

Optimal medical therapy is vital for patients with coronary artery disease and acute coronary syndromes regardless of revascularization strategy

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Coronary artery disease (CAD) manifesting as stable angina pectoris or acute coronary syndrome (ACS) is often treated with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) in the contemporary practice. However, concomitant use of optimal medical therapy (OMT) remains essential for these patients. OMT would include aspirin, a P2Y₁₂ inhibitor (if indicated e.g., post PCI or post ACS), a lipid lowering agent (usually a statin), a β -blocker and possibly an ACE inhibitor. This editorial highlights the importance of initiation and continuation of these vital medications in cardiac patients in the context of recently published data (1,2).

OMT for stable CAD

OMT is the recommended initial choice for patients with stable angina pectoris, especially if the coronary disease is non-prognostic (3). The second Medical, Angioplasty, or Surgery Study (MASS-II), although underpowered for clinical outcomes (n=611), showed no significant difference in survival between OMT and revascularization (OMT 69%, CABG 75%, PCI 75%, P=0.09) at 10-year follow-up, despite difference in rates of myocardial infarction (MI) and repeat revascularization (4). The landmark COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial randomized 2,287

patients with significant 1-, 2- and 3-vessel CAD without left main stem involvement to OMT alone or OMT + PCI and found no significant difference in the composite endpoint of death or non-fatal MI at 4.6 years follow-up (5). Both groups were also equal in-terms of freedom from angina (5). The Fractional Flow Reserve versus Angiography for Multivessel Evaluation 2 (FAME-2) trial randomized 888 patients with stable CAD and at least one functionally significant stenosis (FFR \leq 0.80) to OMT alone versus OMT+PCI. This trial was prematurely terminated due to a highly significant difference in the incidence of the primary endpoint (a composite of death, MI, and urgent revascularization) in favor of PCI but the difference was driven by revascularization with no difference in mortality or MI (6). A meta-analysis of eight randomized clinical trials (n=7,229 patients) comparing initial coronary stent implantation versus OMT found no difference in mortality (OR 0.98; 95% CI, 0.84–1.16); nonfatal MI (OR 1.12; 95% CI, 0.93–1.34) and persistent angina (OR 0.80; 95% CI, 0.60–1.05) over a mean weighted follow-up of 4.3 years (7). CABG, however, confers a survival benefit in patients with unprotected left main stem or three-vessel CAD, particularly in those with severe symptoms, early positive exercise tests, and/or impaired left ventricular function (8). Therefore, it remains appropriate to treat patients with stable CAD with OMT and the indication for

revascularization would be persistence of symptoms despite OMT and/or improvement of prognosis (3).

OMT for ACS

The importance of OMT in patients with ACS is paramount. Aspirin administration is associated with substantial reduction in major vascular events (9). Dual antiplatelet therapy (DAPT) comprising aspirin and a P2Y₁₂ inhibitor improves outcomes in ACS patients compared with aspirin alone (3). Prasugrel and ticagrelor are preferred over clopidogrel (3). DAPT, if tolerated, should be continued for a minimum of 12 months, although evidence for longer duration is emerging (10,11). ACE inhibitor and/or mineralocorticoid receptor antagonist are also indicated in post-ACS patients with evidence of left ventricular systolic dysfunction (12). Similarly β -blockers are recommended after ACS unless patient is in cardiogenic shock or decompensated heart failure (3). Kurlansky *et al.*, have recently published data from CARE (Coronary Artery Revascularization Evaluation) multicenter registry showing a significant improvement in MACE free survival with the use of antiplatelet, lipid-lowering, and β -blocker therapy ($P=0.001$ for all three medications) in 3,228 patients with non-ST elevation MI (2).

OMT post-revascularization

OMT is important and complimentary to revascularization with either PCI or CABG (5,13); however, it remains under-used, particularly after CABG (14-16). In the Euro Heart Survey, a sizeable proportion of patients with chronic stable angina, managed medically or invasively, were not on OMT and this was associated with poor outcomes (17). A post-hoc analysis of the SYNTAX (SYnergy between percutaneous coronary intervention with TAXus and cardiac surgery) trial has shown that prescription of OMT (combination of at least one antiplatelet drug, statin, β -blocker and ACE inhibitor) was only 41% at the time of discharge after revascularization (PCI or CABG) and at 5-year only one-third patients in both treatment groups were taking OMT (PCI 40% and CABG 36%) (1). OMT use was associated with a significant reduction in mortality and composite endpoint of death/MI/stroke (1). The study suggested that all the components of OMT are important for reducing adverse outcomes irrespective of revascularization strategy (1). Another recent study has shown that invasively managed CAD patients gain survival benefit with β -blockers (18).

In the CARE registry, 973 patients undergoing CABG and 2,251 patients undergoing PCI for non-ST elevation MI derived significant benefits from OMT over a long-term (CABG 67 ± 25.8 and PCI 61.8 ± 28.6 months) follow up, regardless of revascularization strategy (2). Cox regression identified continued use of OMT as an independent predictor of major adverse cardiac event-free survival (HR for non-compliance 2.79; 95% CI, 2.19–3.54; $P<0.001$) (2). Therefore it is essential that post-revascularization, patients should continue to use OMT on long-term basis. Authors have also suggested that for patients non-adherent to OMT, CABG outcomes are better than PCI whereas for patients adherent to OMT both PCI and CABG offer similar outcomes (2). Although it is retrospective data derived from sub-group analysis of modest number of patients, it is biologically plausible as CABG outcomes may not be affected by disease progression in native vessels proximal to the graft, whereas PCI only addresses the treated segment. It would therefore be reasonable to consider the likely adherence with OMT in decision making about revascularization strategy but more importantly to improve adherence in both PCI and CABG treated patients.

Improving adherence with OMT

It is well-known that adherence to medical therapy in chronic diseases, especially in asymptomatic patients, remains low. It is important to understand and address the potential reasons for this non-adherence. Patients with cardiovascular disease are generally elderly with other comorbidities and are likely to be on multiple cardiac (and non-cardiac) drugs with their potential side effects and interactions. It is important to address any issues that a patient may have and stress the importance/rationale of each drug to improve patient adherence. Most of post-ACS and post-revascularization patients are eventually followed-up by general practitioners and family physicians. There may be a misconception on part of physicians/patients that long-term OMT is not mandatory after complete revascularization. Therefore, it is important to convey the importance of OMT to wider clinical community, including cardiac surgeons, cardiologists, general practitioners and other healthcare providers to ensure that these patients receive OMT regardless of revascularization strategy. The importance of OMT should be emphasized to patients at each clinical encounter to improve compliance (19). Moreover, hospital- and community-based programs, such as the Get With The Guidelines and the Guidelines

Applied in Practice initiative, may help to improve OMT prescription and patients' compliance (20-22). These measures are likely to enhance the benefits achieved with either PCI or CABG.

Finally, it is also important to monitor the desired therapeutic effect of the medication, for example lipid profile with statins, heart rate control with β -blockers and blood pressure control. Farkouh *et al.* have shown that only 8% patients in FREEDOM (Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease) trial, 18% patients in COURAGE trial and 23% patients in BARI-2D (Bypass Angioplasty Revascularization Investigation 2 Diabetes) trial achieved target for controlling blood pressure, cholesterol, diabetes and smoking cessation (23). In CLARIFY (Prospective observational Longitudinal Registry of patients with stable coronary artery disease) registry (n=33,177), nearly 41% of patients on β -blockers had heart rate above 70 bpm (24). Therefore, it is important to periodically monitor heart rate, blood pressure, lipid profile and HbA1c to optimize the secondary prevention therapy. It was noted that 10% patients were still smoking after complex coronary intervention in the SYNTAX trial, resulting in poor outcomes (25). Therefore, along with OMT, patients should also be encouraged to adopt healthy life style including smoking cessation, healthy eating and regular exercise to gain the best possible outcomes after revascularization.

Conclusions

All patients with stable CAD or ACS should receive OMT, unless contra-indicated or not tolerated. OMT improves outcomes in these patients and may have more impact than the choice of percutaneous versus surgical revascularization. Potential lack of adherence may also affect the choice of revascularization strategy in the favor of CABG but more importantly warrants measures to improve adherence with OMT including patient and physician education and dealing with any concerns or side effects.

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Footnote

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to declare.

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