New concepts in the management of angina

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“Myths” of stable angina management

Myth 1
Ischemia / Angina are all induced by obstructive CAD?

Myth 2
Conventional “first-line” anti-anginal therapy is better than the others?

Myth 3
Personalized angina management – to be or not to be?

Myth 4
How to choose anti-anginal drugs for angina patients?

Myth 5
Anti-anginal therapies is not necessary after invasive treatments (revascularization)?
Myth 1

Ischemia / Angina are all induced by obstructive CAD?
Only around 35% of patients with stable CAD had angina and/or ischaemia.
Angina MUST be caused by obstructive coronary atherosclerosis?

- MOST patients with typical angina indeed DO NOT have coronary atherosclerotic obstructions.
- Coronary stenosis may NOT be the ONLY cause for angina necessarily.
- The widely accepted “plaque-centric” approach for ischemic heart disease management IS NOT comprehensive enough.

**Obstructive Coronary Atherosclerosis and Ischemic Heart Disease: An Elusive Link!**

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Myocardial ischemia is a multifactorial disease…

Whatever the origin of the root cause, ischemia leads to impairment of myocardial ATP production.
Myth 2

Conventional “first-line” anti-anginal therapy is better than the others?
FAQs about anti-anginal agents

As 1st line agents, must have superior antianginal efficacy?

“Conventional” 1st line agents:
- Beta-blocker (BB)
- Calcium-channel blocker (CCB)

Better than other “2nd line agents”?

“Older generation” 2nd line agent:
- Long acting nitrates (LAN)

Prescribe only when BB, CCB and LAN not working?

“Newer generation” 2nd line agents:
- Vastarel MR (Trimetazidine)
- Coralan (Ivabradine)
- Ranexa (Ranolazine)
What did previous 2013 ESC Stable Coronary Artery Disease (SCAD) Management Guideline tell us?

Definite positioning of lines of treatments is advocated for past decades

However, international experts started to challenge this concept in recent years, WHY?

Is superiority established for 1st line therapy over 2nd line therapy?

Is pathogenesis / background / characteristics of patients being considered?
A systematic review covering 50 years of medical treatment for angina shows:

- Paucity of data
- 72 studies in total including only 7000 patients
- Of these only 13 enrolled 100 patients (50 each arm)
- Most of them are early days studies with no understanding of power calculations, hazard ratios, equivalence…
First line is better than second line
Evidence based? Or just a belief?

Beta-adrenergic blockers or CCBs are recommended as the first choice, although no RCT to date has compared this strategy to an alternative strategy using initial prescription of other anti-ischaemic drugs, or the combination of a beta-blocker and a CCB. The negative. Guidelines recommend a first-choice and a second-choice approach, based more on tradition and expert opinion, rather than evidence. This categorical approach has been questioned in the past couple of years. Newer antianginal drugs, which are classified as second choice, have more evidence-based clinical data that are more contemporary to support their use than is available for the traditional first-choice drugs. Equally, the often-needed combination of double or triple therapy is based on expert opinion and not related to the underlying pathophysiology. What constitutes optimal

Personalized angina
management – to be or not to be?
Did we routinely consider the following for our patients before the prescription of anti-anginal drugs?

- Nature of the root cause – Obstructive CAD?
- Microvascular dysfunction? Vasospasm?
- Expected drug adherence & compliance?
- Potential drawbacks of the drugs?
- Background co-morbidities?

Chronic Obstructive Pulmonary Disease (COPD)
Or we just follow the treatment algorithm below?

**Angina relief**

1st line
- Short-acting Nitrates, plus
- **Beta-blockers or CCB-heat rate**
- Consider **CCB-DHP** if low heart rate or intolerance/contraindications
- Consider **Beta-blockers + CCB-DHP** if CCS Angina > 2

May add or switch (1st line for some cases)
- Ivabradine
- Long-acting nitrates
- Nicorandil
- Ranolazine
- Trimetazidine

2nd line

**Event prevention**

- **Lifestyle management**
- **Control of risk factors**
- **Educate the patient**
- Aspirine
- Statins
- Consider ACEI or ARBs

+ Consider Angio → PCI – Stenting or CABG

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What does the new 2019 ESC Chronic Coronary Syndrome (CCS) guideline tell?

Chronic Coronary Syndrome (CCS) patient types

1. Patients with suspected CAD and ‘stable’ anginal symptoms, and/or dyspnoea
2. Patients with new onset of HF or LV dysfunction and suspected CAD
3. Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent revascularization
4. Asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization
5. Patients with angina and suspected vasospastic or microvascular disease
6. Asymptomatic subjects in whom CAD is detected at screening

Why terminology of CCS is used instead of stable CAD?
CAD patients may experience acute events or suffer from disease progression during their life time.
For recently diagnosed CCS patients, more frequent assessment and risk evaluation is required

Newly diagnosed patients should be seen at least 3-4 times within 1st year for treatment assessment and risk evaluation

Life long treatment and monitoring is required as the disease may be progressed with time (from chronic stable to acute, worsening of risk factors etc)
Again, as discussed obstructive CAD is not always the root cause.

Table 5: Pre-test probabilities of obstructive coronary artery disease in 15,815 symptomatic patients according to age, sex, and the nature of symptoms in a pooled analysis of contemporary data.

<table>
<thead>
<tr>
<th></th>
<th>Typical</th>
<th>Atypical</th>
<th>Non-anginal</th>
<th>Dyspnoea</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Men</td>
<td>Women</td>
<td>Men</td>
<td>Women</td>
</tr>
<tr>
<td>30-39</td>
<td>3%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>40-49</td>
<td>22%</td>
<td>10%</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>50-59</td>
<td>32%</td>
<td>13%</td>
<td>17%</td>
<td>6%</td>
</tr>
<tr>
<td>60-69</td>
<td>44%</td>
<td>16%</td>
<td>26%</td>
<td>11%</td>
</tr>
<tr>
<td>70+</td>
<td>52%</td>
<td>27%</td>
<td>34%</td>
<td>19%</td>
</tr>
</tbody>
</table>

CAD = coronary artery disease, PTP = pre-test probability.
For anti-anginal therapies, what are the new and revised concepts and recommendations?

Evolve from a standard "first-second line" approach to a "step-wise, patient-tailored" approach.

From definite positioning of lines of treatments

To more patient centric approach regarding both the initial and also optimal treatment options

3.3.1 Anti-ischaemic drugs
3.3.1.1 General strategy
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 preferences. 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
Despite of the unchanged positioning of BB and CCB as 1st step therapy, the current guideline emphasizes the need of tailored therapy with consideration of patients’ characteristics and preferences.

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**Figure 8** Suggest stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient’s characteristics and preferences. Given the limited evidence on various combinations of drugs in different clinical conditions, the proposed options are only indicative of potential combinations and do not represent formal recommendations. BB = beta-blocker; bpm = beats per minute; CCB = [any class of] calcium channel blocker; DHP-CCB = dihydropyridine calcium channel blockers; LAN = ranolazine; NIC = nicorandil; TRMT = trimetazidine.
Trimetazidine has been upgraded from Class IIB to IIA in the 2019 ESC CCS guideline.

Changes in major recommendations

<table>
<thead>
<tr>
<th>2013</th>
<th>Class²</th>
<th>2019</th>
</tr>
</thead>
<tbody>
<tr>
<td>For second-line treatment, trimetazidine may be considered.</td>
<td>IIb</td>
<td>Nicorandil, ranolazine, ivabradine, or trimetazidine should be considered as a second-line treatment to reduce angina frequency and improve exercise tolerance in subjects who cannot tolerate, have contraindications to, or whose symptoms are not adequately controlled by beta-blockers, CCBs, and long-acting nitrates.</td>
</tr>
<tr>
<td>In selected patients, the combination of a beta-blocker or a CCB with second-line drugs (ranolazine, nicorandil, ivabradine, and trimetazidine) may be considered for first-line treatment according to heart rate, BP, and tolerance.</td>
<td>IIb</td>
<td></td>
</tr>
</tbody>
</table>

The class of recommendation (COR) of Trimetazidine has been UPGRADED from IIB (may be considered) to IIA (should be considered).

Combination of BB / CCB with other agents (e.g. Trimetazidine, Ivabradine) can be prescribed as 1st line treatment.
Myth 4

How to choose anti-anginal drugs for angina patients?
With no doubt, our old friends BBs and CCBs are still very good anti-anginal drugs….but

"Conventional 1st line" agents:

- **Beta-blocker (BB)**

<table>
<thead>
<tr>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ HR</td>
</tr>
<tr>
<td>↓ BP</td>
</tr>
<tr>
<td>↓ myocardial contractility</td>
</tr>
<tr>
<td>↑ diastolic perfusion time</td>
</tr>
</tbody>
</table>

- **Calcium-channel blocker (CCB)**

<table>
<thead>
<tr>
<th>Mechanisms</th>
</tr>
</thead>
<tbody>
<tr>
<td>↓ Myocardial contractility</td>
</tr>
<tr>
<td>Peripheral vascular dilatation</td>
</tr>
<tr>
<td>↓ BP &amp; systemic vascular resistance</td>
</tr>
<tr>
<td>↓ Coronary vascular resistance</td>
</tr>
</tbody>
</table>

As discussed, did we consider the following?

- **NOT all angina origins are not the same!**
  Ischemic? Microvascular dysfunction? Vasospasm?

- **NOT all angina patients are the same!**
  With own characteristics, co-morbidities, difficulty for up-titration owing to drawbacks etc

- Do angina patients encounter recurrent angina attacks and restore good QoL?
Similar concept has been also advocated by a group of international experts in cardiology for the positioning of all anti-anginal drugs at the same line to tailor for individual patients’ needs.
The “Diamond” approach takes co-morbidities and pathophysiology as the key determining factors for the choices of anti-anginal drugs.
Examples illustration of “Diamond Approach” regarding the anti-anginal drugs choices.
In clinical practice - good efficacy and tolerability, synergy with other medications, wide patients applicability are key attributes for drug prescriptions

Hemodynamically active
β-Blockers
Ca++ channel blockers
Long-acting nitrates
Ivabradine
PCI...

Unique MOA of Trimetazidine—Directly acts at cardiac cell level and address the root of angina/ischemia (oxygen deficiency for effective ATP production)

Cardiac cell
Trimetazidine

3.3.1.2.7 Trimetazidine. Trimetazidine appears to have a haemodynamically neutral side effect profile. Trimetazidine (35 mg b.i.d.) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the European Medicines Agency in June

Trimetazidine helps to shift cardiac energy metabolism to maximize the ATP production during hypoxia state.

By shifting cardiac energy metabolism, from FFA to glucose, Trimetazidine provides +33% more ATP.
Chinese swim star Sun Yang failed drugs test

Multiple Olympic champion given three-month punishment for taking prohibited stimulant

China’s Olympic swimming star Sun Yang failed a doping test in May and was subsequently banned for three months, the official Xinhua news agency reported Monday.

The ban, following a positive test for the stimulant trimetazidine, was imposed in July, the agency said, citing the China Anti-Doping Agency (CHINADA).

Trimetazidine was added to the World Anti-Doping Agency’s banned list in January this year, Xinhua said. Sun said he used it for medical reasons and had been unaware that it was included on the list, it added.
Significant early and sustained reduction in angina attacks regardless of patients’ background angina duration/history

Large scale, multicenter, 6-month, open-label, prospective observational study on 741 patients with stable angina pectoris. Treatment was well tolerated and no related serious adverse events were reported.

Complementary action to other anti-anginal agents to derive extra early and long term anti-anginal efficacy

Large scale, multicenter, 6-month, open-label, prospective observational study on 741 patients with stable angina pectoris. Treatment was well-tolerated and no related serious adverse events were reported.

With its well proven efficacy and excellent tolerability, Trimetazidine can be prescribed for angina patients with different backgrounds in daily clinical practice.
How about Ivabradine? A drug for treating heart failure only? NO! It is also an useful anti-anginal agent

Unique MOA for pure heart rate reduction without affecting other parameters like BP, lipid, glucose levels

Iβ inhibition reduces the diastolic depolarization slope, and thereby lowers heart rate

Apart from heart failure, heart rate control is also important for angina patients – as optimal heart rate helps to reserve heart function and its energy demand
Synergistic anginal efficacy for Coralan plus BBs vs BB uptitration alone and Ivabradine is recommended as the preferred agent for angina patients with high HR, LVD and/or HF right after BBs by the new ESC CCS guideline.
Myth 5

Anti-anginal therapies is not necessary after invasive treatments (revascularization)?
For stable coronary disease patients, is revascularization plus medical therapy better than medical therapy alone?

A controversial topic over past 1-2 decades

COURAGE trial published in 2007

ISCHEMIA trial published in 2020
ISCHEMIA trial – simplified study design for illustration

Stress Test → Narrowing(s) coronary CT angiogram → Conservative
- medication (statins, BP), exercise, and diet
- Successful!

Stress Test → Narrowing(s) coronary CT angiogram → Invasive
- Angiogram confirmation
- Medication (statins, BP), exercise, and diet + stents and/or CABG (open heart)
ISCHEMIA trial – who are included and excluded?

Clinical and Stress Test Eligibility Criteria

**Inclusion Criteria**
- Age $\geq 21$ years
- **Moderate or severe ischemia***
  - Nuclear $\geq 10\%$ LV ischemia (summed difference score $\geq 7$)
  - Echo $\geq 3$ segments stress-induced moderate or severe hypokinesis, or akinesis
  - CMR
    - Perfusion: $\geq 12\%$ myocardium ischemic, and/or
    - Wall motion: $\geq 3/16$ segments with stress-induced severe hypokinesis or akinesis
  - Exercise Tolerance Testing (ETT) $\geq 1.5$mm ST depression in $\geq 2$ leads or $\geq 2$mm ST depression in single lead at $< 7$ METS, with angina

**Major Exclusion Criteria**
- NYHA Class III-IV HF
- Unacceptable angina despite medical therapy
- EF < 35%
- ACS within 2 months
- PCI or CABG within 1 year
- eGFR $< 30$ mL/min or on dialysis

*Ischemia eligibility determined by sites. All stress tests interpreted at core labs.

CCTA Eligibility Criteria

**Inclusion Criteria**
- $\geq 50\%$ stenosis in a major epicardial vessel (stress imaging participants)
- $\geq 70\%$ stenosis in a proximal or mid vessel (ETT participants)

**Major Exclusion Criteria**
- $\geq 50\%$ stenosis in unprotected left main
Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest

Adjusted Hazard Ratio = 0.93 (0.80, 1.08)
P-value = 0.34

Absolute Difference INV vs. CON

6 months:
$\Delta = 1.9\%$ (0.8\%, 3.0\%)

4 years:
$\Delta = -2.2\%$ (-4.4\%, 0.0\%)

Myocardial Infarction

Adjusted Hazard Ratio = 0.92 (0.76, 1.11)
P-value = 0.38
Cardiovascular death and all-cause death

Adjusted Hazard Ratio = 0.87 (0.66, 1.15)
P-value = 0.33

Adjusted Hazard Ratio = 1.05 (0.83, 1.32)
P-value = 0.67

CV death

All-cause death

Cardiovascular death and all-cause death

Adjusted Hazard Ratio (CV death): 0.87 (0.66, 1.15)
P-value: 0.33

Adjusted Hazard Ratio (All-cause death): 1.05 (0.83, 1.32)
P-value: 0.67

Subjects at Risk
CON 2591, 2065, 1445, 844, 349
INV 2588, 2061, 1431, 827, 317

Follow Up Time (Years)
CON: 2591, 2065, 1445, 844, 349
INV: 2588, 2061, 1431, 827, 317

Rationale behind why randomized trials may not demonstrate a CV/survival benefit for revascularization in SIHD patients

Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

Severe fibrotic plaque
- Severe obstruction
- No lipid
- Fibrosis, Ca\(^{2+}\)

Vulnerable plaque
- Minor obstruction
- Eccentric plaque
- Lipid pool
- Thin cap

Exertional angina
- (+) ETT

Revascularization
Anti-anginal Rx

Pharmacologic stabilization
Early identification of high-risk?

Plaque rupture
- Acute MI
- Unstable angina
- Sudden death
Optimal medical therapy indeed remained the cornerstone for patients suffering from ischemia/angina with or without PCI.
ATPCI study – the landmark trial of trimetazidine for angina patients after PCI

Objective of the study
- To demonstrate the long term efficacy and safety of trimetazidine 35mg twice daily in addition to standard therapy, in patients after PCI

Study design
- Phase III, international, multicenter, randomized, double-blind, placebo-controlled
- Trimetazidine 35mg vs. placebo on top of standard CAD therapy
- Post-PCI patients (n = 5,800)
- Duration: 2-4 years

Primary end points
A composite of
- Cardiac death
- Cardiac hospitalization
- Change of antianginal therapy due to recurrent angina
- Revascularization

Expected data publication
- ESC 2020 (late Aug to early Sept)

The efficacy and safety of trimetazidine in patients with angina pectoris having been treated by percutaneous coronary intervention.
Take home messages (1)

• Ischemia / Angina are all induced by obstructive CAD? **NO**, chronic ischemia is a multifactorial and a life-long dynamic syndrome

• Conventional “first-line” anti-anginal therapy is better than the others? **NO**, there is paucity of data supporting this claim and indeed majority of the studies for BBs/CCBs are early days study (Habit/Belief > Evidence)

• Personalized angina management – to be or not to be? **YES**, because “NOT all angina are the same and NOT all patients are the same”, both life-long follow-up and tailored medical treatment from the very beginning of diagnosis are essential
Take home messages (2)

- How to choose anti-anginal drugs for angina patients? **Apart from our old friends BBs and CCBs, can also consider other anti-anginal drugs with good efficacy and tolerability, synergy with other medications, wide patients applicability etc. As patients’ drug adherence/compliance as well as using the right drug to address the root cause of ischemia are of utmost importance, e.g. ivabradine, trimetazidine**

- Anti-anginal therapies is not necessary after invasive treatments (revascularization)? **NO, optimal medical therapy indeed remained the cornerstone for patients suffering from ischemia/angina with or without PCI**
THANK YOU FOR YOUR TIME AND PATIENCE
STAY SAFE ALL THE TIME