

## Optimizing Angina Treatment: How Far Have We Come?

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J Inv Clin Cardiol 2023; 5(2): 29-31

Stable angina represents the most prevalent symptom of ischemic heart disease, affecting around 112 million people worldwide.<sup>1</sup> The prevalence varies across regions increasing with age in both sexes.<sup>2,3</sup> More frequent angina results in greater physical limitation, poorer quality of life, and increased risks of disability, depression and job loss.<sup>4,5,6</sup> Angina symptoms also predict worse cardiovascular outcomes, but are commonly under-recognized in clinical practice. In Cadence study performed with 2031 angina patients, Physicians considered patients' angina to be optimally controlled in 80% of cases, despite the prevalence of frequent angina.<sup>7</sup> In a study conducted in the US with 1257 outpatients with coronary artery disease (CAD) managed by 155 cardiologists, only 56% patients with frequent angina symptoms were on optimal antianginal medication.<sup>8</sup>

The current approach to managing myocardial ischemia predominantly emphasizes on "epicardial coronary obstruction-first" strategy. This approach assumes that obstructive atherosclerosis serves as the primary and immediate cause of myocardial ischemia. Consequently, when obstructive atherosclerosis is present, there is often minimal exploration of other potential alternative or coexisting mechanisms contributing to ischemia. Despite guideline recommendations advocating a broader perspective, contemporary clinical practice predominantly revolves around addressing obstructive epicardial coronary artery disease (CAD). The therapeutic objective remains focused on alleviating flow-limiting coronary stenoses. Consequently, revascularization procedures are commonly performed. However, in several clinical studies and meta-analyses, revascularization was not found to be associated with improved survival in ischemic patients.<sup>9-10</sup>

In recent years, our understanding of ischemic heart disease (IHD) has evolved significantly. Recent

research has prompted a reconsideration that other mechanisms can also lead to myocardial ischemia, either independently or in combination. This new perspective acknowledges that myocardial ischemia is a multifactorial condition. Scientific evidence has shown that obstructive coronary atherosclerosis is not consistently associated with myocardial ischemia, and conversely, myocardial ischemia can occur even in the absence of obstructive atherosclerosis.<sup>11-16</sup> Several studies and registries have found an inconsistent association between atherosclerosis and myocardial ischemia.<sup>15-19</sup> Non-vascular factors such as abnormalities in cardiac energy metabolism and changes in blood rheology due to platelet activation or inflammation should be considered as contributors to myocardial ischemic syndromes on top of vascular mechanisms.<sup>11</sup>

Chronic stable angina, the most common symptom of ischemic heart disease, necessitates effective management strategies. While revascularization procedures such as percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) are often performed, drug therapy remains the cornerstone of management. Over the past one and half centuries, numerous pharmacological therapies have been developed and utilized to alleviate the symptoms of angina. The journey of anti-anginal drug development began in 1867 with the introduction of amyl nitrate<sup>20</sup>, followed by nitroglycerine in 1879<sup>21</sup>. The landscape of angina treatment was significantly transformed in 1964 with the advent of propranolol, the first beta-blocker for chronic stable angina<sup>22</sup>. Calcium antagonists became available in 1975<sup>23</sup>, and long-acting nitrate in the form of isosorbide dinitrate was introduced around the same time<sup>24</sup>. However, the earlier preparations of long-acting nitrate were hampered by the development of drug tolerance<sup>25</sup>. Subsequently, several other classes of drugs, including metabolic modulators (trimetazidine)<sup>26</sup>, ATP-

dependent potassium channel openers (nicorandil)<sup>27</sup>, I<sub>f</sub> channel inhibitors (ivabradine)<sup>28</sup>, and late inward sodium channel inhibitors (ranolazine)<sup>29</sup> were developed. Today, these therapies are broadly classified into first-line drugs (beta-blockers, calcium channel blockers, short-acting nitrates) and second-line drugs (long-acting nitrates, ivabradine, nicorandil, ranolazine, and trimetazidine). However, the comparative effectiveness of these drugs remains a topic of debate. Roberto Ferrari and colleagues conducted a comprehensive systematic review to evaluate the evidence supporting the efficacy of these treatments and concluded that There is no evidence to support the use of first and second-line treatments for the management of angina, rather the drug therapy should be tailored to each patient's need.<sup>30</sup>

Optimal medical therapy can be defined as satisfactory symptom control and prevention of events with good adherence and minimal adverse effects. In order to achieve optimal treatment in patients with CCS, drug therapies must be adapted to each patient's characteristics and preferences.<sup>31</sup> More than one antianginal is often needed for relief and early response assessment is important.<sup>31</sup>

The individualized, patient-tailored approach to treating patients from the start with any antianginal, based on the estimated mechanisms of stable angina and taking into consideration the comorbidities and tolerability of the patient, is a key aspect of optimal medical therapy. This approach ensures that patients receive tailored treatment from the start which is best suited to their specific needs and circumstances.

Traditionally, studies evaluating anti-anginal agents did not consider the underlying pathophysiology of angina symptoms when selecting patients for investigation. However, it has become evident that various mechanisms contribute to myocardial ischemia, and their impact may vary from patient to patient. In individuals with angina, increased myocardial oxygen demand and reduced coronary blood flow (due to factors like epicardial vasospasm or coronary microvascular dysfunction) play a role in the pathophysiology. Recently improved understanding of microvascular angina, including post-angioplasty angina, has added a new dimension to angina treatment.

Different classes of drugs work in distinct ways. For instance, beta blockers effectively reduce myocardial

oxygen demand but may increase coronary vascular resistance in some cases. Consequently, patients with microvascular spasm might deteriorate with beta blockers but benefit from vasodilators like calcium antagonists. Additionally, add-on therapy should align with the potential mechanisms of action, such as combination of a hemodynamic agent such as beta blocker along with a metabolic modulator like trimetazidine may be considered to achieve optimal treatment outcome. Furthermore, co-morbidities significantly influence treatment decisions. When choosing an anti-anginal drug, it's essential to consider common comorbidities such as hypertension, diabetes, mitral regurgitation, atrial fibrillation, and autonomic dysfunction, heart failure etc. In cases where specific comorbidities contraindicate certain drug classes, the appropriate treatments become clearer. Anti-anginal drugs without significant hemodynamic effects may be preferable for patients with low heart rate or low blood pressure.

In conclusion, a comprehensive understanding of myocardial ischemia, beyond the traditional "stenosis-centric" view, is essential for providing effective and personalized care to patients with angina. By embracing this multifaceted approach, we can optimize medical therapy and improve outcomes for individuals with ischemic heart disease.

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