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Chronic Coronary Syndrome and anti-angina Ranolazine

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Introduction

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive.

Coronary artery disease (CAD) is a pathological process characterized by atherosclerotic plaque accumulation in the epicardial arteries, whether obstructive or non-obstructive. This process can be modified by lifestyle adjustments, pharmacological therapies, and invasive interventions designed to achieve disease stabilization or regression. The disease can have long, stable periods but can also become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. However, the disease is chronic, most often progressive, and hence serious, even in clinically apparently silent periods. The dynamic nature of the CAD process results in various clinical presentations, which can be conveniently categorized as either acute coronary syndromes (ACS) or chronic coronary syndromes (CCS).

Discussion

The aims of pharmacological management of CCS patients are to reduce angina symptoms and exercise-induced ischaemia, and to prevent cardiovascular events. Initial drug therapy usually consists of one or two antianginal drugs. Beta-adrenergic blockers or CCBs are recommended as the first draw firm conclusions about their relative efficacies. Several second-line add-on anti-ischaemic drugs (long-acting nitrates, ranolazine, trimetazidine, and, to a lesser extent, ivabradine) may prove beneficial in combination with a beta-blocker or a CCB as first-line therapy. Ranolazine is a selective inhibitor of the late inward sodium current. Side effects include dizziness, nausea, and constipation. In addition, ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT prolonging drugs. In a placebo- controlled trial, chronic angina (n = 3565), significant reductions in recurrent ischaemia, worsening angina, and intensification of antianginal therapy were observed. In another placebo-controlled trial of patients with diabetes and CAD receiving one or two antianginal drugs, ranolazine reduced angina and sublingual nitroglycerin use with good tolerability.

Symptoms

The most frequently encountered clinical scenarios in patients with suspected or established CCS are: (i) patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea; (ii) patients with new onset of heart failure (HF) or left ventricular (LV) dysfunction and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS, or patients with recent revascularization;

(iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; and (vi) asymptomatic subjects in whom CAD is detected at screening.

Diagnostic

The general approach for the initial diagnostic management of patients with angina and suspected obstructive CAD. The diagnostic management approach includes six steps. The first step is to assess the symptoms and signs, to identify patients with possible unstable angina or other forms of ACS (step 1). In patients without unstable angina or other ACS. the next step is to evaluate the patient's general condition and quality

of life (step 2). Comorbidities that could potentially influence therapeutic decisions are assessed and other potential causes of the symptoms are considered. Step 3 includes basic testing and assessment of LV function. Thereafter, the clinical likelihood of obstructive CAD is estimated (step 4) and, on this basis, diagnostic testing is offered to selected patients to establish the diagnosis of CAD (step 5). Once a diagnosis of obstructive CAD has been confirmed, the patient's event risk will be determined (step 6) as it has a major impact on the subsequent therapeutic decisions.[1]

Patient-reported outcome measures can provide relevant and systematic information about patients' symptoms, functioning, and concerns. Patient- reported outcome measures are increasingly being implemented sequentially in healthcare, and have been shown to improve clinical care and patient experiences, communication between providers and patients (including sensitive subjects), save time in consultations, and improve provider satisfaction.[2]

Management Lifestyle Modification

Implementing healthy lifestyle behaviors decreases the risk of subsequent cardiovascular events and mortality, and is additional to appropriate secondary prevention therapy. Lifestyle recommendations and interventions are described in more detail in the 2016 ESC Guidelines on CVD prevention in clinical practice. Lifestyle factors are important and the implementation of healthy behaviors (including smoking cessation, recommended physical activity, a healthy diet, and maintaining a healthy weight) significantly decreases the risk of future cardiovascular events and death, even when controlling for evidence based secondary prevention therapy and interventions.[3]

Pharmacological treatment

Optimal treatment can be defined as the treatment that satisfactorily controls symptoms and prevents cardiac events associated with CCS, with maximal patient adherence and minimal adverse events. However, there is no universal definition of an optimal treatment in patients with CCS, and drug therapies must be adapted to each patient's characteristics and preference.[5]

The aims of pharmacological management of CCS patients are to reduce angina symptoms and exercise- induced ischaemia, and to prevent cardiovascular events. Immediate relief of anginal symptoms, or the prevention of symptoms under circumstances likely to elicit angina, is usually obtained with rapidly acting formulations of nitroglycerin. Anti-ischaemic drugs but also lifestyle changes, regular exercise training, patient education, and revascularization all play a role in minimizing or eradicating symptoms over the long-term (long-term prevention). Prevention of cardiovascular events targets MI and death associated with CAD, and focuses primarily on reducing the incidence of acute thrombotic events and the development of ventricular dysfunction. Strategies include pharmacological and lifestyle interventions, as detailed in the 2016 European Guidelines on CVD prevention in clinical practice.[4]

Conventional pharmacologic therapies exert an anti-ischemic effect by lowering determinants of myocardial O2 demand (heart rate, myocardial contractility, or wall stress). Although combination regimens of conventional antianginal therapies may provide incremental efficacy, such combination regimens may lead to excessive side effects or to a decrease in anti-ischemic efficacy.[5]

Availability of a new agent that could be used in concert with other antianginal therapies without causing excessive reductions in myocardial O2 demand determinants would be of enormous value. Ranolazine is a new antianginal agent with a novel mechanism of action that involves selective inhibition of the late sodium current. This action reduces the magnitude of ischemia-induced sodium and calcium overload and thereby improves myocardial function as well as myocardial perfusion.[6]

Initial drug therapy usually consists of one or two antianginal drugs, as necessary, plus drugs for secondary prevention of CVD. The initial choice of antianginal drug(s) depends on the expected tolerance related to the individual patient's profile and comorbidities, potential drug interactions with co-administered therapies, the patient's preferences after being informed of potential adverse effects, and drug availability. Whether combination therapy with two antianginal drugs [e.g., a beta-blocker and a calcium channel blocker (CCB)] is superior to monotherapy with any class of antianginal drug in reducing clinical events remains unclear.[8]

Beta-adrenergic blockers or CCBs are recommended as the first draw firm conclusions about their relative efficacies. When taken choice, although no RCT to date has compared this strategy to an alternative strategy using initial prescription of other anti- ischaemic conversion and is generally lower than the bioavailability of isosorbide drugs, or the combination of a beta-blocker and a CCB.[9] The results of a network meta-analysis of 46 studies and 71 treatment comparisons supported the initial combination of a beta-blocker and a CCB.[10]

The same meta-analysis suggested that several second-line add-on anti- ischaemic drugs (long-acting nitrates, ranolazine, trimetazidine, and, to a lesser extent, ivabradine) may prove beneficial in combination with a beta- blocker or a CCB as first-line therapy, while no data were available for nicorandil. However, it should be noted that the study pooled RCTs using endpoints of nitrate use, angina frequency, time to angina or to ST- segment depression, and total exercise time, and no study or meta-analysis has yet assessed with sufficient power the influence of combining a beta-blocker or a CCB with a second line anti-ischaemic drug on morbidity or mortality events.

One of the choices from 2nd line anti- angina is Ranolazine. Ranolazine is a selective inhibitor of the late inward sodium current. Side effects include dizziness, nausea, and constipation. In addition, ranolazine increases QTc, and should therefore be used carefully in patients with QT prolongation or on QT prolonging drugs.

In a placebo-controlled trial of 6560 patients with non-ST-segment elevation ACS, the addition of ranolazine to standard treatment did not prove effective in reducing the primary efficacy endpoint of cardiovascular death, MI, or recurrent ischemia.[11] However, in the relatively large

subgroup of patients with chronic angina (n = 3565), significant reductions in recurrent ischaemia, worsening angina, and intensification of antianginal therapy were observed.[12] In another placebo-controlled trial of patients with diabetes and CAD receiving one or two antianginal drugs, ranolazine reduced angina and sublingual nitroglycerin use with good tolerability.[13]

In the RIVER-PCI (Ranolazine for Incomplete Vessel Revascularization Post-Percutaneous Coronary Intervention) trial, ranolazine did not reduce the composite of ischaemia- driven revascularization or hospitalization without revascularization in 2651 patients with a history of chronic angina and incomplete revascularization after PCI, including those with and without PCI for a CAD indication, nor did it reduce angina symptoms at 1 year.[14]

Conclusions

In summary, we identified that frontal QRS-T angle have a positive correlation with moderate strength correlation to myocardial perfusion defect (MPD) in this study. The wider FQRST angle will show the higher myocardial perfusion defect in STEMI patients. We also found FQRST angle $\geq 70^{o}$ has a 70,6% sensitivity and 82,6% specificity to predict large infarct area (MPD > 22,8). The limitations of this study are small sample size over another previous study, and only performed in single center. The further study is needed with larger sample size.

These results support the use of ranolazine as a second-line drug in CCS patients with refractory angina despite commonly used anti- anginal agents such as beta-blockers, CCBs, and/or long-acting nitrates. Conversely, there is a lack of evidence to support the use of ranolazine in patients with CCS following PCI with incomplete revascularization.

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