improve time to ST-segment depression in patients with chronic stable angina (n = 65).¹⁴⁰ Most of the patients were treated with at least a β -blocker (87%) and 1 additional anti-anginal medication, such as oral nitrate (48%), calcium channel blockers (22%), or nicorandil (22%).¹⁴⁰ Interestingly, patients treated with allopurinol showed an improved double-product at the peak of the stress test, suggesting indeed that allopurinol reduced myocardial ischemia independently of the usual chronotropic and vasodilatory mechanisms seen with more traditional anti-anginal medications. As noted by the authors, allopurinol had an anti-ischemic effect

size similar to other anti-anginal agents, such as amlodipine (+ 36 seconds), nitrates (+60 seconds) or β -blockers (+50 seconds).¹⁴⁰ No adverse effects were reported. Results of this RCT are promising but their applicability to those with true RFA is unclear. Additional work is also needed to corroborate the observed anti-ischemic effects of allopurinol.

Quality of evidence according to GRADE. The anti-ischemic effects of allopurinol require validation and the applicability of the current evidence to RFA patients is uncertain. Pilot trials to date are also small. Therefore (in the context of RFA), we rate the overall quality of the evidence as very low (Table 2).

RECOMMENDATION

More robust RCTs are needed before allopurinol can be recommended as an anti-anginal agent for RFA patients (Strong Recommendation, Very Low-Quality Evidence).

Values and preferences. This recommendation recognizes the potential benefits of allopurinol and the need for high-quality, RFA-specific evidence to support future practice recommendations.

Ranolazine. Ranolazine is the first molecule approved by the United States Food and Drug Administration in 2 decades for the treatment of stable angina, but not RFA specifically. Ranolazine is believed to exert an anti-anginal effect by partially inhibiting the late sodium current (l_{Na+}). During myocardial ischemia, defective trans-cellular sodium currents would lead to sodium overload if it was not for the Na⁺/Ca⁺⁺ exchanger that maintains ionic homeostasis. The sodium expelled outside the cell via the exchanger leads in return to a calcium overload. The abnormal calcium con-

McGillion et al. Joint CCS/CPS RFA Guidelines



Figure 14. Comparison of SCS vs controls, outcome health-related quality of life, between-group difference. Based on NHP Part 1 score for ESBY 1993;⁸⁷ SF-36 physical health scale at 2 years for SPiRiT 2006;⁸⁸ ADL score for DeJongste 1994,⁸⁶ EQ-5D VAS score for Eddicks 2007;⁸³ LASA score for Hautvast 1998.⁸⁵ ADL, Activities of Daily Living; CABG, coronary artery bypass grafting; CI, confidence interval; df, degree of freedom; EQ-5D VAS, EuroQol 5 Dimensions Visual Analogue Scale; ESBY, Electrical Stimulation vs Coronary Artery Bypass Surgery in Severe Angina Pectoris study; IV, inverse variance; LASA, Linear Analogue Self-Assessment; NPH, Nottingham Health Profile; PMR, percutaneous myocardial laser revascularization; SCS, spinal cord stimulation; SD, standard deviation; SF-36, Medical Outcomes Study Short Form-36; SPiRiT, Spinal Cord Stimulation vs Percutaneous Myocardial Laser Revascularization in Patients With Refractory Angina Pectoris Trial. Reproduced from Taylor et al.⁸¹ with permission granted under BioMed Central's general open access terms. © 2009 Taylor et al; licensee BioMed Central Ltd.

centration impairs the myocardial contraction-relaxation coupling, leading to relaxation abnormalities and reduced endocardial perfusion.

In the Combination Assessment of Ranolazine in Stable Angina (CARISA) trial, the combination of ranolazine with either atenolol, diltiazem, or amlodipine significantly improved the time to 1 mm ST-segment depression and the total exercise time during stress testing.^{141,142} The CARISA trial was followed by the Efficacy of Ranolazine in Chronic Angina (ERICA) trial to determine whether ranolazine improves angina in stable coronary patients with persisting symptoms despite maximum therapy with 1 of the agents listed above.¹⁴³ Though the participants in CARISA were not strictly defined as RFA patients, their characteristics in terms of unrelenting angina despite best available treatment suggest that they closely resemble the definition of RFA proposed in these guidelines. In ERICA, patients had to remain symptomatic (more than 3 anginal attacks per week) despite optimal dose of amlodipine (10 mg daily). Over a course of 6 weeks, the addition of ranolazine 1000 mg twice daily to amlodipine was superior to the matching placebo at reducing the weekly frequency of angina episodes (2.88 \pm 0.19 episodes vs 3.31 \pm 0.22 episodes, respectively; P = 0.03) and of nitroglycerin caps administration (2.03 \pm 0.20 caps vs 2.68 \pm 0.22, respectively; P = 0.01).¹⁴³ Ranolazine appears to be safe and generally well tolerated;¹⁴⁴ fewer than 10% of



Figure 15. Enhanced external counter-pulsation: comparison of pre- vs post-treatment, outcome Seattle Angina Questionnaire-anginal stability. CI, confidence interval; df, degree of freedom; IV, inverse variance; SE, standard error.



Figure 16. Comparison of self-management training with controls, outcome frequency of angina episodes per week. CI, confidence interval. Modified and reproduced from McGillion et al.¹³² with permission from Bentham Science Publishers Ltd. © 2008 Bentham Science Publishers Ltd.

the patients discontinued ranolazine because of adverse events.¹⁴⁵ Clinically, ranolazine can improve myocardial ischemia without affecting heart rate or blood pressure. Its unique mode of action makes it a potentially useful agent for the care of patients with persistent symptoms despite optimal doses of β -blockers, calcium agonists, or nitrates, especially when patients are limited by bradycardia and orthostatic hypotension. However, the use of ranolazine in a population of optimally medicated patients with advanced CAD has not been sufficiently studied; the applicability of findings to RFA patients is therefore unknown.

Quality of evidence according to GRADE. The current evidence demonstrates that ranolazine appears to be an effective antianginal agent in patients with stable CAD. However, the ERICA trial was limited to short-term follow up (ie, 6 weeks) and the use of amlodipine alone in combination with ranolazine. More trials are needed to further examine the effectiveness of ranolazine in combination with clinically relevant, maximally-tolerated combination medical therapy for patients with advanced CAD and a confirmed diagnosis of RFA. We therefore rate the overall quality of the evidence as moderate (Table 2).

RECOMMENDATION

Robust RCTs focused on patients with RFA are needed before ranolazine can be recommended definitively as an anti-anginal agent (Strong Recommendation, Moderate-Quality Evidence).

Ranolazine may hold promise for reduction in angina symptoms, particularly for those patients who cannot tolerate upward titration of conventional anti-anginal agents due to depressive effects on heart rate and blood pressure (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. The recommendations place a high value on the need for high-quality, RFA-specific evidence to support future practice recommendations, as well as the potential benefit of ranolazine to reduce angina symptoms, particularly among those who cannot tolerate upward titration of conventional anti-anginal agents.



Trimetazidine. Trimetazidine is an anti-ischemic metabolic agent that stimulates myocardial glucose consumption through

Figure 17. Comparison of self-management training with controls, outcome sublingual nitrate usages per week. CI, confidence interval. Modified and reproduced from McGillion et al.¹³² with permission from Bentham Science Publishers Ltd. © 2008 Bentham Science Publishers Ltd.



Figure 18. Comparison of self-management training with controls, outcome Seattle Angina Questionnaire-physical limitation. CI, confidence interval. Modified and reproduced from McGillion et al.¹³² with permission from Bentham Science Publishers Ltd. © 2008 Bentham Science Publishers Ltd.

inhibition of fatty acid metabolism.¹⁴⁶⁻¹⁴⁸ Trimetazidine inhibits reduction of intracellular adenosine triphosphate levels via conservation of cellular metabolism in ischemic regions. Such inhibition facilitates performance of ionic pumps, flow of transmembranous sodium-potassium, and ongoing cellular homeostasis. Recommended dosing of trimetazidine includes 20 mg 3 times daily; a 30 mg modified-release formulation is also available in some countries for twice-daily dosing. Contraindications include pregnancy, breastfeeding, and history of allergy. No known drug interactions have been reported.

In a Cochrane Review, Ciapponi et al.¹⁴⁹ meta-analyzed the results of 23 RCTs published between 1967 and 2003 including 1378 patients in total. Trimetazidine was either administered as monotherapy (11 studies), compared with placebo (8 studies), or compared with another anti-anginal drug (3 studies). In an additional 13 studies, trimetazidine was examined as combination therapy vs placebo (11 studies), isosorbide mononitrate (1 study), and isosorbide dinitrate (1 study). Methodological quality of the studies ranged from good to poor.¹⁴⁹ The trial with the highest noted overall methodological quality (ie, allocation concealment, double blinding, losses to followup, and blinding of outcome assessment)¹⁵⁰ did not analyze outcomes according to ITT principles.

With respect to symptoms, trimetazidine as compared with placebo significantly reduced the frequency of weekly angina episodes by approximately 1 episode per week (SMD -1.44; 95% CI, -2.10 to 00.79; P < 0.0001). SL nitrate consumption was similarly reduced (SMD -1.47; 95% CI, -2.20 to -0.73; P < 0.0001), yet significant statistical heterogeneity was detected for this outcome (I^2 47.5%; P =0.05). Time to 1-mm ST-segment depression was also significantly increased (SMD 0.32; 95% CI, 0.15-0.48; P =0.0002). Despite some positive findings, the review found a lack of clear data on mortality, cardiovascular events, and quality of life outcomes.¹⁴⁹

The available data to date suggest that trimetazidine may be effective in the treatment of RFA symptoms either alone, or as combination therapy with other anti-anginal agents. Before this can be concluded definitively, robust clinical trials of trimetazidine, specific to RFA patients, and with long-term follow up are needed to clearly establish its ther-

Figure 19. Comparison of self-management training with controls, outcome Seattle Angina Questionnaire-disease perception. CI, confidence interval. Modified and reproduced from McGillion et al.¹³² with permission from Bentham Science Publishers Ltd. © 2008 Bentham Science Publishers Ltd.

apeutic effectiveness. Careful attention should be paid to evaluation of mortality risk and adverse events, as well as the impact of trimetazidine on functional status, using wellestablished measures of HRQL.

Quality of evidence according to GRADE. Given the lack of clear data on anti-anginal efficacy of trimetazidine, mortality risk and adverse events, we rate the overall quality of the evidence as very low (Table 2).

RECOMMENDATION

Robust, adequately powered RCTs with long-term follow up are needed to more definitively examine the antianginal effects, mortality risk, and adverse events associated with trimetazadine before it can be recommended for the treatment of RFA (Strong Recommendation, Very Low-Quality Evidence).

Values and preferences. This recommendation places a high value on patient safety and the need for highquality, RFA-specific evidence to support future practice recommendations.

Nicorandil. Nicorandil is a nicotinamide ester with a dual mode of action. A first nitrate-like moiety reduces angina by dilating the systemic veins and the coronary arteries. A second moiety protects ischemic myocytes by opening the mitochondrial adenosine triphosphate-sensitive potassium channels. This later property is thought to mimic the ischemic preconditioning phenomenon. The potassium channel opening is also thought to dilate the peripheral and coronary resistance arterioles which further increases the coronary blood flow.¹⁵¹ The anti-anginal properties of nicorandil have been known for more than 30 years.

A series of small RCTs suggested that nicorandil can exert an anti-ischemic effect comparable to conventional doses of β -blockers, oral nitrates, and calcium antagonists in patients with stable effort angina pectoris.¹⁵¹⁻¹⁵⁸ Because of the large individual variations in the rates of anginal attack and exercise duration on treadmill stress test, these studies were underpowered to detect any significant differences between nicorandil and other anti-anginal agents. Thus, nicorandil has been positioned as a cardioprotective agent.

In the Impact of Nicorandil in Angina (IONA) trial, nicorandil 10 mg twice daily was formally tested against placebo for the reduction of cardiovascular events in patients with recently diagnosed angina with established CAD. 159 Nicorandil 20 mg twice daily was superior to placebo at reducing the combined occurrence of cardiovascular death, nonfatal MI, or unplanned hospital admission for cardiac chest pain (hazard ratio [HR] 0.83; 95% CI, 0.72-0.97). While nicorandil reduced the rate of acute coronary syndromes (7.6% vs 6.1%; HR 0.79; 95% CI, 0.64-0.98), it did not significantly improve mortality (5.2% vs 4.2%; HR 0.79; 95% CI, 0.61-1.02; P = 0.07).¹⁵⁹ In the United Kingdom, nicorandil was later found to be cost-effective, as the additional cost of nicorandil was offset by the reduced use of hospital services.¹⁶⁰ To date, most of the clinical experience with this agent relies on patients with newly diagnosed angina.

Quality of evidence according to GRADE. Given the lack of applicability of current data to RFA specifically, we rate the overall quality of the evidence as very low (Table 2).

RECOMMENDATION

Robust RCTs are needed to examine the effectiveness of nicorandil for RFA patients before specific recommendations can be made (Strong recommendation, Very Low-Quality Evidence).

Values and preferences. This recommendation recognizes the potential benefits of nicorandil and the need for high-quality, RFA-specific evidence to support future practice recommendations.

Heart rate modulating agent

Ivabradine. Ivabradine is a heart rate lowering agent that inhibits the $I_{\rm f}$ pacemaker current in the sinoatrial node.¹⁶¹ Ivabradine produces its anti-ischemic effect as a result of heart rate reduction¹⁶² with no effect on blood pressure, intra-atrial, atrioventricular, or intraventricular conduction times, or myocardial contractility or ventricular repolarisation.¹⁶³⁻¹⁶⁶ Heart rate reduction results in improved myocardial perfusion as a result of increased diastolic filling time and reduced myocardial oxygen demand.¹⁶⁷

Early trials of ivabradine^{161,167} supported that it is a welltolerated heart rate lowering agent with anti-ischemic and anti-anginal properties,¹⁶¹ and that it can be effective in producing dose-dependent improvements in exercise tolerance as well as time to 1-mm ST-segment depression.¹⁶⁷ Subsequent studies have compared ivabradine to conventional β -adrenoceptor and calcium channel blockade.^{168,169} In a multicentre, 3-armed RCT examining 939 patients with chronic stable angina, Tardif et al.¹⁶⁸ compared ivabradine with atenolol. The primary end point was change in total exercise duration 16 weeks from baseline, performed at trough of drug activity. Ivabradine was found equivalent to atenolol based on noninferiority analysis. Total exercise duration at trough drug levels increased by 86.8 ± 129.0 seconds with ivabradine 7.5 mg twice daily, 91.7 ± 118.8 seconds with ivabradine 10 mg twice daily, and 78.8 ± 133.4 seconds with atenolol 100 mg daily.¹⁶⁸ Angina episodes and short-acting nitrate consumption were reduced across treatment groups. Ivabradine was well tolerated, with minor visual disturbances (ie, phosphenes) being the most frequently reported adverse effect.¹⁶⁸

In the Morbidity-Mortality Evaluation of the I_f Inhibitor Ivabradine in Patients With Coronary Disease and Left-Ventricular Dysfunction (BEAUTIFUL) trial, Fox et al.¹⁷⁰ examined a variety of safety outcomes in patients with stable CAD and left ventricular systolic dysfunction (ie, left ventricular ejection fraction < 40%). Over 10,000 patients were randomized to either ivabradine (n = 5479) or placebo in addition to usual care (n = 5438); median follow-up was 19 months. Ivabradine did not affect the primary endpoint of a composite of cardiovascular death, admission to hospital for acute MI, and admission to hospital for new onset or worsening heart failure (HR 1.00; 95% CI, 0.91-1.1; P = 0.94.).¹⁷⁰ A post hoc analysis of the effect of ivabradine was conducted on 13% (n = 1507) of patients enrolled whose limiting symptom at baseline was angina (n = 734 ivabradine group, n = 773 placebo group).¹⁷¹ For this subgroup, ivabradine was found to be associated with a 24% reduction in the primary endpoint (cardiovascular mortality or hospitalization for fatal and nonfatal MI, or heart failure) (HR 0.76; 95% CI, 0.58-1.00) as well as a 42% reduction in hospitalization for MI (HR 0.58; 95% CI, 0.37-0.92). Hospitalization for MI and coronary revascularization was also reduced by 73% (HR 0.27; 95% CI, 0.11-0.66) and 59% (HR 0.41; 95% CI, 0.17-0.99) respectively, for those with heart rate \geq 70 beats per minute.¹⁷¹

Based on the available evidence, ivabradine appears to be well-tolerated by patients with chronic stable angina, and may also prove to be beneficial in reducing major adverse cardiovascular events for those with stable CAD, limiting angina, and left ventricular systolic dysfunction.¹⁷¹ The more recent Systolic Heart Failure Treatment With the I_f Inhibitor Ivabradine Trial (SHIFT) trial^{172,173} supports that ivabradine reduces hospitalization for worsening heart failure and may reduce heart failure-related deaths for those with left ventricular ejection fraction \leq 35%. The benefits of ivabradine, specific to the RFA population, have yet to be determined.

Quality of evidence according to GRADE. The effectiveness of ivabradine has been evaluated in robust clinical trials with mixed results. Some evidence suggests anti-anginal efficacy equivalent to atenolol, and there may be some cardioprotective effects for select patients with stable angina symptoms. More definitive evidence of effectiveness for RFA patients is required. We therefore rate the overall quality of the evidence (in the context of RFA) as moderate (Table 2).

RECOMMENDATION

Robust RCTs focused on patients with RFA are needed before ivabradine can be recommended definitively (Strong Recommendation, Moderate-Quality Evidence).

Ivabradine may have potential for future use to reduce angina symptoms and SL nitrate consumption, as well as to improve exercise tolerance (Strong Recommendation, Moderate-Quality Evidence).

Ivabradine may reduce the occurrence of major adverse cardiac events for patients with limiting angina symptoms and left ventricular systolic dysfunction (Weak Recommendation, Moderate-Quality Evidence).

Values and preferences. These recommendations place a high value on the potential of ivabradine to improve symptoms and exercise tolerance, as well as reduce the occurrence of major adverse cardiac events. The need for high-quality, RFA-specific evidence to support future practice recommendations is also recognized.

Intermittent thrombolytic agents

The intermittent administration of thrombolytic agents, mainly urokinase, was first explored in the 1990s in patients with RFA.¹⁷⁴⁻¹⁷⁶ Hyperfibrinogenemia in patients with vadvanced CAD has been shown to increase plasma viscosity and cause erythrocyte aggregation.¹⁷⁷ By depleting plasma fibrinogen, thrombolytic agents reduce blood viscosity and therefore improve the rheological properties of blood in the

microcirculation.¹⁷⁴⁻¹⁷⁶ The anti-anginal and anti-ischemic properties of urokinase were initially reported in 1996.¹⁷⁶ In a single-blinded, dose-response randomized trial, the weekly administration of high doses of urokinase (500,000 IU) was superior to low dose urokinase (50,000 IU) at improving angina, exercise capacity, and time to 1-mm ST-segment depression (n = 98).¹⁷⁵ Bleeding complications were rare (1%) in both groups. Chronic intermittent urokinase administrations (500,000 IU) 3 times weekly is currently administered in some areas of Europe to treat patients with RFA.¹⁷⁷ Despite the absence of placebo control in the trials currently available, the concordant dose-response effect in clinically subjective, objective and biological parameters all suggest that intermittent thrombolytic agents may have potential in the treatment of RFA. Although promising, the efficacy and safety of intermittent thromoblysis needs to be confirmed in appropriately designed and robust randomized placebo-controlled trials.

Quality of evidence according to GRADE

In the absence of robust, placebo-controlled trials, the quality of the available evidence for the intermittent administration of thrombolytic agents for RFA is very low (Table 2).

RECOMMENDATION

Robust RCTs are needed to examine the effectiveness and safety of intermittent thrombolysis for RFA patients before recommendations can be made (Strong Recommendation, Very Low-Quality Evidence).

Values and preferences. This recommendation places a high value on patient safety.

Emerging Therapies

Emerging therapies for RFA include shock wave therapy,^{178,179} coronary sinus reducer,^{180,181} and myocardial cryotherapy.¹⁸² The evidence for these therapies remains limited and does not meet our inclusion for review; practice recommendations cannot yet be made (Table 2).

Implications for Practice and Research

RFA is a debilitating condition characterized by severe, unremitting cardiac pain caused by coronary insufficiency in the presence of CAD.^{1,15} While the presence of myocardial ischemia must be clinically established to be the root cause, the pain experienced may arise or persist with or without ischemia.¹⁵ The ischemic and neuropathophysiological mechanisms underlying RFA are complex and pose unique management challenges. Given the complexity of the mechanisms at play, establishing the diagnosis of RFA is difficult and multiple treatment modalities have been proposed. Effective care for the RFA population in Canada is critical; this patient group has severely impaired quality of life with considerable cost implications.^{13,14} We offer the following final recommendations for future direction in RFA management and research.

FINAL SUMMARY RECOMMENDATION

The use of the term 'refractory angina' is recommended as opposed to the term 'no option angina' (or similar terms).

Effective care of patients with RFA requires an integrated understanding of the underlying ischemic and neural pain mechanisms involved. As such, the collaboration of cardiovascular and pain experts is critical for comprehensive patient assessment and management.

More RCTs, employing robust methods, are needed. Particular attention should be paid to the use of standardized outcome measures (for comparison across trials), patient-centred outcomes, as well as stricter inclusion criteria, exclusive to those meeting the definition of RFA.

It is recommended that a working group be struck to examine (1) existing infrastructure, (2) access to care issues, and (3) feasibility, costs, and potential benefits of specialized, multidisciplinary centres of care for RFA.

Values and preferences. These final summary recommendations place a high value on patient-centred outcomes such as symptom reduction and improvements in HRQL, as well as addressing current gaps in health care for people living with RFA.

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APPENDIX I. Panelists and collaborators

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