HEALTHY HEART

VOLUME-11 | ISSUE-122 | JANUARY 05, 2020

Honorary Editor :
Dr. Anish Chandarana

Many Patients are termed as stable coronary artery disease patients. It has been witnessed that quite a few patients from this large group do develop acute deterioration and need admission to hospital or even die suddenly. It is very important to identify those who are at higher risk of events and treat them with more effective preventive therapies, This article discusses about such high-risk stable coronary artery patients and treatment option for them.

Optimizing Long Term Cardiovascular Care: Pharmacological Options Available after 1 Year of Index Coronary Event

'Stabilized' CAD, after Acute Coronary Syndrome (ACS)- What is the risk?

In general, CAD patients receive intensive care for up to 6-12 months after an acute coronary event or after having undergone percutaneous or surgical intervention. After this time frame, patients are considered to be in stable phase, and there is leniency in treatment approach at patients' and often at care provider level as well.

However, "stable CAD" is quite huge and heterogenous group, and not all subgroups are at equal risk. Large, well designed studies report ischemic recurrence occurs in 5-10% of patients with stable CV disease each year. Patients with prior ischemic event, those who have undergone revascularization procedure, those with multivessel disease, those with comorbid disease like peripheral artery disease (PAD)/carotid artery disease, Diabetes Mellitus (DM), Chronic Kidney Disease (CKD) and Heart Failure (HF) are at increased risk of future CV events. As per estimates, patients with CV disease have a 20-60% increased risk of MI, 40% increased risk of stroke, and two-fold to six-fold increased risk of death. Thus, preventive therapy in 'stable' phase also has to be effective, intensive, and continued for long term, more so for high-risk CAD patients.

Chronic Coronary Syndromes

Recognizing and endorsing this high risk in stable CAD patients, Guidelines published by European Society of Cardiology (ESC) in 2019 have used new terminology Chronic Coronary Syndrome (CCS), instead of Stable CAD. CCS, rather than stable CAD, accurately describes the dynamic continuum of CAD. Even in clinically apparent silent periods, disease is progressing at varying pace in all individuals; and it can become unstable at any time, typically due to an acute atherothrombotic event caused by plaque rupture or erosion. Thus, Stable CAD is just a myth for few, and this word can be misleading in providing optimum care to high-risk CAD patients.

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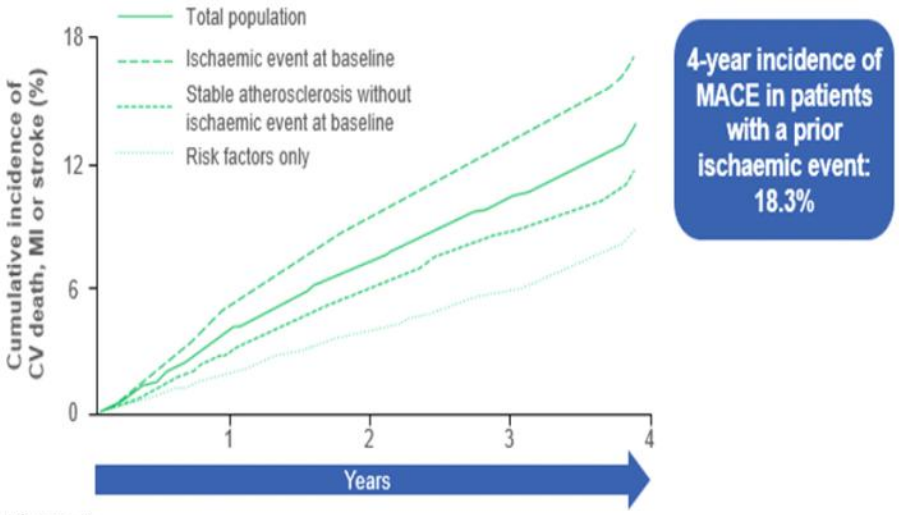
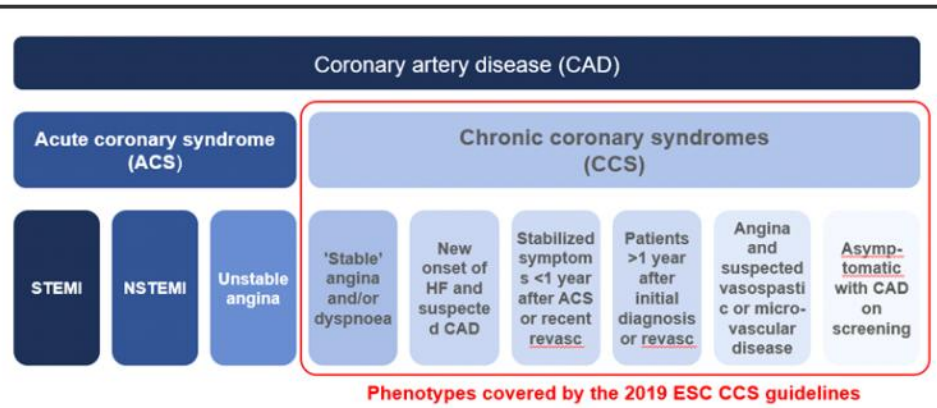


Figure 1:
Incidence of MACE according to the history of ischaemic events in the REACH registry

The dynamic nature of CAD process results in various clinical presentations that is categorized either as Acute Coronary Syndrome (ACS) or Chronic Coronary Syndrome (CCS). Most frequently encountered clinical scenarios in patients with CCS can be described as shown below.



Event Prevention: Evolution of Anti-thrombotic therapies

Lifestyle changes including smoking cessation, regular exercise, healthy diet, weight management, and medical therapies to control dyslipidemia, hypertension, diabetes mellitus play an important role in limiting atherosclerosis and reducing CV risk.

In terms of Antithrombotic options, antiplatelet therapies that inhibit platelet function, and anticoagulant therapy that interferes in coagulation cascade are relevant, and have been widely studied.

All guidelines do recommend one antiplatelet therapy, preferably aspirin (or clopidogrel, if patient is allergic to aspirin) to be continued indefinitely in all patients (if there is no serious bleeding risk) after 1 year of index acute coronary event or revascularization procedure for secondary prevention. Aspirin is good, but not sufficient to prevent subsequent all ischemic events.

Many trials have tested impact of adding or continuing another antiplatelet agent (Clopidogrel, Prasugrel, Ticagrelor) or anticoagulant agent (vitamin K antagonist [VKA] namely Warfarin or one of the direct oral anticoagulants [DOAC] namely Apixaban, Rivaroxaban, Dabigatran) beyond one year of index ACS event or revascularization. One common (and intuitively appealing also,) finding of all these trials using two agents, has been reduction in ischemic event at a small but significant cost of major and minor bleeds. Finding right candidates who have more ischemic risk and less bleeding risk is the prime important point. Various comorbid clinical conditions and high-risk markers obtained through blood investigations/imaging or history do help to define who would benefit most. On the other hand, not all combinations of medicines do equally well in terms of net clinical benefits (ischemic protection minus bleeding risk). Science has done quite good efforts to find the best combination with proper doses of each medicine.

1. ASPIRIN AS A SINGLE AGENT:

The Antithrombotic Trialists' (ATT) Collaboration's meta-analysis, comprising of 195 RCTs of antiplatelet therapy, concluded that antiplatelet therapy, particularly with aspirin significantly reduced the relative risk of subsequent vascular events (nonfatal MI, nonfatal stroke, and vascular death) by approximately 22%. Patients with prior evidence of CV disease including prior or acute MI, prior or acute stroke or TIA, and other high-risk groups such as unstable angina, stable angina, PAD, Post CABG, Post PCI, atrial fibrillation and valvular disease were included.

American College of Cardiology (ACC) and European Society of Cardiology (ESC) recommend life-long daily use of aspirin for

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secondary prevention in patients with coronary artery disease. In case of Aspirin intolerance, guidelines recommend Clopidogrel for secondary prevention.

2. ADDING CLOPIDOGREL TO ASPIRIN:

Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events CHARISMA Trial compared a small dose of Aspirin (75-150 mg) with placebo vs a small dose of aspirin with Clopidogrel 75 mg daily with a mean follow up of 28 months. This trail enrolled two different categories of patients: 1. Those with clinically evident atherothrombosis (N=12,153; symptomatic) 2. Those with multiple risk factors without clinical manifestation (asymptomatic). The first group is relevant for our topic. There was 12% RRR in the primary end point (a composite of myocardial infarction, stroke, or death from cardiovascular causes) among patients treated with clopidogrel as compared to placebo(P=0.046). Clopidogrel had no significant effect on death from cardiovascular causes. The rates of GUSTO-defined severe bleeding among these symptomatic patients were numerically more in clopidogrel arm (1.6% and 1.4%; P=0.39). The rates of moderate bleeding were worse with Clopidogrel (2.1% and 1.3%; P<0.001). The investigators concluded, though there was a potential benefit of combination therapy in symptomatic patients (those with established vascular disease); this finding required further study.

3. ADDING CLOPIDOGREL OR PRASUGREL TO ASPIRIN:

Twelve or 30 Months of Dual Antiplatelet Therapy after Drug-Eluting Stents- DAPT Trial enrolled 9961 patients after they had undergone a coronary stent (Bare Metal or Generation 1 Drug Eluting Stents) procedure. After 12 months of treatment with a thienopyridine drug (clopidogrel or prasugrel) and aspirin, patients were randomly assigned to continue receiving thienopyridine treatment or to receive placebo for another 18 months; all patients continued receiving aspirin. Continued treatment with thienopyridine, as compared with placebo, reduced the rates of stent thrombosis (0.4% vs. 1.4%; P<0.001) and major adverse cardiovascular and cerebrovascular events (4.3% vs. 5.9%; P<0.001). The rate of myocardial infarction was lower with thienopyridine treatment than with placebo (2.1% vs. 4.1%; P<0.001). The rate of death from any cause was 2.0% in the group that continued thienopyridine therapy and 1.5% in the placebo group (P=0.05). This difference was due to more cancer deaths in thienopyridine group, which was a chance finding. The rate of moderate or severe bleeding was increased with continued thienopyridine treatment (2.5% vs. 1.6%, P=0.001). This trial did inspire the medical world to define a model which can help to select patients who would have significant net clinical benefit by dual antiplatelet treatment beyond 1 year.

4. ADDING TICAGRELOR TO ASPIRIN:

Long-Term Use of Ticagrelor in Patients with Prior Myocardial Infarction: PEGASUS-TIMI 54 Trial randomly assigned, in a double-blind 1:1:1 fashion, 21,162 patients who had a myocardial infarction 1 to 3 years earlier and had one of the following additional high-risk features: age of 65 years or older, diabetes mellitus requiring medication, a second prior spontaneous myocardial infarction, multivessel coronary artery disease, or chronic renal dysfunction, defined as an estimated creatinine clearance of less than 60 ml per minute. Patients were followed for a median of 33 months. Ticagrelor 60 mg BD with Aspirin reduced the rate of the primary efficacy end point (composite of cardiovascular death, myocardial infarction, or stroke) at 3 years vs placebo (P=0.004). Rates of TIMI major bleeding were higher with ticagrelor than with placebo (P<0.001); the rates of intracranial hemorrhage or fatal bleeding in the three groups were 0.63%, 0.71%, and 0.60%, respectively. There was no difference in mortality. Thus, in general, the 60-mg Ticagrelor with Aspirin may offer a more attractive benefit–risk profile with a lower rate of discontinuation of the study drug.

5. ADDING A SMALL DOSE OF RIVAROXABAN:

Rivaroxaban is a direct Factor Xa inhibitor, and it prevents thrombosis by interfering with conversion of prothrombin to thrombin (coagulation pathway). By inhibiting thrombin generation, rivaroxaban reduces platelet activation also. Dual pathway inhibition with Rivaroxaban and Aspirin; exerts synergistic effects. Rivaroxaban has high oral bioavailability and routine monitoring of any bleeding profile is not required. For vascular protection, Rivaroxaban 2.5 mg BID, in addition to Aspirin 75-100 mg is tested.

In COMPASS (Cardiovascular Outcomes for People Using Anticoagulation Strategies) trial of 27395 patients with stable atherosclerotic vascular disease (coronary artery disease and/or peripheral artery disease), Rivaroxaban 2.5 mg BID in addition to Aspirin, significantly lowered the rate of primary outcome by 24% (composite of MI, CV death, stroke) as compared to Aspirin 100 mg OD monotherapy (P<0.001) at a mean follow up of 23 months. Total death was reduced by 18% (P<0.01) in the combination arm as compared to Aspirin monotherapy. Major bleeding was increased in combination therapy (3.1%), compared to

Aspirin monotherapy (1.9%) by 70% (P<0.001). But fatal bleeding or intracranial bleeding was not significantly different between two arms. Net-clinical-benefit outcome clearly favored Rivaroxaban 2.5 mg BID plus Aspirin (P<0.001). In 7470 patients with peripheral artery disease (PAD), rivaroxaban plus aspirin reduced the composite endpoint of MACE by 28%, MALE (major Adverse Limb Events) by 46% and major amputation by 70%.

For the First time, a NOAC, Rivaroxaban, in addition to Aspirin, showed significant reduction in MACE in patients with stable cardiovascular disease, without significantly increasing fatal or critical organ bleeding. First time, any therapy showed significant benefit in reducing all-cause mortality. Greater absolute reduction was seen in higher risk patients i.e. CAD patients with PAD, DM, CKD, HF.

Based on all above evidence, ESC CCS 2019 guidelines have recommended addition of second antithrombotic drug to Aspirin in moderate-high ischemic risk patients.

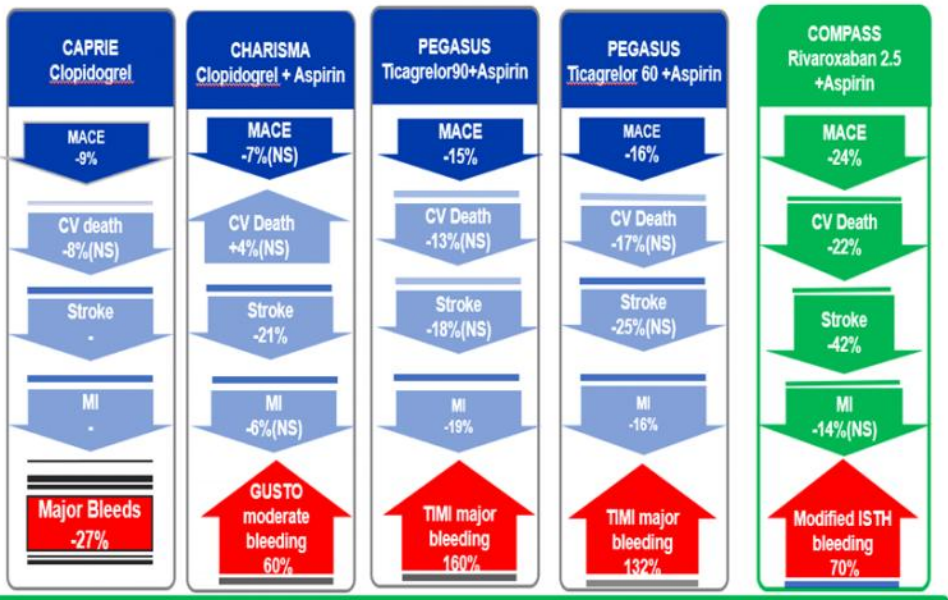
Recommendations	Class	Evidence level
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events and without high bleeding risk	IIa	A
Adding a second antithrombotic drug to aspirin for long-term secondary prevention may be considered in patients with at least a moderately increased risk of ischaemic events and without high bleeding risk	IIb	A

Moderate ischaemic risk defined as:

- **At least 1** of the following:
  - Multivessel/diffuse CAD
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - HF
  - CKD with eGFR 15–59 ml/min/1.73 m²

High ischaemic risk defined as:

- Diffuse multivessel CAD with **at least 1** of the following:
  - Diabetes mellitus requiring medication
  - Recurrent MI
  - PAD
  - CKD with eGFR 15–59 ml/min/1.73 m²



COMPASS is the only antithrombotic regimen showing significant reduction in All cause mortality

SELECTION OF ANTITHROMBOLIC THERAPY FOR LONG TERM PREVENTION :

Below table provides snapshot of MACE and safety outcomes of currently available and approved strategies for long term risk reduction in CCS/CAD patients.

Needless to say, cross-trial results are not meant for direct comparison. As seen above, studies with single/dual antiplatelet approach show 9-16% of MACE reduction, whereas dual pathway inhibition approach with Rivaroxaban and Aspirin, showed overwhelming 24% MACE reduction. Individual component of MACE outcomes also largely favor Rivaroxaban based long term preventive approach. CV death (22%), stroke (42%) is reduced significantly; and MI is reduced by 14% (non-significant). In case of ticagrelor studies, MI as individual component is significantly reduced compared to Aspirin alone.

In patients with chronic coronary syndrome, with or without history of acute event, optimal duration is still a topic of debate, but multiple RCT evidence now supports use of DAPT (dual antiplatelet therapies) or use of DPI (dual pathway inhibition with Aspirin and Rivaroxaban) for at least up to 3 years duration, especially in patients with high ischemic risk. Bleeding incidence increases with combination therapies. However, net clinical benefit favors use of combination therapies.

Careful assessment of ischemia and bleeding risk is recommended for each patient. A continued dialogue with patient to make him a partner in decision process is necessary in providing optimum care as part of long-term preventive strategy.

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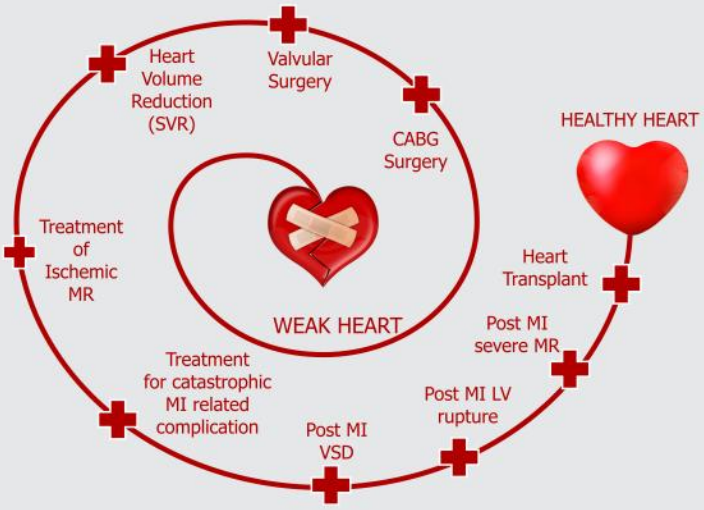

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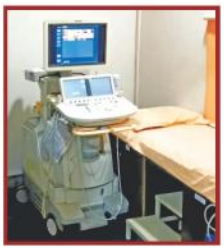

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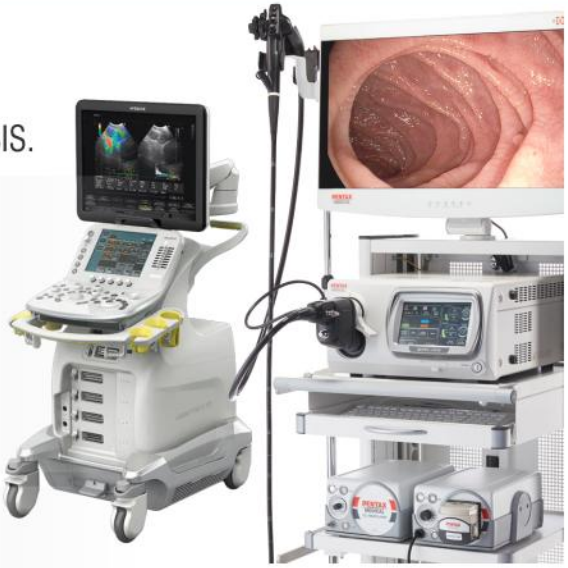

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Echocardiography Fellowship Programme

Registration Fees : ₹ 35,000/-*

CIMS Learning Centre 2020

Course Directors : Dr. Satya Gupta / Dr. Milan Chag / Dr. Tejas V. Patel / Dr. Vineet Sankhla
Date : One Week (Monday to Saturday)
Duration : 6 days
Number of Seats : 15
Venue : CIMS Auditorium

Programme Highlights:

- 6 days extensive teaching of echocardiography
- Easy access to faculty members
- Supervised hands-on practice
- Provision of course materials (Textbook of Echocardiography)

Programme Overview:

Sights and Sounds of Echocardiography at CIMS Hospital is a premier education course for Echocardiologists, Fellows in training, and Physicians in clinical practice. Over the past few years, we have trained and taught more than 1000 candidates. This unique programme is intended for those who want to learn Echocardiography right from basics. Overall programme includes lectures on basics of Echocardiography, theoretical and practical aspects of Ischemic, Valvular and Congenital Heart Disease in relation to Echocardiography and hands-on supervised training. This is the star educational programme of the CIMS Learning Centre and has been appreciated worldwide.

Schedule of Echocardiography Fellowship 2020

Month	Start Date	End Date
April	20-04-2020	25-04-2020
June	22-06-2020	27-06-2020
September	24-08-2020	29-08-2020
November	19-10-2020	24-10-2020

Online registration & payment on www.cims.org /clc

> Certificate of attendance will be given at the end of the course.

* Hotel Registration Separate

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CIMS Learning Centre

Skills Development Centre

Basic ECG Learning Course

February 23, 2020 (Sunday)

Course Directors	:	**Dr. Vineet Sankhla / Dr. Ajay Naik / Dr. Tejas V. Patel / Dr. Vipul Kapoor**
Date	:	**February 23, 2020 (Sunday)**
Duration	:	**1 day**
Number of Seats	:	**50**
Venue	:	**CIMS Auditorium**

Programme Overview:

It is important to have a sound knowledge and correct interpretation of 12-lead ECG to help in diagnosis and management of medical patients. This necessiates that not only specialists, but also other healthcare professionals like General Practitioners, Interns, Post- graduate Students, Nurses and Paramedical Staff should have basic understanding of ECG for timely diagnosis.The Basic ECG course has been designed to provide understanding on basic concepts of 12-lead ECG which will be very useful in treating Ischemic and Rhythm Disorders of heart.

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Registration Fees: ₹ 500/- | Spot Registration Fees: ₹ 1,000/-

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For any query, please email on : communication@cimshospital.org

› Certificate of attendance will be given at the end of the course.

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Printed, Published and Edited by Dr. Keyur Parikh on behalf of the CIMS Hospital
Printed at Hari Om Printery, 15/1, Nagori Estate, Opp. E.S.I. Dispensary, Dudheshwar Road, Ahmedabad-380004.
Published from CIMS Hospital, Nr. Shukan Mall, Off Science City Road, Sola, Ahmedabad-380060.