ABSTRACT
Coronary artery disease (CAD) remains an important cause of morbidity and mortality. Angina pectoris (angina) is one of the classic symptoms of CAD, originally described in 1772 by the English physician William Heberden, who had encountered a group of patients with “a painful and most disagreeable sensa-
tion in the breast which seems as if it would extinguish life if it were to increase or to continue.” He went on to describe that those suffering from this affliction “are seized while they are walking (more especially if it be uphill, and soon after eating) . . . but the moment they stand still, all this uneasiness vanishes.”

Coronary artery disease (CAD) remains an important cause of morbidity and mortality. Angina pectoris (angina) is one of the classic symptoms of CAD, originally described in 1772 by the English physician William Heberden, who had encountered a group of patients with “a painful and most disagreeable sensa-
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RÉSUMÉ
La maladie coronarienne (MC) demeure une cause importante de morbidité et de mortalité, en plus d’être un sérieux problème de santé publique. Depuis les 4 dernières décennies, il y a eu des avancées considérables dans la prévention et dans le traitement de la MC. La prise en charge thérapeutique de la MC a été révolutionnée par le développement de techniques efficaces de revascularisation chirurgicale et percutanée. Dans cette revue, nous discutons de l’importance du traitement de l’angine stable symptomatique. Les approches médicale et percutanée dans le traitement et la prévention de l’ischémie myocardique symptomatique sont résumées. Au Canada, les nitrates organiques, les inhibiteurs des récepteurs β-adrénergiques et les antagonistes des canaux calciques sont disponibles pour le traitement de l’angine depuis plus de 25 ans. Les 3 classes se sont avérées advantageuses dans l’amélioration des symptômes et de la capacité d’exercice chez les patients ayant une angine stable. Bien qu’aucune de ces classes d’agents antiangineux ne retienne la première place, la présence de maladies préalables ou concomitantes (par exemple, l’infarctus du myocarde ou l’hypertension, ou les deux) joue un rôle important dans le choix de la classe d’agents antiangineux pour un patient. Pour quelques patients, la combinaison d’agents antiangineux différents peut être efficace. Toutefois, il est recommandé de s’en tenir à une approche individualisée. Bien qu’elles ne soient pas disponibles au Canada pour le moment, d’autres classes d’agents antiangineux ont été créées; leur mécanisme d’action et leur efficacité clinique sont discutés. Les patients ayant une angine stable ont un excellent pronostic. Les patients de cette catégorie qui obtiennent du soulagement de l’ischémie myocardique symptomatique peuvent bien se porter sans intervention effective.
In this document, we discuss 4 select areas relevant to the management of stable angina pectoris. First, we briefly discuss evidence concerning the prevalence of symptomatic angina in the modern era. Second, pharmacologic approaches to the management of exertional angina are reviewed. Third, information concerning the impact of long-term anti-anginal therapy on outcomes in patients with angina are summarized. Finally, a perspective concerning prognosis in patients with stable angina and its relevance to management decisions are presented.

While the importance and effectiveness of anti-anginal therapy is emphasized, there is no intention to enter into the controversy of pharmacologic vs interventional approaches to the management of ischemia in this population. Further, the role of antiplatelet agents, lipid modification, and other pharmacologic disease modification approaches in patients with chronic stable angina are not discussed.

**Prevalence of Stable Angina**

The advent of revascularization procedures, initially with coronary artery bypass graft (CABG) surgery and subsequently with percutaneous coronary intervention, provided highly effective options to manage patients with stable angina. As these revascularization procedures improved in terms of efficacy and safety, many physicians (and often their patients) developed a preference for intervention vs medical management in this population. The reality of this is supported by the dramatic rise in rates of revascularization procedures during the 1980s and 1990s. Despite the availability of interventional procedures, exertional angina continues to be a significant clinical problem. Evidence of this comes from multiple sources, including epidemiologic surveys and data collected in the setting of clinical trials. In Canada, the Canadian Cardiovascular Research Outcomes Team reported that approximately 500,000 Canadians have symptomatic angina (representing 2% of the population >12 years of age). Surveys carried out in the United Kingdom confirm that angina is similarly prevalent in the adult population. Finally, a large review of angina prevalence confirms these findings, suggesting angina is consistently more prevalent in women and that the overall prevalence varies broadly across countries.

**Why Skilled Medical Management of Stable Angina Remains Critical**

The current review limits itself to patients with symptoms of angina in the setting of stable CAD and does not involve management decisions made in the setting of acute coronary syndromes. Although there is controversy concerning the role of medical vs interventional management of ischemia in those with stable coronary disease, there are many situations in which the choice of management strategy is clear. Any patient with continued symptoms of angina despite a trial of medical management warrants consideration for revascularization. While the choice of surgical vs percutaneous intervention must consider multiple clinical features, CABG appears to have the best long-term benefit in those with complex, multivessel CAD. There are patients who are not candidates for any form of revascularization because of their coronary anatomy and/or concurrent medical conditions. Importantly, it is this subgroup of patients who can most benefit, symptomatically, from the skilled administration of anti-anginal therapy. Finally, it should be emphasized that while the focus of this report is on anti-anginal therapy, all patients with stable coronary disease should benefit from the broad spectrum of lifestyle and secondary prevention interventions with proven beneficial effects in the setting of established CAD.

**Medical Management of Stable Angina**

The pharmacologic prevention of exertional symptoms of angina has classically involved the use of agents that reduce myocardial oxygen demand and/or increase myocardial oxygen supply in response to exercise. In Canada, the classes of anti-anginal agents available for the prophylaxis/prevention of angina have not changed in approximately 30 years. These include organic nitrates, β-blockers, and calcium channel antagonists. A complete review of the pharmacology of available anti-anginal agents is beyond the scope of this publication, although some general comments about mechanism(s) are in order. Agents for the therapy of angina have traditionally been approved by regulatory agencies based on their ability to improve exercise duration in the setting of controlled clinical trials. In North America, exercise testing is done using treadmill exercise testing (with either the standard or modified Bruce protocol) while in Europe bicycle testing is more commonly employed. In the past, drugs were approved based on their ability to improve exercise capacity as compared with placebo in the absence of other anti-anginal agents, although more recent approvals have involved the testing of agents used in addition to specified background therapy. Drugs approved for the therapy of angina produce modest increases in exercise duration, usually less than a 1-minute increase in exercise duration on treadmill exercise testing, as compared with placebo. Despite the modest increase in mean exercise duration, some patients experience quite dramatic increases in exercise capacity in response to medical therapy. Importantly, all available classes of anti-anginal agents have similar effects on exercise duration and thus there is not clear indication to choose 1 class vs another based on this outcome.

**Organic nitrates**

Despite being in use for more than 100 years, the mechanism of action of organic nitrates remains uncertain. Traditionally, their primary mechanism of action was felt to be secondary to preload reduction mediated by potent venodilator effects. Preload reduction can reduce myocardial oxygen consumption by reducing left ventricular chamber size and, as a consequence, systolic and diastolic wall stress. Further, when given using dosing regimens that avoid nitrate tolerance, these agents reduce blood pressure and increase conduit artery distensibility, actions that can reduce myocardial oxygen consumption. Although nitrates dilate conduit epicardial arteries, their ability to increase coronary blood flow in the setting of obstructive coronary stenoses remains uncertain. Finally,
although never investigated in humans, in vitro and animal data suggest that nitrates and other nitric oxide donors may be able to improve left ventricular efficiency, favourably altering the ratio of myocardial oxygen consumption per unit work.22,26

In Canada, 3 different types of organic nitrates are available in a number of formulations (Table 1). All have been shown to be effective in the therapy of exertional angina including transdermal nitroglycerin,17,25 isosorbide dinitrate,28 and isosorbide-5-mononitrate in a phasic release formulation.29,30 Nitroglycerin, for oral ingestion (as compared with sublingual formulations) is available, but there is no evidence that it is clinically effective. Although isosorbide dinitrate is produced in sustained release formulations, they are no longer available in Canada. Standard release isosorbide dinitrate is widely available, although it is not commonly used based on its pharmacokinetics and need for administration 3 times per day.

A classic pharmacodynamic feature of the organic nitrates is the development of tolerance during sustained therapy. Tolerance has been shown to develop with all types of organic nitrates when they are administered using dosing patterns or preparations that lead to continuous nitrate concentrations in plasma over a 24-hour period.31 Tolerance is manifested by loss of the hemodynamic and symptomatic effects of nitrates. Tolerance has been known to occur for approximately 30 years and has been a major limitation to the therapeutic long-term application of nitrates. Tolerance develops rapidly with all nitrates (within 24 hours) when they are administered in a manner that leads to constant plasma concentrations. The etiology of nitrate tolerance has been the subject of much debate with a number of theories proposed. Details of this pharmacologic mystery have been reviewed in detail elsewhere.32-34 Based on proposed mechanisms, a number of potential interventions to prevent the development of nitrate tolerance have been investigated in both animal and human models. To date, the only approach that has been applied clinically is the use of intermittent therapy where dosing regimes or nitrate formulations that yield low or nitrate-free concentrations in plasma for 10-12 hours per day are employed.22

Sublingual nitroglycerin is typically prescribed for the relief of acute attacks of angina. Most patients receive prescriptions for sublingual nitroglycerin to be used in the event that they have symptoms at rest or if exertional symptoms are not promptly relieved by rest. It is important to remember that sublingual nitroglycerin can also be used prophylactically when patients with exertional symptoms embark on patterns of activity that generally lead to the development of angina. Several decades ago, when long-acting anti-anginal therapy was not available, this approach was used much more often than it is today. There is controlled clinical trial evidence demonstrating that sublingual nitroglycerin does have potent anti-anginal effects.35-37 Most studies have quantified the effect of sublingual nitroglycerin within 5-15 minutes of administration, however, many patients describe that this therapy prevents the development of angina for at least 1-2 hours. Although never formally tested, this more prolonged pharmacodynamic effect may well be secondary to sublingual nitroglycerin’s activity as a pharmacologic preconditioning agent.38-40 Isosorbide dinitrate is also available in a 5 mg tablet that can be used sublingually. Although not generally used for the treatment of acute episodes of angina it can be effective when taken prior to activity in patients with refractory effort angina.

**Table 1. Pharmacologic characteristics of common the organic nitrates**

<table>
<thead>
<tr>
<th></th>
<th>SL GTN</th>
<th>TD GTN</th>
<th>ISDN</th>
<th>IS-5-MN (phasic release)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Half-life</td>
<td>6-9 min</td>
<td>6-9 min</td>
<td>1-2 (4-5) hrs*</td>
<td>4-5 hrs</td>
</tr>
<tr>
<td>Elimination</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>1-2 (4-5) hrs*</td>
</tr>
<tr>
<td>Heart Rate</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Vascular resistance</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
<td>↔</td>
</tr>
<tr>
<td>Usual dosage (mg)</td>
<td>0.4-0.6 mg</td>
<td>0.2-0.6 mg/h (intermittent)</td>
<td>5-30 mg TID (eccentric)</td>
<td>60-240 mg OD</td>
</tr>
</tbody>
</table>

GTN, glyceryl trinitrate; IS-5-MN, isosorbide-5-mononitrate; ISDN, isosorbide dinitrate; OD, once daily; SL, sublingual; TD, transdermal; TID, three times daily.

*Half-life of active metabolite isosorbide-5-mononitrate.
†ISDN (5 mg) may be administered sublingually for prevention of angina.

**β-Adrenergic blockers**

β-Blockers have become a mainstay in the treatment of coronary disease and are effective in the therapy of exertional angina.19,20,41-43 Their mechanism of action is based primarily on reducing myocardial oxygen demand in response to exercise by decreasing heart rate, blood pressure, and myocardial inotropic responses. Further, via negative chronotropic effects, they can improve coronary blood flow by increasing the duration of diastole, the period during which coronary blood flow occurs. A number of β-adrenergic blocking agents are available for the therapy of angina in Canada. The pharmacokinetic and pharmacodynamic effects of the available agents vary based on their half-life, β-1 receptor selectivity, route of elimination, and lipophilicity (Table 2). In individual patients, the choice of β-blocker for the therapy of angina is determined primarily by these pharmacologic characteristics. Importantly, drugs with β-1 receptor selectivity can be used in patients with either diabetes or chronic obstructive lung disease, situations in which they are usually very well tolerated. With increasing numbers of patients having concomitant renal insufficiency, prescribers must keep in mind those agents that have a major component of renal elimination (Table 2).

Clinically effective doses of β-blockers vary. There is broad variation in the rate of elimination of these drugs across patients and their effect is dependent on underlying sympathetic activity. In most cases dose is determined by resting heart rate, blood pressure, and, at times, their side effect profile. Importantly, many practitioners forget that the effect of β-adrenergic blockers on resting heart rate can be a poor predictor of their effect on the heart rate response to exercise. Because modification of the chronotropic response to exercise is a major determinant of effectiveness, it is strongly recommended that this response be assessed with either a treadmill or formal exercise testing in patients who exhibit poor responses to initial...
dosing. This, unfortunately, seems to be an underutilized approach to the clinical application of these important agents in the therapy of angina. β-Blockers with partial sympathomimetic activity (pindolol and acebutalol) have been promoted for use in patients with stable angina; however, they appear to be less effective and are no longer in common clinical use.

**Calcium channel blocking agents**

Calcium channel blockers are also effective anti-anginal agents.41-51 The calcium channel antagonists are all effective antihypertensive agents, a feature that is particularly helpful in the management of patients with both angina and hypertension. Although their basic mechanism of action is similar (ie, blockade of the L-type calcium channel and reduction of intracellular calcium concentrations), there are 3 different classes of calcium channel antagonists having quite different chronotropic, hemodynamic, and inotropic effects. The dihydropyridines (the prototype is nifedipine) have little effect on heart rate or atrioventricular conduction while having the most prominent effect on peripheral resistance. Although nifedipine was the first of this class to be introduced, another effective dihydropyridine is amlodipine, a drug that has become very widely used in the therapy of angina and hypertension. The benzothiazepines (the prototype is diltiazem) and the phenylalkylamines (the prototype is verapamil) also reduce peripheral vascular resistance, although both these classes have prominent negative chronotropic effects and impair atrioventricular conduction. All 4 calcium channel antagonists approved for angina in Canada are available in once per day formulations (amlodipine, nifedipine GITS, diltiazem CD, and verapamil SR) (Table 3). Immediate release nifedipine, diltiazem, and verapamil are still available but generally not used (and for nifedipine not recommended) for long-term therapy. Nifedipine GITS and amlodipine are commonly used in patients with angina and are particularly helpful in those with concomitant hypertension. Diltiazem CD, given in its once-daily formulation, is very effective in the therapy of angina as it is well tolerated reducing both blood pressure and chronotropic responses. Verapamil, although effective as an anti-anginal, has generally been less popular, presumably because of the realization that it has prominent negative inotropic effects.

The mechanisms of action of calcium channel antagonists are complex and vary by class. The dihydropyridines decrease myocardial consumption via their effects on afterload and their negative inotropic effects but have no negative chronotropic effects and in some cases can lead to an increase in heart rate. Both diltiazem and verapamil have multiple effects that cause a reduction in myocardial oxygen consumption including negative chronotropic and inotropic effects along with a reduction in peripheral vascular resistance. Although there is evidence that calcium channel antagonists can increase coronary blood flow32-34 there is little information concerning the relevance of this effect in humans with stable angina. Indeed, their impact in coronary blood flow is complex with variations depending on their actions at rest vs exercise, differences in their effects on coronary perfusion pressure, variable changes in myocardial oxygen demand, autoregulation of coronary flow, and differential impact on diastolic perfusion time. Calcium channel antagonists, particularly the dihydropyridines, are also postulated to improve the relative bioavailability of coronary artery

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### Table 2. Pharmacologic characteristics of common β-1 selective and nonselective β-adrenergic blockers

<table>
<thead>
<tr>
<th></th>
<th>Atenolol</th>
<th>Metoprolol</th>
<th>Bisoprolol</th>
<th>Acebutalol</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>6-9</td>
<td>3-4</td>
<td>10-12</td>
<td>3-4*</td>
</tr>
<tr>
<td><strong>β-1 selectivity</strong></td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td><strong>Sympathomimetic activity</strong></td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Lipophilicity</strong></td>
<td>Low</td>
<td>Moderate</td>
<td>Moderate</td>
<td>Moderate</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Renal</td>
<td>Hepatic</td>
<td>Hepatic and renal</td>
<td>Hepatic and renal</td>
</tr>
<tr>
<td><strong>Usual dosage (mg)</strong></td>
<td>50-100 OD</td>
<td>50-100 BID</td>
<td>2.5-10 OD</td>
<td>200-600 BID</td>
</tr>
</tbody>
</table>

BID, twice daily; OD, once daily.  
* Active metabolite of acebutalol (diacetolol) has half-life of 8-12 h.

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### Table 3. Pharmacologic characteristics of common calcium channel antagonists

<table>
<thead>
<tr>
<th></th>
<th>Nifedipine (GITS)</th>
<th>Amlodipine</th>
<th>Diltiazem (CD)</th>
<th>Verapamil (SR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Half-life (h)</strong></td>
<td>2-5</td>
<td>30-50</td>
<td>4-6</td>
<td>5-12</td>
</tr>
<tr>
<td><strong>Elimination</strong></td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
<td>Hepatic</td>
</tr>
<tr>
<td><strong>Heart rate</strong></td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Vascular resistance</strong></td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓↓</td>
<td>↓</td>
</tr>
<tr>
<td><strong>Dosage (mg)</strong></td>
<td>20-90 OD</td>
<td>2.5-10 OD</td>
<td>120-360 OD</td>
<td>180-360 BID</td>
</tr>
</tbody>
</table>

BID, twice daily; CD, controlled delivery; GITS, gastrointestinal therapeutic system; OD, once daily; SR, slow release.
nitric oxide, improving endothelium-dependent vasodilator responses; this has led some to postulate that they may favourably modify the natural history of atherosclerosis. Whether such findings are a direct pharmacologic effect of the calcium channel antagonist or secondary to their blood pressure-lowering effects is not clear. All calcium channel antagonists are similar in terms of their anti-anginal efficacy. The choice of 1 agent vs another is based primarily on pharmacodynamic characteristics, in particular whether a negative chronotropic effect is desired or not.

Effect on long-term clinical outcomes

Information concerning the effect of the specific classes of anti-anginal therapy on long-term clinical outcome is limited. As such, there is little rationale, in many patients, to choose 1 class of anti-anginal over another based on a different effect of therapy on clinical outcome or events. These comments pertain to those with isolated exertional angina with normal left ventricular function. In practice, there are often logical choices to be made based on the presence of angina in those with other concurrent characteristics such as the choice of β-blockers in those with prior infarction or the use of a calcium channel antagonist in patients with systemic hypertension. However, in the absence of such concurrent conditions, evidence of a clear long-term clinical benefit is less clear.

There is essentially no evidence concerning clinical outcome with respect to long-acting nitrates. Studies leading to approval of long-acting nitrates for the therapy of angina have been small, with short-term follow up. There have been no long-term trials of organic nitrates in patients with CAD (with or without angina). Of note, over the past decade there has been increasing evidence from animal and human experiments that sustained nitrate therapy causes abnormalities in endothelial function associated with evidence of increased free radical bioavailability. These findings have led to some concern about the long-term safety of the organic nitrates in patients with CAD. β-Blockers are a mainstay of therapy in patients with CAD. It is commonly assumed that β-blockers are protective in the setting of chronic CAD and improve clinical outcomes. However, clear benefit has only been determined in patients with prior myocardial infarction and congestive heart failure due to left ventricular systolic dysfunction. Of note, no large-scale outcome study has ever been conducted to examine the clinical effect of β-blockers in patients with stable CAD. Studies specifically addressing their ability to improve exercise tolerance were not adequately powered to determine the effects of β-blockers on long-term outcome. Furthermore, some of these studies did not employ a placebo control. Despite these shortcomings, it has never been suggested that β-blockers are unsafe in the context of chronic stable angina.

After the introduction of calcium channel antagonists in the 1980s they became extremely popular agents in the therapy of hypertension and in patients with angina. Findings from meta-analyses raised concern that calcium channel antagonists could have adverse effects leading to an increased risk of myocardial infarction in both patients with hypertension and those with angina. These concerns prompted the largest clinical trial ever performed in patients with stable angina. The A Coronary Disease Trial Investigating Outcome With Nifedipine GITS (ACTION) study randomized 7765 patients with known chronic CAD, preserved left ventricular systolic function, and angina to sustained release nifedipine vs placebo. After a mean follow-up period of approximately 5 years, the nifedipine group had fewer cardiovascular events and less need for revascularization (Fig. 1). Importantly, this study confirmed the safety of this calcium channel antagonist in patients with chronic CAD (although it is important to recall that 80% of the sample was receiving concomitant β-blocker therapy).

Combination therapy

Many patients with stable angina are treated with more than 1 class of anti-anginal drug. In clinical practice it has become common to encounter patients taking 2 and, at times, 3 different types of anti-anginal therapy. In some patients, particularly where revascularization is not possible, this approach has merit. On the other hand, many patients without refractory symptoms are treated with combination therapy. Physicians take this approach using the rationale that lower doses of 2 different drugs will achieve the same degree of symptomatic relief with fewer side effects. It is also assumed that combination therapy, using drugs with different mechanisms of action, should have additive or potentially synergistic effects in the prevention of ischemia and resulting symptoms. Unfortunately, there is little evidence to support this therapeutic approach. Clinical trials examining the efficacy of combination therapy are limited in terms of sample size and yield inconsistent results with respect to the efficacy of combinations vs 1 drug alone. Most studies employed fixed drug dosing regimens and did not examine the effect of adding a second drug to maximally tolerated doses of a single agent. In studies that included a true placebo (ie, no active drug), the efficacy of combination therapy was usually significant in comparison with the placebo period, but not clearly different as compared with single drug therapy alone. This controversial area was reviewed in detail by Packer, who argued that in the absence of clear benefit, use of more than 1 anti-anginal agent puts patients at risk for side effects of combination therapy. Combination therapy should be used with caution and consider-
iation should be given to ensuring maximally-tolerated doses of single-drug therapy before the addition of another class of anti-anginal. Consistent benefit has been demonstrated from the addition of a second agent when patients remain symptomatic on maximal monotherapy.79,82,91

**Choice of anti-anginal therapy**

As discussed above, all 3 available classes of anti-anginal therapy are approximately equivalent in terms of their effect on exercise capacity and angina symptoms. There remains no clear ‘first choice’ in the therapy of angina. Canadian, American, and European guidelines recognize this uncertainty but are generally supportive of β-blockers as first line therapy, particularly in the presence of prior infarction. 103-105 Choice of therapy is often based on the presence of associated clinical conditions in a given patient such as the presence of a prior infarction (β-blocker) or significant concomitant hypertension (dihydropyridine calcium channel antagonist). Many physicians choose β-blockers as their first line therapy for patients with angina. These drugs are very effective anti-anginal agents, which can be easily dose-titrated to their effect on heart rate; their efficacy and safety are also well established in a number of cardiovascular conditions. Some physicians prefer calcium channel antagonists as first line therapy, presumably based on the assumption that they have a favourable side-effect profile. Therefore, in the absence of left ventricular systolic dysfunction or prior infarction there is no clear guidance to choose a β-blocker vs a calcium channel antagonist, although the use of β-blockade would seem to be a logical choice in the absence of a contraindication or striking hypertension. A schematic presentation of a suggested approach to anti-anginal therapy is presented in Figure 2.

**Other anti-anginal agents**

A number of anti-anginal agents are available in other jurisdictions that have not been approved in Canada (please see the Canadian Cardiovascular Society Guidelines for the Management of Refractory Angina by McGillion et al.,106 in this supplement to the *Canadian Journal of Cardiology*).

Combination therapy with anti-anginal agents received increased attention during development of the new anti-anginal agents ivabradine and ranolazine. The approval of these drugs has been based on evidence of their efficacy when used in combination with another class of anti-anginal.108,109 These drugs are labelled for use only in those who remain symptomatic or are intolerant of therapy with another agent.
Nicorandil is an anti-anginal that has been available for many years outside of North America. It is effective in the therapy of exertional angina and is generally well-tolerated. Nicorandil appears to have dual mechanisms of action; the drug increases cyclic guanosine monophosphate presumably via a nitric oxide-mediated mechanism but also facilitates the opening of mitochondrial K⁺-adenosine triphosphate channels.

It is effective in the therapy of exertional angina and a large-scale clinical trial in patients with chronic CAD revealed that it improved long-term clinical outcome, confirming its safety in this patient population.

Ivabradine is a drug that belongs to a class of drugs termed sinus node inhibitors. Advances in the understanding of the electrophysiologic mechanisms of sinus node function have led to the development of therapeutic approaches with quite specific sinus node effects. It is now understood that the Iᵢ channel (the so-called inward funny channel) which mediates an inward, mixed Na⁺/K⁺ current is a critical determinant of sinus node activity. This channel is activated by hyperpolarization and its activity is modulated by inputs of the autonomic nervous system. Specific sinus node inhibiting agents have selective effects on both resting and exercise-induced increases in heart rate, do not modify other aspects of the cardiac conduction system, and have no direct myocardial or vascular effects.

Ivabradine is effective in the treatment of stable angina both as monotherapy and when given in combination with a β-blocker. Sinus node inhibiting agents, including ivabradine, have unique visual side effects in some patients. These drugs also inhibit the Ih current in the retina and therefore may cause unusual increased sensitivity to bright light (referred to as luminous phenomena).

Visual symptoms are generally transient, have been found to resolve during treatment in the majority (77%) of patients, and led to few withdrawals in clinical testing (<1%).

Trimetazidine is an effective anti-anginal that is believed to work by inhibiting myocardial free fatty acid oxidation and is unique in that it does not modify heart rate or blood pressure and thus appears to have no hemodynamic effect. This agent has been available for many years in Europe and is quite commonly prescribed in patients with angina. There is reasonable clinical trial evidence that it is an effective anti-anginal both as monotherapy and when given in combination with other anti-anginal agents. Despite this, documented clinical experience is limited and trimetazidine has never been tested in a large-scale clinical outcome trial.

Ranolazine, approved in the United States and the European Union is another effective anti-anginal. Originally, it was believed to have a primary metabolic mechanism of action, inhibiting myocardial free fatty acid oxidation and thus improving efficiency of myocardial oxygen utilization. Recent evidence has suggested that this metabolic effect requires higher concentrations of the compound than are obtained with current clinical dosing regimens. Currently, the consensus is that the compound inhibits the late inward sodium channel thus limiting the harmful effects of increased intracellular sodium concentrations on myocardial function. Ranolazine is effective in patients with angina as monotherapy but was approved on the basis of studies where it was used in addition to other anti-anginal agents. The effect of ranolazine on clinical outcomes in patients with acute coronary syndromes was tested in the Metabolic Efficiency With Ranolazine for Less Ischemia in Non-ST–Elevation Acute Coronary Syndromes (MERLIN) study, which included approximately 6500 patients followed for a median time of 348 days. Although ranolazine did not significantly reduce the incidence of adverse cardiac events it did confirm the safety of the compound in a high-risk patient population. Based on this confirmation of safety, ranolazine is now approved for first-line therapy of angina in the United States. To date, this novel anti-anginal has not been approved for use in Canada.

Prognosis of Stable Angina

An appreciation of the morbidity and mortality of patients with stable angina has an important effect on decision-making with respect to management. The choice of medical management vs revascularization is driven by many factors including, but not limited to: patient age, comorbidities, coronary anatomy, mode of presentation, degree of ischemia on exercise testing, and symptomatic response to medical management. It is worthwhile emphasizing that patients with stable angina (particularly those with preserved left ventricular function) have an excellent prognosis. In 1972, data from the Framingham study revealed a mortality of approximately 4% per year. This is very similar to the mortality rate of patients with angiographically proven CAD, 80% who had a history of angina, reported by Burgraf and Parker in 1975. More recent series document that prognosis has improved in the modern era with reported mortality rates of 1%-3% per year. Mortality rates in the setting (primarily) of stable CAD have been reported in the Swedish Angina Pectoris Aspirin Trial (SAPAT) (2% per year), long-term follow-up of the Angina Prognosis Study in Stockholm (APSIS) study (1.1% per year), the ACTION study (1.5% per year), the Impact of Nicorandil in Angina (IONA) study (3.0% per year) and the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study (2.4% per year). Variations in mortality rates from studies in the modern era almost certainly reflect differences in baseline risk and concomitant medical management. Despite this variation, the mortality rates reported confirm the fact that patients with stable angina have an excellent prognosis. From this perspective, patients with stable symptoms of chronic CAD who respond well to therapy (particularly monotherapy) who do not have high risk features likely to benefit from revascularization, can be safely and deservedly treated medically. Without doubt, some may go on to need revascularization, but it is clear that many patients with low risk CAD and stable angina will do well with long-term medical management in terms of quality of life and symptomatic benefit.

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