Diagnostic and Therapeutic Considerations to Tailor Treatment for Angina Patients

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Key discussion focus

Chronic Ischemic Syndromes (CIS) has been formerly known as an inevitable result of atherosclerotic obstruction of the coronary vessels, yet recent discoveries have revealed that myocardial ischemia is indeed a complex and multifactorial syndrome.[1]

Late clinical events of stable angina patients are not essentially the aftermath of ischemic vascular territory subtending a stenotic coronary segment, but may be due to new plaque ruptures in remote coronary segments without flow-limiting stenoses or even for other vascular and/or non-vascular causes which may not be amendable by percutaneous coronary intervention (PCI).[2]

In view of the new scenario of CIS as a complex and multifactorial condition, medical therapy and revascularization procedures are no longer competitive options but treatment shall be customized according to individual patient needs.

Trimetazidine as a versatile agent with promising cardioprotective efficacy and good tolerability profile, is an ideal choice for most of the CIS patients.

Overthrowing mistaken belief in CIS

The belief that atherosclerotic obstruction of coronary blood vessels is an essential cause of CIS has been rooted in the medical field.[1] However, a lot of patients presenting with evidence of myocardial ischemia may not have visible coronary atherosclerosis at angiography and some patients with severe coronary atherosclerosis do not suffer from myocardial ischemia the other way round.[1] According to the pre-test probability (PTP) from 2019 European Society of Cardiology (ESC) Chronic Coronary Syndrome (CCS) Guidelines, only an insignificant 32% of males and 13% of females in the age group of 50-59 were presented with typical angina symptoms, reflecting that the prevalence of coronary stenosis in anginal patients may not be that high.[3] This leads to a question of whether the direct causal relationship between coronary atherosclerosis and ischemic heart disease (IHD) has been casually postulated. In view of this, cardiology experts have called for a Copernican Revolution to look into the real causes of CIS.[1] It was found that there are a number of other mechanisms that could trigger myocardial ischemia, including "spontaneous" thrombosis, coronary vasospasm, inflammation, microvascular dysfunction, endothelial dysfunction, and angiogenesis (Figure 1).[1] Therefore, myocardial ischemia shall be focused upon rather than obstructive coronary atherosclerosis.

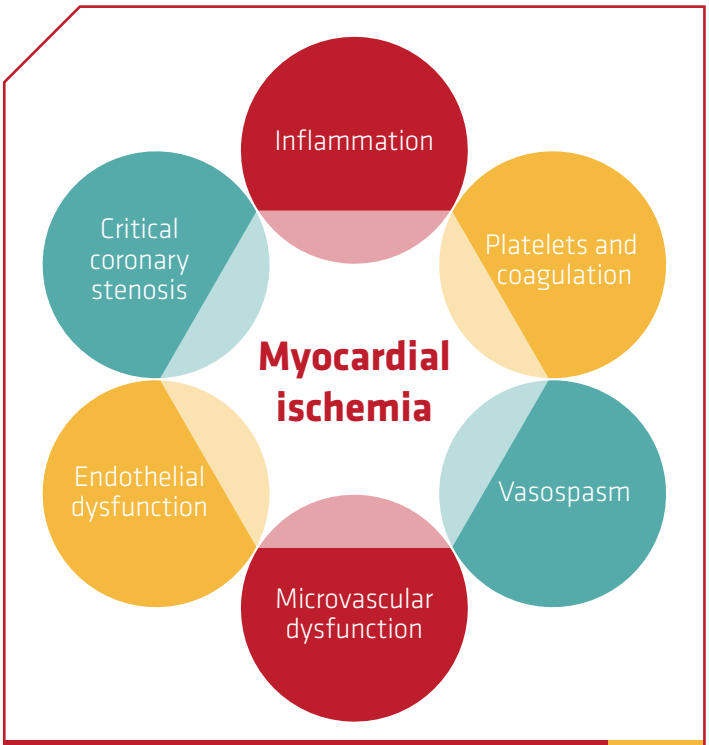


Figure 1.
The Copernican Revolution: the "ischemia-centric" hypothesis

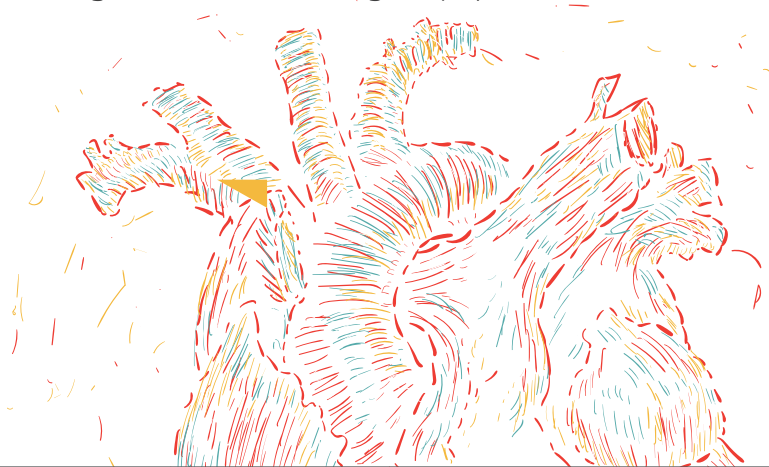
Myocardial ischemia is indeed a complex and multifactorial syndrome[1]

PCI may not be the panacea for all types of IHD

Multiple studies have shown that PCI on top of medical therapy had not lowered mortality and the risk of ischemic cardiovascular events as compared to medical therapy alone in stable patients with ischemia. A study randomly assigned 5,179 patients with stable ischemic heart disease to an initial management strategy of medical therapy alone or medical therapy plus PCI (PCI group). Over a median of 3.2 years, 318 primary outcome events occurred in the PCI group and 352 occurred in the medical therapy group. There were 145 deaths in the PCI group and 144 deaths in the medical therapy group.[4] The results did not show that the PCI group had reduced risk of ischemic cardiovascular events or death from any cause when compared with the medical therapy group. Similarly, a US study followed up the survival of 1,121 patients with stable ischemic heart disease (sIHD) for up to 15 years also showed that there was no outcomes difference between the groups receiving PCI plus medical therapy group and medical therapy alone.[5] Another notable fact is that even with contemporary drug eluting stents (DES), patients with sIHD remain at considerable risk for long-term major adverse cardiovascular events after revascularization with PCI.[6]

So can we assert that PCI is unproductive for stable angina patients? The reason that PCI may not yield satisfactory results for patients with sIHD is that late clinical events are not essentially the aftermath of ischemic vascular territory subtending a stenotic coronary segment, but may be due to new plaque ruptures in remote coronary segments without flow-limiting stenoses, or even other vascular and/or non-vascular causes.[2] Therefore, the distinct benefit of PCI primarily manifests in patients with unstable coronary artery disease (CAD), in which it almost halves the mortality in patients with ST-elevation myocardial infarction (STEMI) when compared with initial conservative therapy.[7]

On the other hand, medical therapy remains the cornerstone for CAD treatment, irrespective of whether patients have undergone PCI and the different possible underlying cause(s) for ischemia/angina.[3] It is because medical therapy aims to reduce angina symptoms and exercise-induced ischemia and to prevent cardiovascular events, which favours both stable and unstable CAD.[3,8] Anti-anginal drug therapy is also recommended by current clinical guidelines to control angina symptoms.[8]



Personalized medical therapy to achieve maximum efficacy

Owing to the fact that CIS has complex causes, medical therapy has to be customized to meet individual patient needs. First and foremost, early detection and diagnosis of ischemia is the pre-requisite.[1] Therefore, whether patient has ischemia has to be cautiously examined, looking into symptoms, ECG, regional wall function, myocardial perfusion defect and lactate production, according to Prof. Marzilli. Following the diagnosis of ischemia, identifying the precipitating mechanism is the next step. Chronic stable angina can be categorized into stable, vasospastic and microvascular, with sub-causes such as metabolic dysfunction, vasospasm, endothelial dysfunction, microvascular dysfunction and inflammation. Ideally, the choice of anti-anginal drugs should take the underlying mechanism of angina, efficacy, tolerability, comorbidities and potential drug-drug interaction into account.

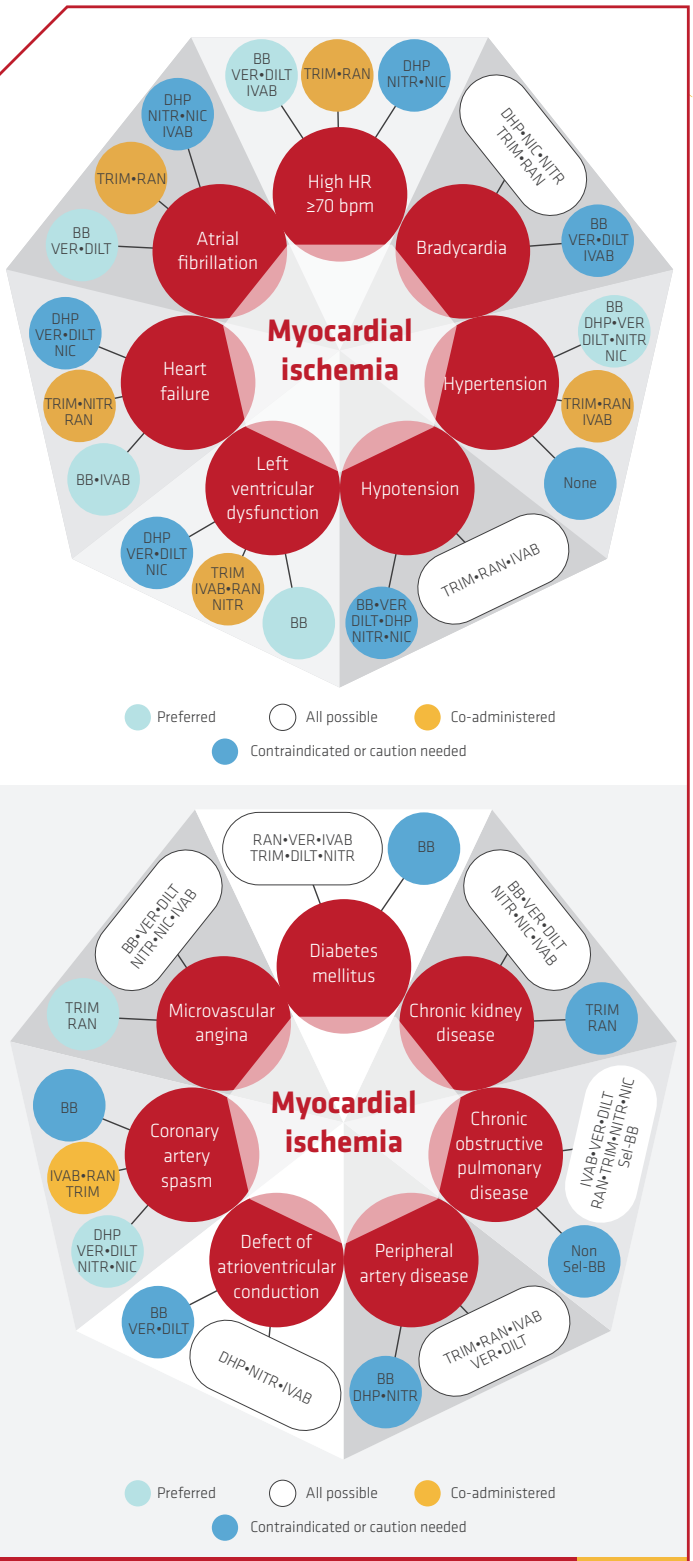
Anti-anginal drug therapy aims to ameliorate symptoms of chronic stable angina, to prolong angina-free walking time and to improve quality of life.[8] The "Diamond" approach which has been advocated to adopt particular drugs or combinations of drugs for specific pathophysiologies or comorbidities. Figures 2 and 3 show the recommendations of anti-anginal drugs used in different conditions.

Trimetazidine as a multi-functional complementary drug

Trimetazidine is a metabolic agent that inhibits fatty acid oxidation and boosts adenosine triphosphate (ATP) production during ischemic state for cardiac cells, hence effectively ameliorates angina symptoms and improves quality of life as well as exercise tolerance.[8] In contrast to other anti-anginal drugs that aim to reduce energy demand, trimetazidine enhances the energy supply by increasing cardiac ATP production by 33% and therefore relieves ischemia, even when the underlying cause(s) of CIS are complicated and often unknown.[9]

In addition, trimetazidine is a haemodynamically neutral drug[3,8] which partially contributes to its versatility of being suitable to 12 out of 14 clinical comorbidities such as hypotension, diabetes, atrial fibrillation, left ventricular dysfunction, microvascular angina, to name but a few.[8] This advantageous property makes it more superior than other haemodynamic agents e.g. long acting nitrates (LAN) in terms of its applicability.[8] Together with the fact that it has mild and well-tolerated side effects, its class of recommendation has being upgraded from IIB to IIA in the 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes.[3]

Trimetazidine also demonstrates cardioprotective efficacy in a study evaluating the effects of pre-procedural acute oral administration of trimetazidine on PCI-induced myocardial injury.[10] After taking an acute loading dose of trimetazidine prior to PCI, post-procedural cardiac troponin levels were significantly reduced in the trimetazidine group compared with the control group at all time points (6, 12, 18 and 24 hours after PCI, $p<0.001$ in all 4 time points).[10] Additionally, the total amount of cardiac troponin produced after PCI was significantly smaller in the trimetazidine group ($p<0.05$) by measuring the area under curve.[10]



Figures 2 and 3.
Possible combinations of classes of anti-anginal drugs according to different comorbidities (The Diamond approach)

BB=ß blockers; DHP=dihydropyridine calcium-channel blockers; DILT=diltiazem; HR=heart rate; IVAB=ivabradine; NIC=nicorandil; NITR=nitrates; RAN=ranolazine; TRIM=trimetazidine; VER=verapamil

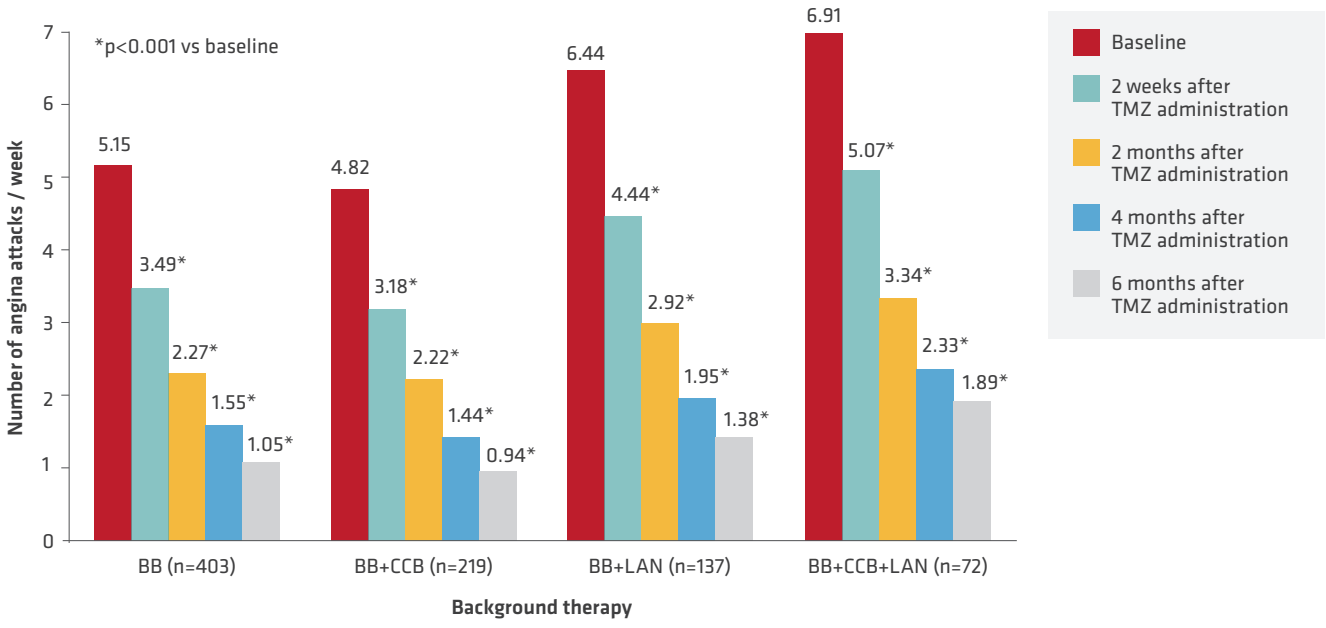


Figure 4.
Changes in weekly angina attacks in 6 months with add-on trimetazidine in the four treatment groups

BB=ß blockers; CCB=calcium channel blockers; LAN=long-acting nitrates; TMZ=trimetazidine.

Besides, a Chinese study exhibited the cardiac benefits of trimetazidine in patients after DES implantation. A total of 700 patients were randomized to receive trimetazidine or placebo post-DES implantation on top of conventional coronary heart disease treatment.[11] Patients in the trimetazidine group illustrated significant reduction in the incidence ($p = 0.024$) and severity of angina pectoris when compared with the control group, at 2-year follow-up.[11] The trimetazidine group also showed relatively stable left ventricular function and structure whereas that of control group worsened ($p < 0.01$).[11]

Furthermore, the addition of trimetazidine was shown to be effective in reducing weekly angina frequency in both short- and long-term regardless of the initial background therapy (Figure 4).[12] This result was consistent across the different treatment groups consisting of combinations among ß blockers, calcium channel blockers and LANs.[12]

Conclusion

The theory that atherosclerotic obstruction is the root cause of CIS has been subverted. Instead, CIS could be induced by intricate mechanisms. Thus, PCI, which chiefly targets the removal of atherosclerotic obstruction, may not be able to achieve anticipated goals of lessening cardiovascular risk or angina episodes in stable angina. Anti-anginal therapy on the other hand helps to reduce recurrent angina episodes in both stable and unstable CAD, with its benefit boosted by personalizing drug therapy, through targeting mechanism of CIS and comorbidities (The Diamond approach). Trimetazidine, exhibiting proven efficacy, maximum applicability, satisfactory tolerability and favourable side effect profile, is a promising anti-anginal drug to be recommended.

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