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

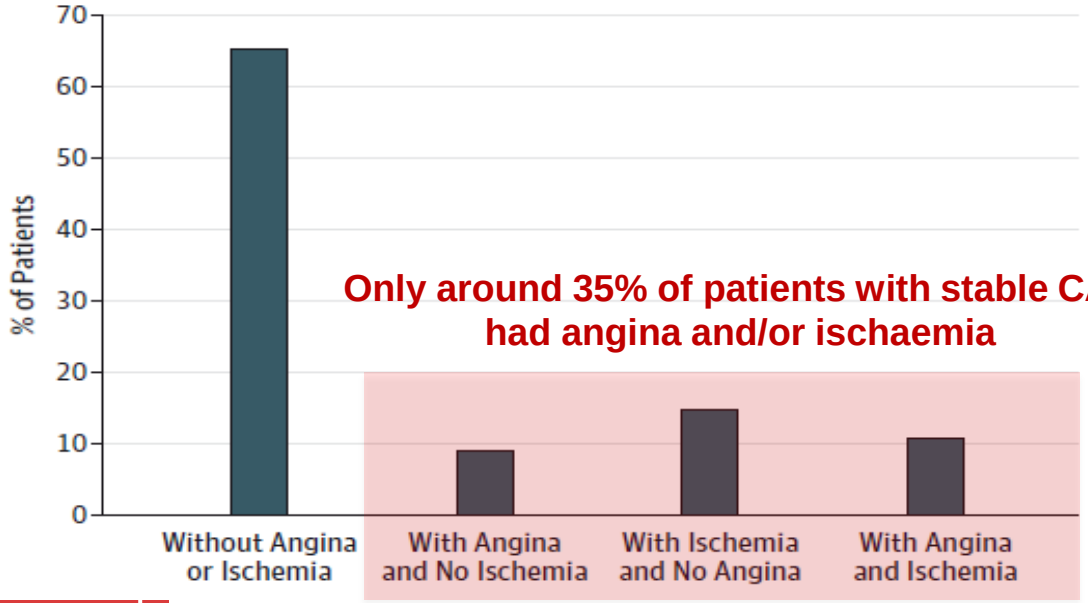
Anti-anginal therapies is not necessary after invasive treatments (revascularization)?

Myth 1

Ischemia / Angina are all induced by obstructive CAD?

Angina and ischemia? Are they 100% couple?

Figure 2. Clinical Patterns of Stable Coronary Artery Disease



Only around 35% of patients with stable CAD had angina and/or ischaemia

CLARIFY

ProspeCtive observational LongitudinAl RegIstry oF patients with stable coronary arterY disease

Steg PA et al. JAMA Intern Med. 2014;174:1651-59

Angina MUST be caused by obstructive coronary atherosclerosis?

- MOST patients with typical angina indeed DO NOT have <u>coronary atherosclerotic obstructions</u>
- 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

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STATE-OF-THE-ART REVIEW AND

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

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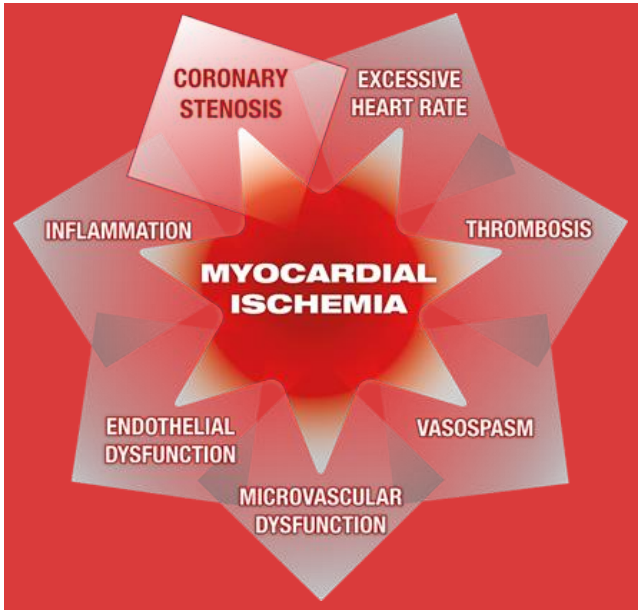
Marzilli M et al. *J Am Coll Cardiol.* 2012, 60:951-956.

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:

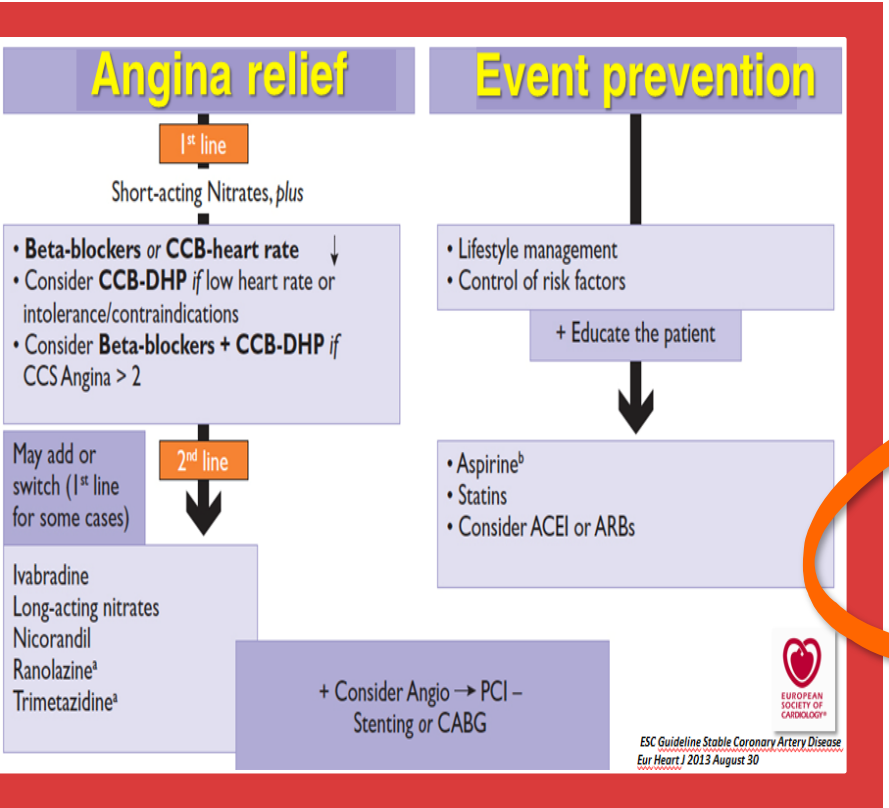
- Long acting nitrates (LAN)

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?

European Heart Journal (2013) 34, 2949–3003 doi:10.1093/eurheartj/eht296

First line is better than second line
Evidence based? Or just a belief?

VS

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.[191,195] The

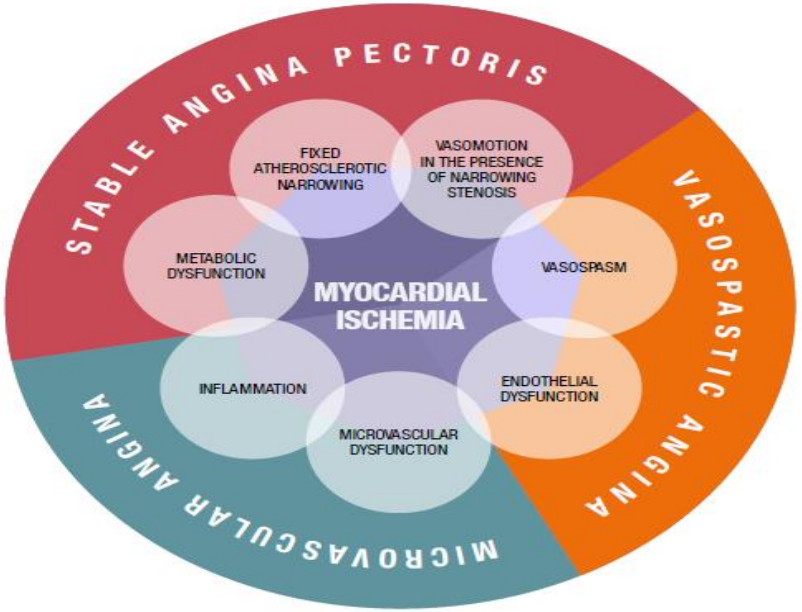
negative. Guidelines recommend a first-choice and a second-choice approach, based more on tradition and expert opinion, rather than evidence. This categorical approach has been questioned in the past couple of years[5–8]. Newer antianginal drugs, which are classified as second choice, have more evidence-based 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

1. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425
2. Roberto Ferrari et al. - Experts consensus statement: A 'diamond' approach to personalized treatment of angina - Nature Reviews Cardiology volume 15, pages 120 – 132 (2018)

Myth 3

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?

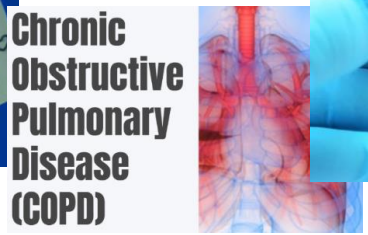
Improving our Patient's Health Outcomes

It's not just ***IF*** a patient is non-adherent, but ***WHY***

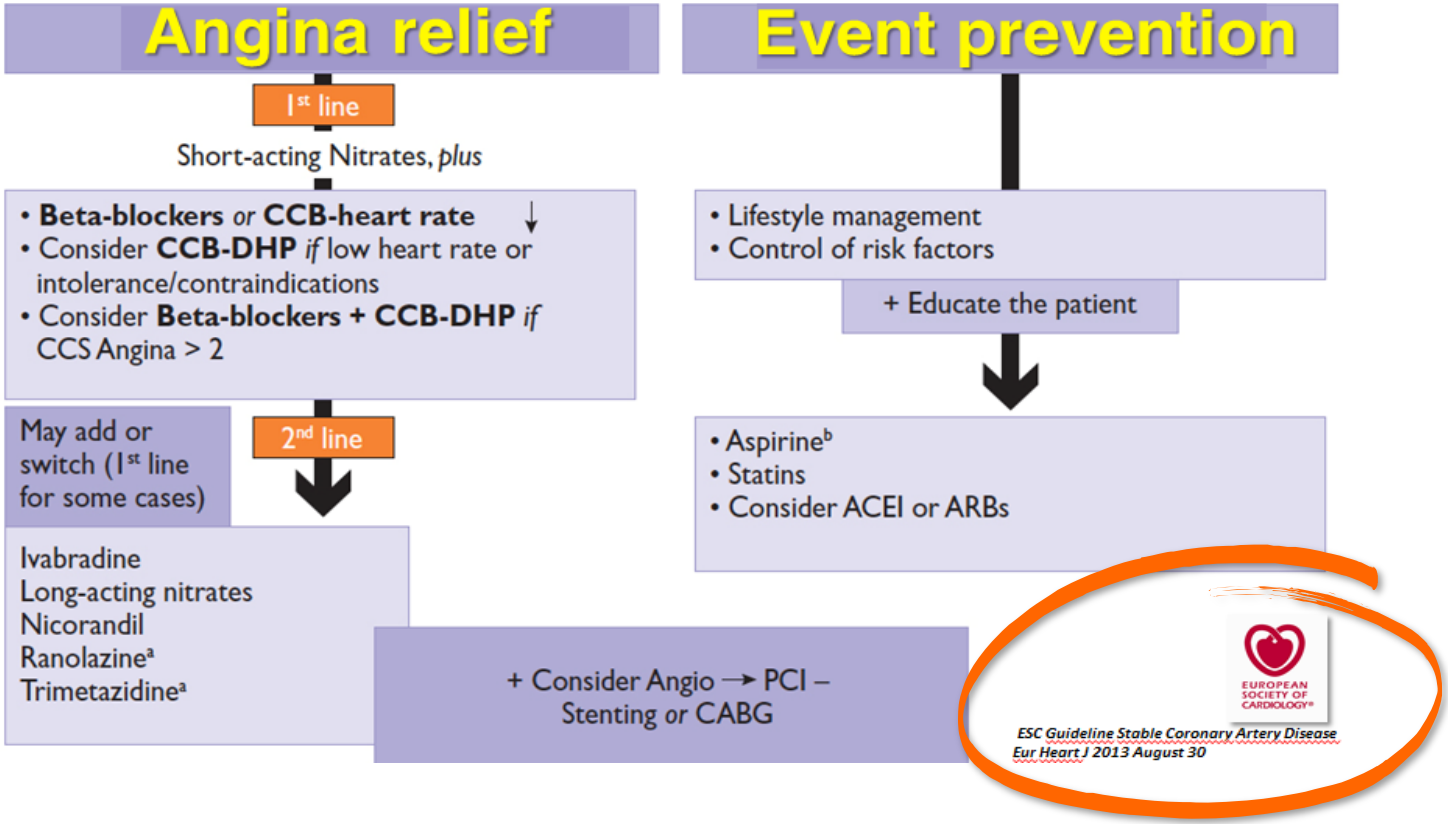
Expected drug adherence & compliance?

Potential drawbacks of the drugs?

Background co-morbidities?



Or we just follow the treatment algorithm below?



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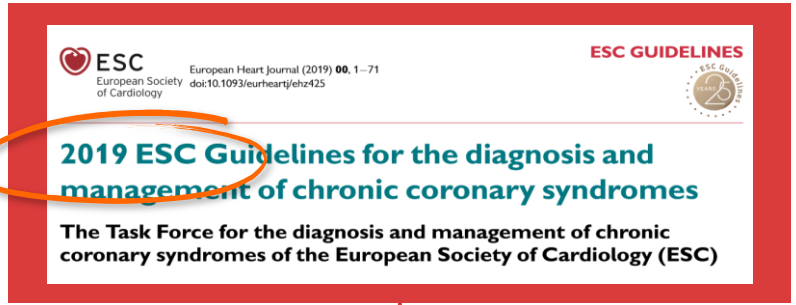
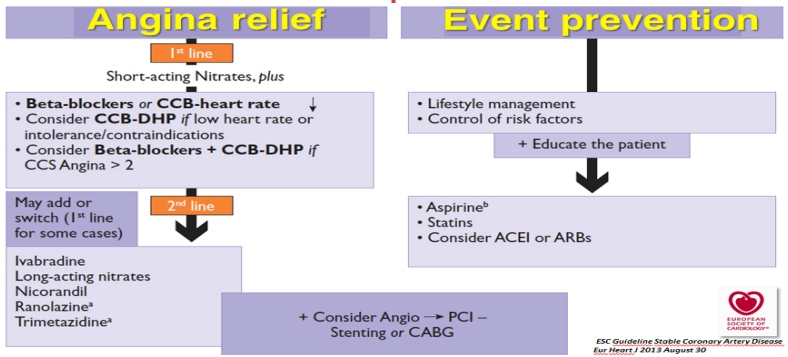
What does the new 2019 ESC Chronic Coronary Syndrome (CCS) guideline tells?





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2. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

Why terminology of CCS is used instead of stable CAD?

New/revised concepts in 2019

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The Guidelines have been revised to focus on CCS instead of stable CAD.

This change emphasizes the fact that the clinical presentations of CAD can be categorized as either ACS or CCS. CAD is a dynamic process of atherosclerotic plaque accumulation and functional alterations of coronary circulation that can be modified by lifestyle, pharmacological therapies, and revascularization, which result in disease stabilization or regression.

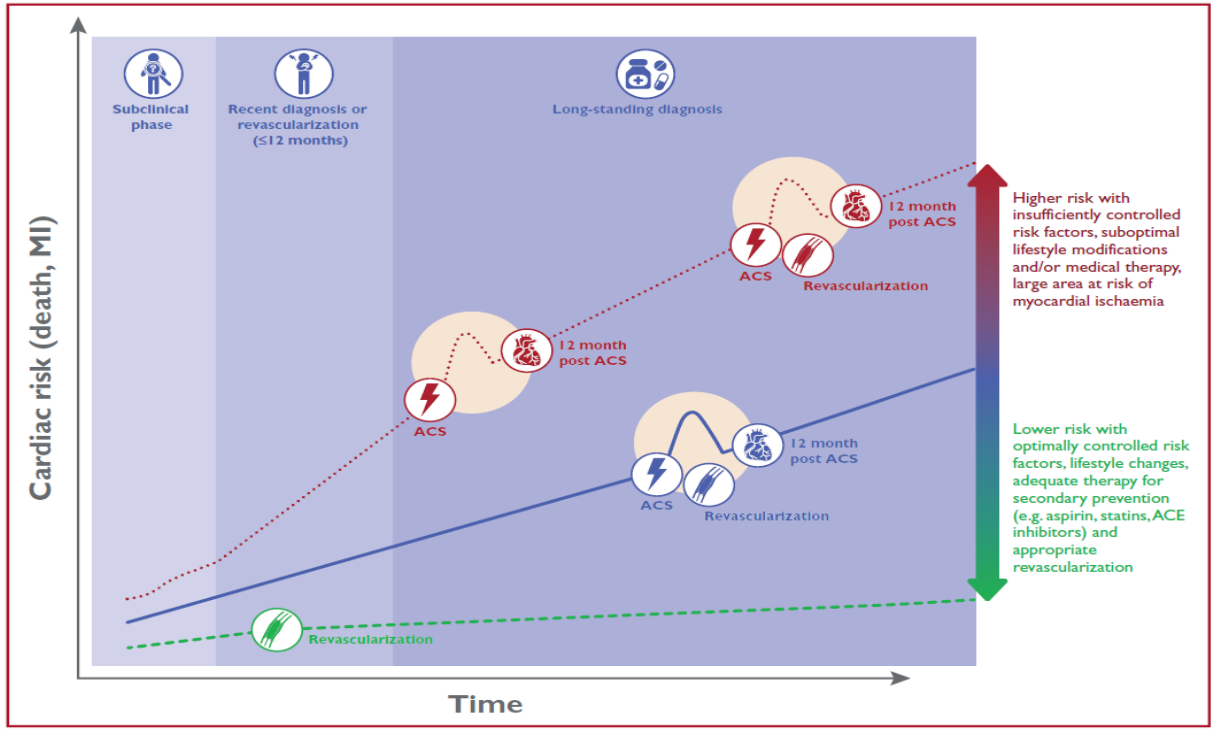
	Chronic Coronary Syndrome (CCS) patient types
1.	Patients with suspected CAD and 'stable' anginal symptoms, and/or dyspnoea
2.	Patients with new onset of HF or LV dysfunction and suspected CAD
3.	Asymptomatic and symptomatic patients with stabilized symptoms <1 year after an ACS or patients with recent 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

2 Introduction

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). The Guidelines presented here refer to the management of patients with CCS. The natural history of CCS is illustrated in *Figure 1*.

2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

CAD patients may experience acute events or suffer from disease progression during their life time



2 Categories

Acute Coronary Syndromes (ACS)

Chronic Coronary Syndromes (CCS)

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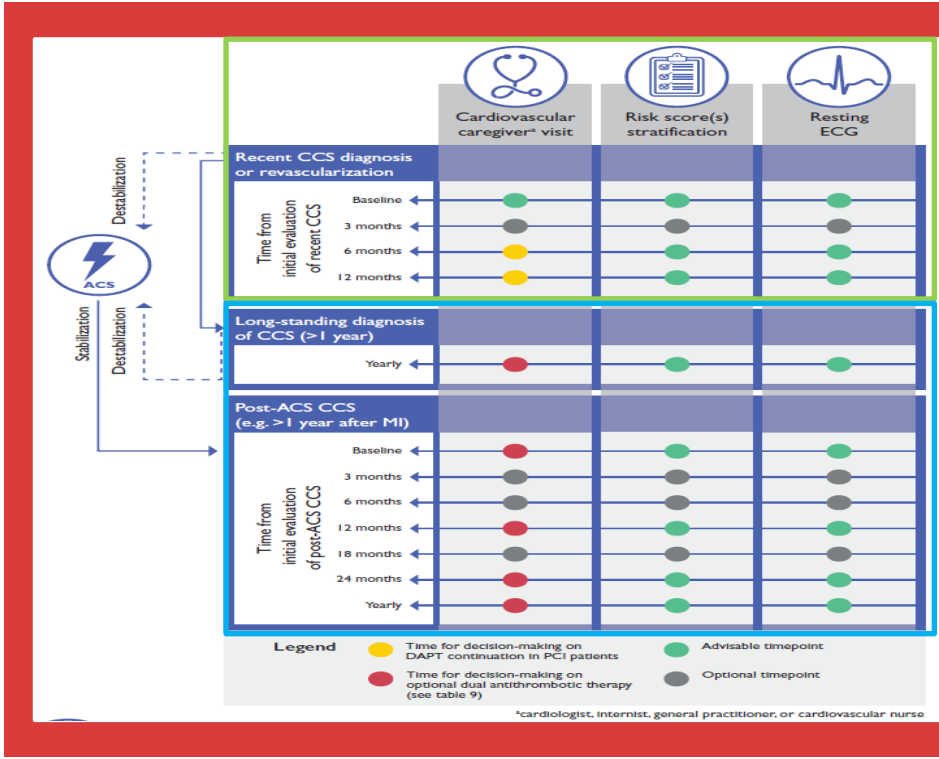
For recently diagnosed CCS patients, more frequent assessment and risk evaluation is required

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)



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Again, as discussed obstructive CAD is not always the root cause

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Not high percentage for obstructive CAD in symptomatic patients with expression in typical, atypical and even non-anginal

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[64] of contemporary data[7,8,62]

	Typical		Atypical		Non-anginal		Dyspnoea[a]	
Age	Men	Women	Men	Women	Men	Women	Men	Women
30–39	3%	5%	4%	3%	1%	1%	0%	3%
40–49	22%	10%	10%	6%	3%	2%	12%	3%
50–59	32%	13%	17%	6%	11%	3%	20%	9%
60–69	44%	16%	26%	11%	22%	6%	27%	14%
70+	52%	27%	34%	19%	24%	10%	32%	12%

CAD = coronary artery disease; PTP = pre-test probability.

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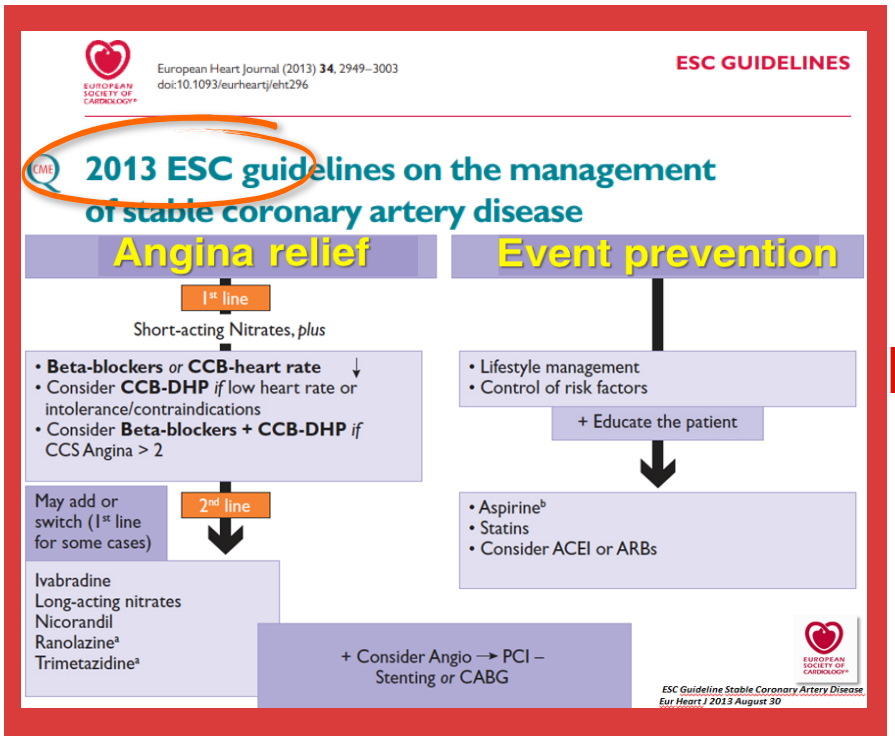
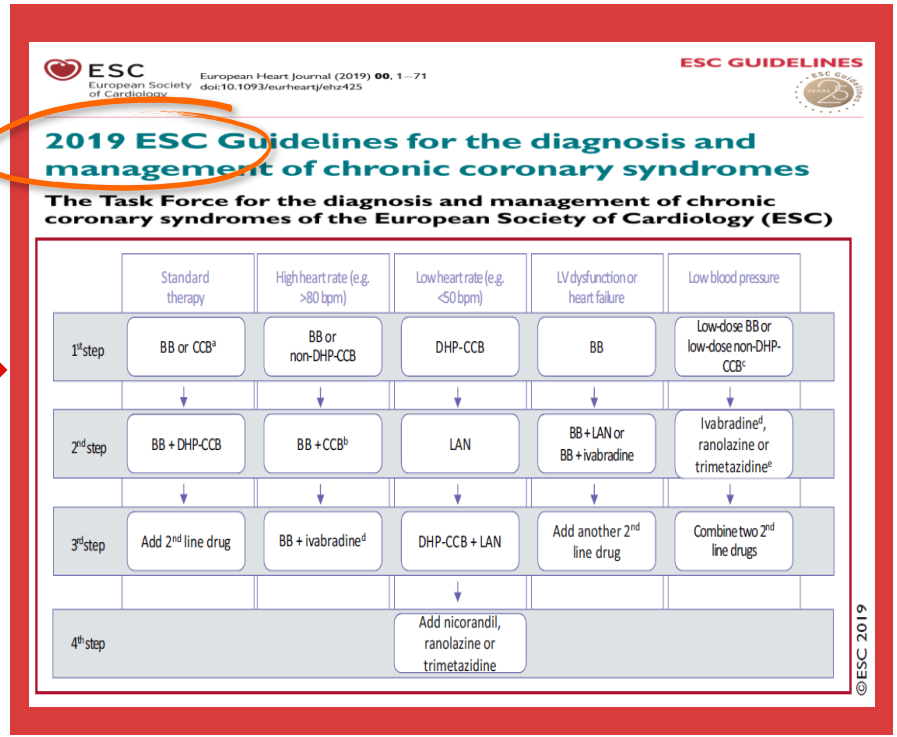
For anti-anginal therapies, what are the new and revised concepts and recommendations?





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

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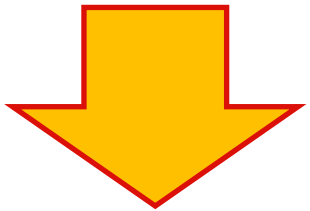
From definite positioning of lines of treatments



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.[188–191] 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.[192] Initial drug therapy usually consists of one or two antianginal drugs, as necessary, plus drugs for secondary prevention of CVD.[193] 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

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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

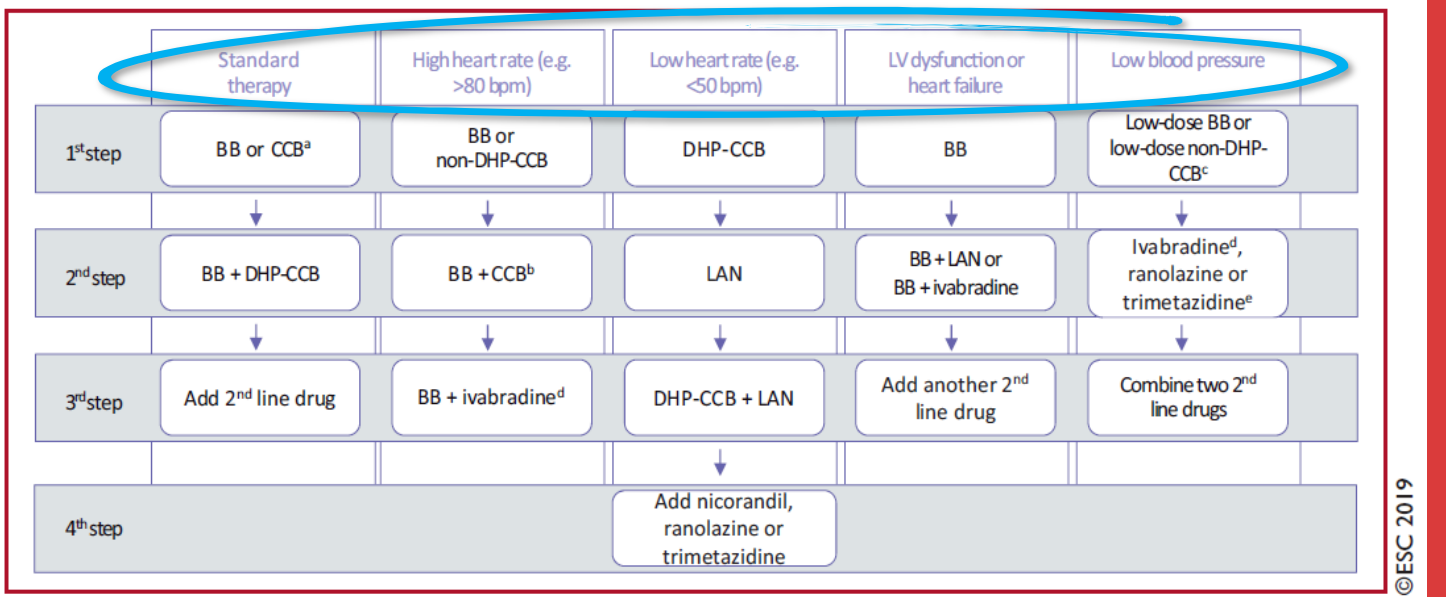

Figure 8 Suggest stepwise strategy for long term anti-ischaemic drug therapy in patients with chronic coronary syndromes and specific baseline characteristics. The proposed stepwise approach must be adapted to each patient's characteristics and preferences. Given the limited evidence on various combinations 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 chan-

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Trimetazidine has been upgraded from Class IIB to IIA in the 2019 ESC CCS guideline

Changes in major recommendations

2013	Class[a]	2019	Class[a]
For second-line treatment, trimetazidine may be considered,	IIb	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.	IIa
		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.	IIb

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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

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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)

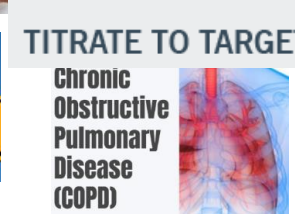
Mechanisms	**⇩ HR** **⇩ BP** **⇩ myocardial contractility** **⇧ diastolic perfusion time**

- Calcium-channel blocker (CCB)

Mechanisms	**⇩ Myocardial contractility** **Peripheral vascular dilatation ➔ ⇩ BP & systemic vascular resistance** **⇩ Coronary vascular resistance**

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

CONSENSUS STATEMENT

OPEN

EXPERT CONSENSUS DOCUMENT

A 'diamond' approach to personalized treatment of angina

Roberto Ferrari[1,2], Paolo G. Camici[3], Filippo Crea[4], Nicolas Danchin[5], Kim Fox[6], Aldo P. Maggioni[7], Athanasios J. Manolis[8], Mario Marzilli[9,10], Giuseppe M. C. Rosano[11,12] and José L. Lopez-Sendon[13]

Abstract | In clinical guidelines, drugs for symptomatic angina are classified as being first choice (β-blockers, calcium-channel blockers, short-acting nitrates) or second choice (ivabradine, nicorandil, ranolazine, trimetazidine), with the recommendation to reserve second-choice medications for patients who have contraindications to first-choice agents, do not tolerate them, or remain symptomatic. No direct comparisons between first-choice and second-choice treatments have demonstrated the superiority of one group of drugs over the other. Meta-analyses show that all antianginal drugs have similar efficacy in reducing symptoms, but provide no evidence for improvement in survival. The newer, second-choice drugs have more evidence-based clinical data that are more contemporary than is available for traditional first-choice drugs. Considering some drugs, but not others, to be first choice is, therefore, difficult. Moreover, double or triple therapy is often needed to control angina. Patients with angina can have several comorbidities, and symptoms can result from various underlying pathophysiologies. Some agents, in addition to having antianginal effects, have properties that could be useful depending on the comorbidities present and the mechanisms of angina, but the guidelines do not provide recommendations on the optimal combinations of drugs. In this Consensus Statement, we propose an individualized approach to angina treatment, which takes into consideration the patient, their comorbidities, and the underlying mechanism of disease.

Chronic stable angina pectoris is the most prevalent symptomatic manifestation of ischaemic heart disease, and its management is a priority (BOX 1). Current clinical guidelines recommend antianginal therapy to control symptoms, before considering coronary artery revascularization[1–4]. However, revascularization by either percutaneous coronary angioplasty or CABG surgery is indicated in patients who have significant artery stenosis (50% left main narrowing or proximal three-vessel disease) to reduce myocardial ischaemia and its adverse clinical manifestation. Antianginal agents are approved by documenting that they improve total exercise duration, together with a reduction in daily frequency of chronic stable angina compared with placebo and/or equivalence to an active comparator. Cardiovascular outcomes, although highly advocated, are not a prerequisite for regulatory approval. None of the antianginal drugs has been proved to reduce cardiovascular mortality or the rate of myocardial infarction. When patients are optimally treated, mortality for chronic stable angina is low, which might explain why all trials designed to improve prognosis have been 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[5–8]. 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 antianginal treatment, therefore, varies considerably between countries, and the majority of doctors treat their patients according to their own preconceptions.

A group of experts with experience and interest in chronic stable angina met at the University of Ferrara, Italy, to discuss an individualized approach to medical treatment of chronic stable angina, on the basis

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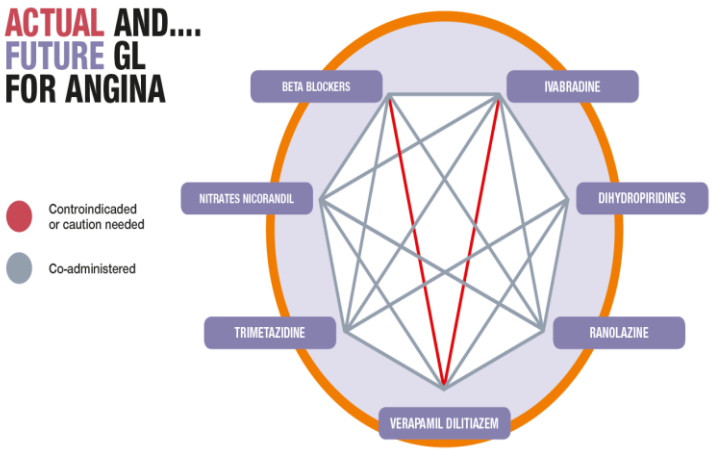
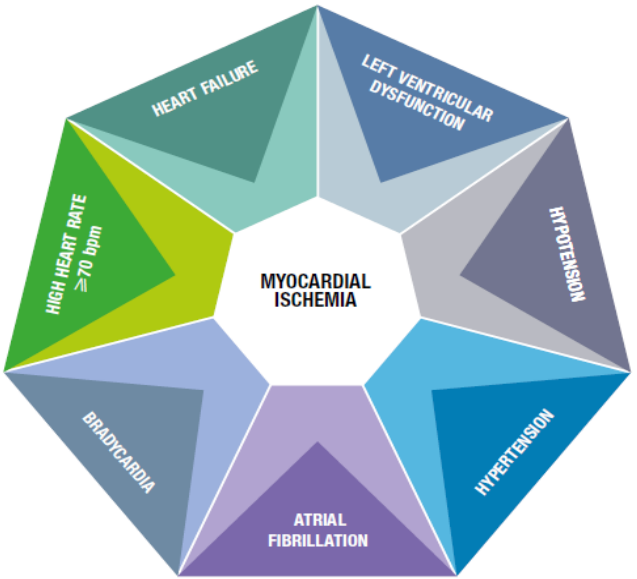
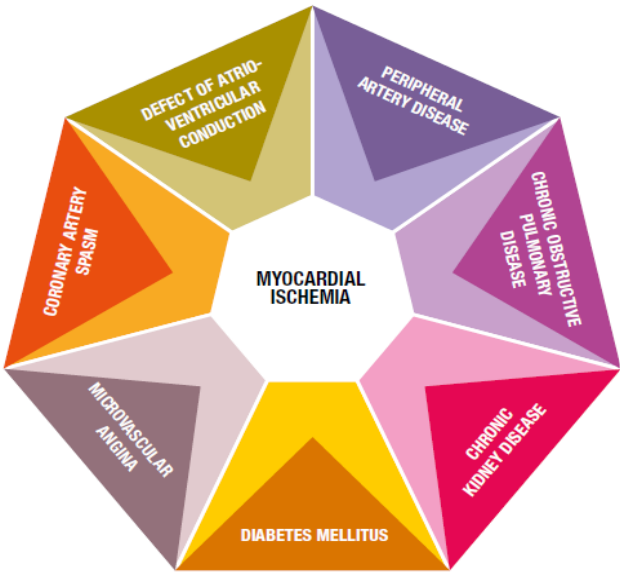


Roberto Ferrari et al. - Experts consensus statement: A 'diamond' approach to personalized treatment of angina - Nature Reviews Cardiology volume 15, pages 120 – 132 (2018)

The “Diamond” approach takes co-morbidities and pathophysiology as the key determining factors for the choices of anti-anginal drugs





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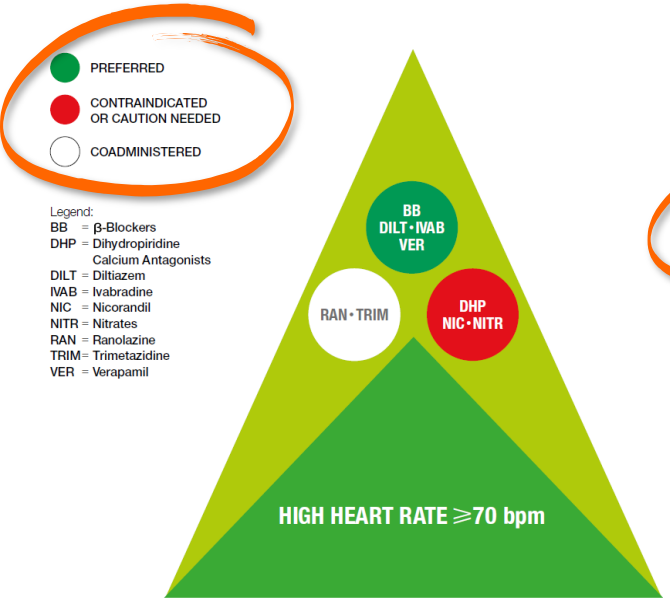
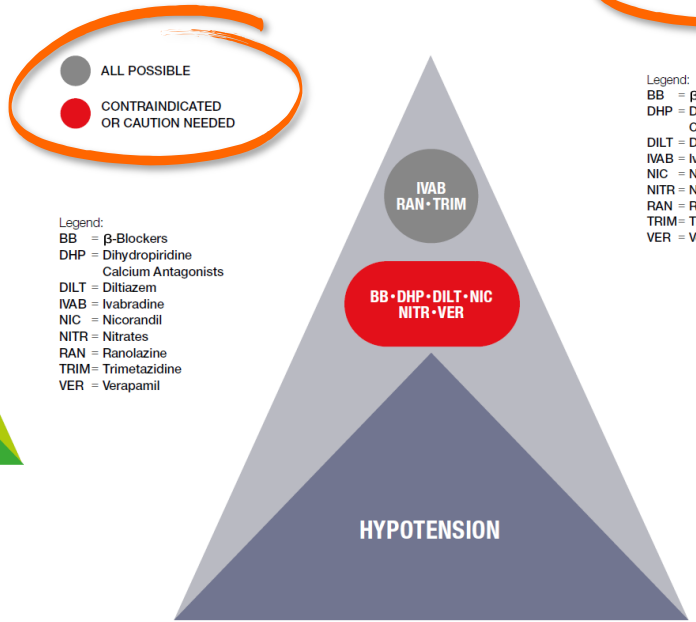
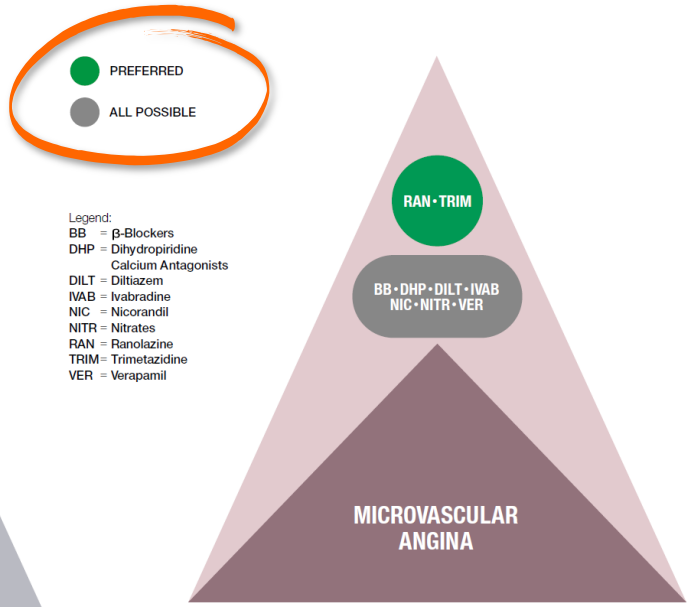
Examples illustration of “Diamond Approach” regarding the anti-anginal drugs choices







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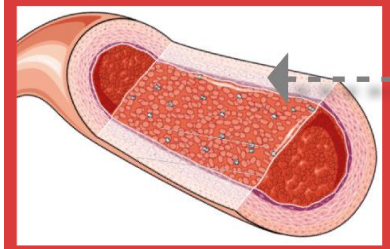
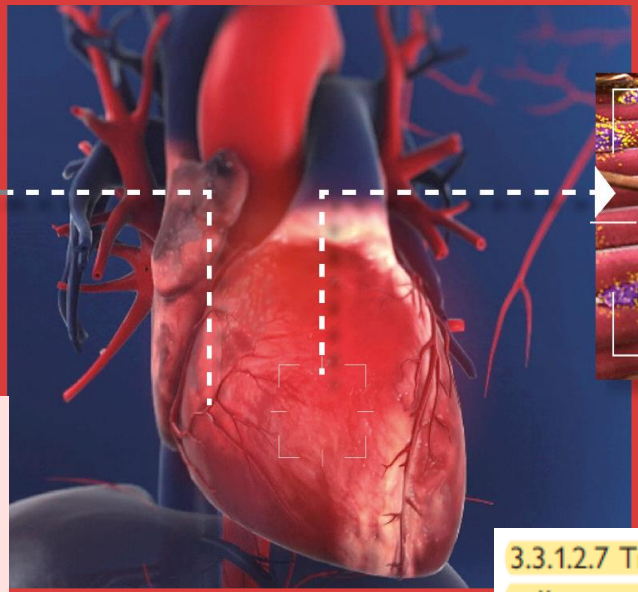
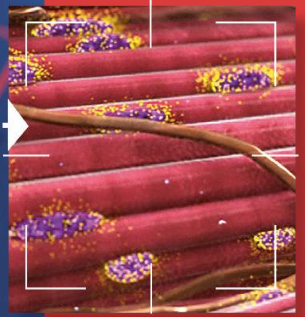
In clinical practice - good efficacy and tolerability, synergy with other medications, wide patients applicability are key attributes for drug prescriptions







Cardiac cell
Trimetazidine

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)

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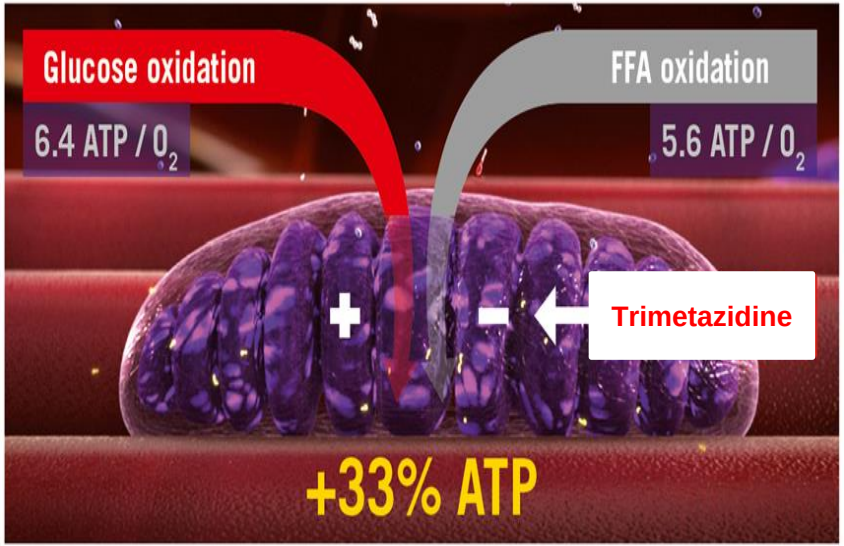
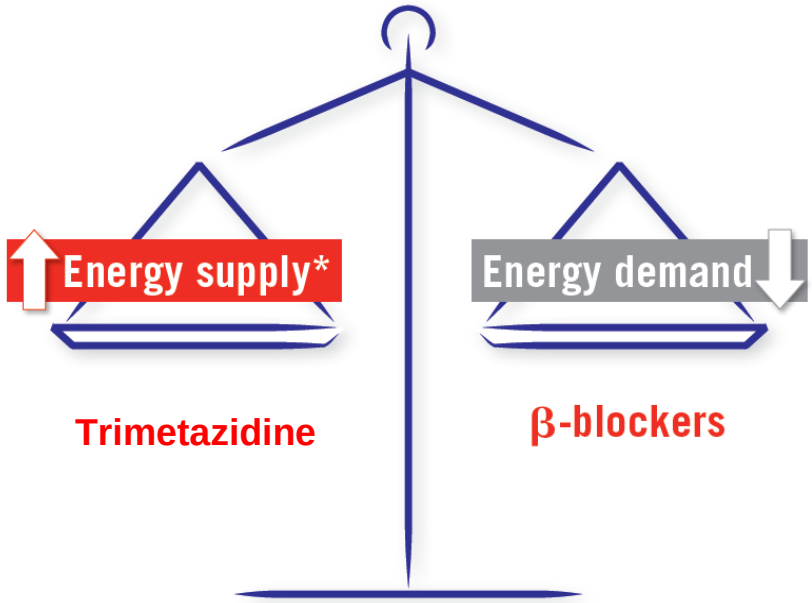
3.3.1.2.7 Trimetazidine. Trimetazidine appears to have a haemodynamically neutral side effect profile.[252] Trimetazidine (35 mg b.i.d.) added to beta-blockade (atenolol) improved effort-induced myocardial ischaemia, as reviewed by the European Medicines Agency in June

1. Fillmore N et al. – British Journal of Pharmacology. 2014;171:2080–2090.
2. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

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





Fragasso G et al. – Eur Heart J. 2006;27:942-948.

Side story - Trimetazidine

Sport / China

Chinese swim star Sun Yang failed drugs test

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

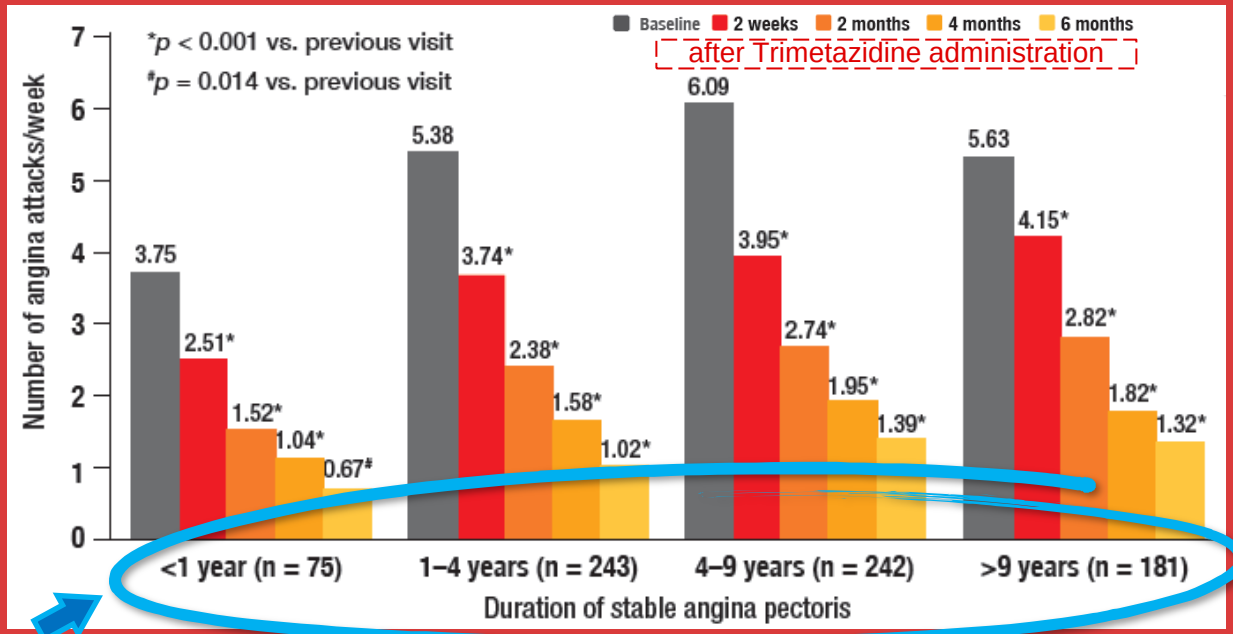
China's Olympic swimming star Sun Yang failed a doping test in May and was subsequently banned for three months, the official Xinhua news agency reported Monday.

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.

Glezer M, CHOICE-2 study investigators. Real-world evidence for the antianginal efficacy of trimetazidine from the Russian Observational CHOICE-2 Study Adv Ther. 2017 ;34(4):915-924. doi 10.1007/s12325-017-0490-2.

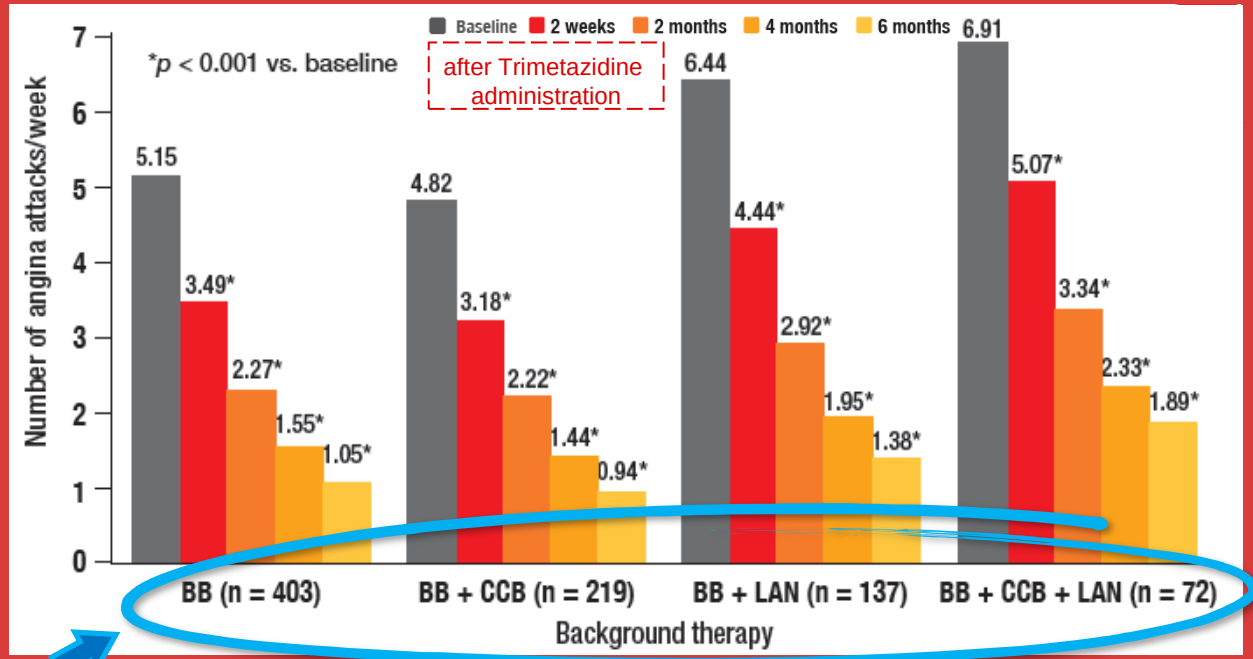
Significant early and sustained reduction in angina attacks regardless of patients' background angina duration/history



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.

Glezer M, CHOICE-2 study investigators. Real-world evidence for the antianginal efficacy of trimetazidine from the Russian Observational CHOICE-2 Study Adv Ther. 2017 ;34(4):915-924. doi 10.1007/s12325-017-0490-2.

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.

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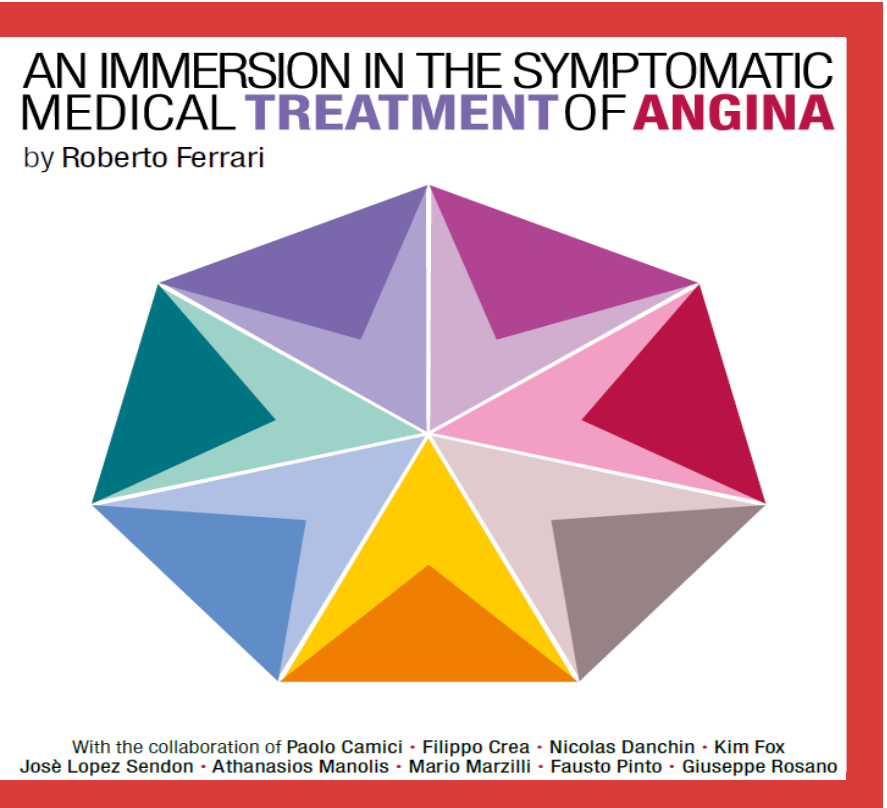
orders, and restless leg syndrome. A 2014 meta-analysis of 13, mostly Chinese, studies consisting of 1628 patients showed that treatment with trimetazidine on top of other antianginal drugs was associated with a smaller weekly mean number of angina attacks, lower weekly nitroglycerin use, longer time to 1 mm ST-segment depression, higher total work, and longer exercise duration at peak exercise than treatment with the other antianginal drugs for stable angina pecto-

1. Glezer M, CHOICE-2 study investigators. Real-world evidence for the antianginal efficacy of trimetazidine from the Russian Observational CHOICE-2 Study Adv Ther. 2017 ;34(4):915-924. doi 10.1007/s12325-017-0490-2.
2. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

With its well proven efficacy and excellent tolerability, Trimetazidine can be prescribed for angina patients with different backgrounds in daily clinical practice



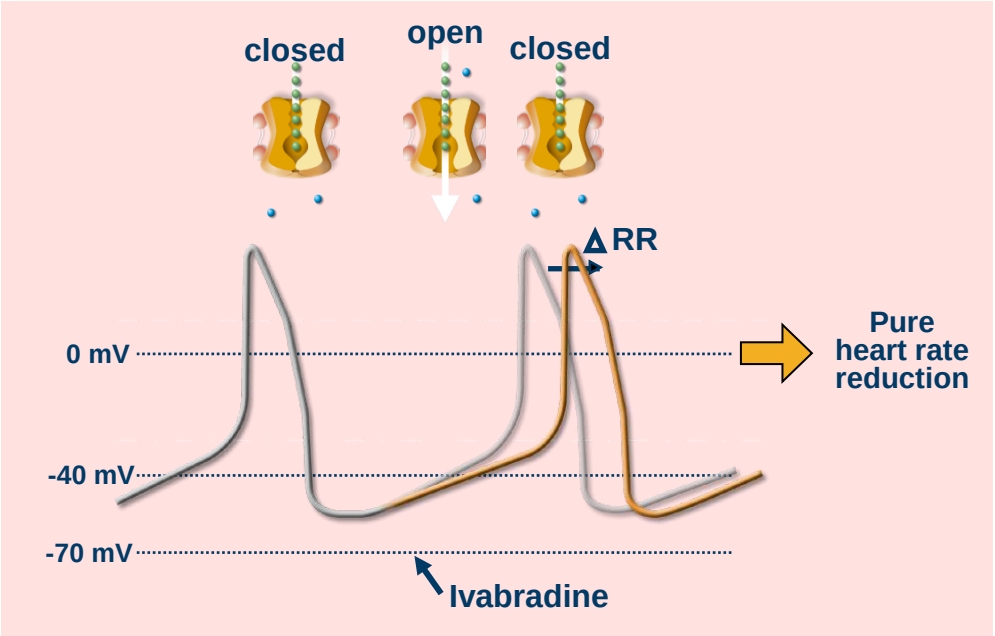
- High HR >70 bpm
- Bradycardia
- Hypertension
- Hypotension
- LVD
- Heart failure
- Atrial fibrillation
- Diabetes mellitus
- COPD
- PAD
- Coronary artery spasm
- Microvascular angina
- Defect of AV conduction
- CKD

recommended in 12 out of 14 clinical conditions

Roberto Ferrari et al. - Experts consensus statement: A 'diamond' approach to personalized treatment of angina - Nature Reviews Cardiology volume 15, pages 120 – 132 (2018)

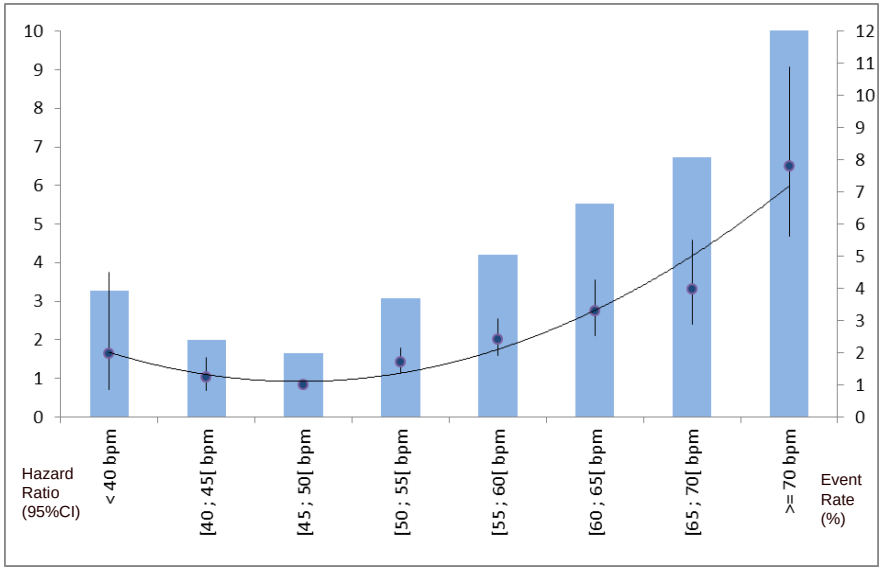
How about Ivabradine? A drug for treating heart failure only? NO! It is also an useful anti-anginal agent

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



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

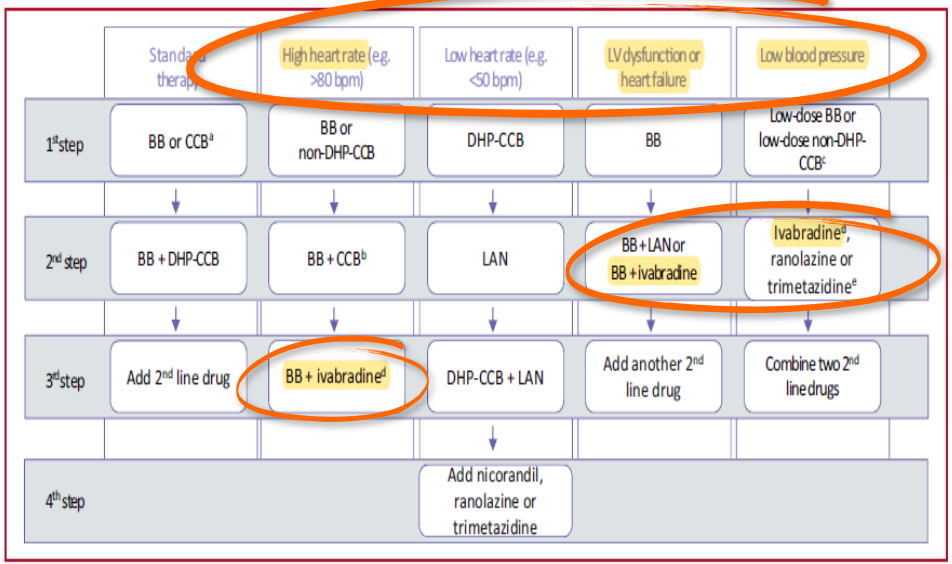
Apart from heart failure, heart rate control is also important for angina patients – as optimal heart rate helps to reserve heart function and its energy demand

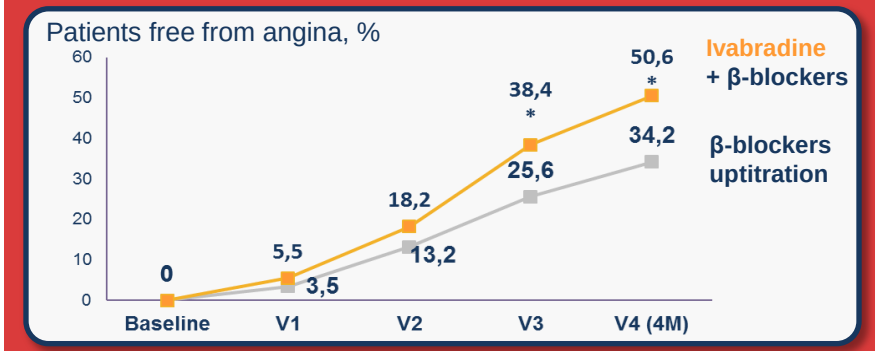


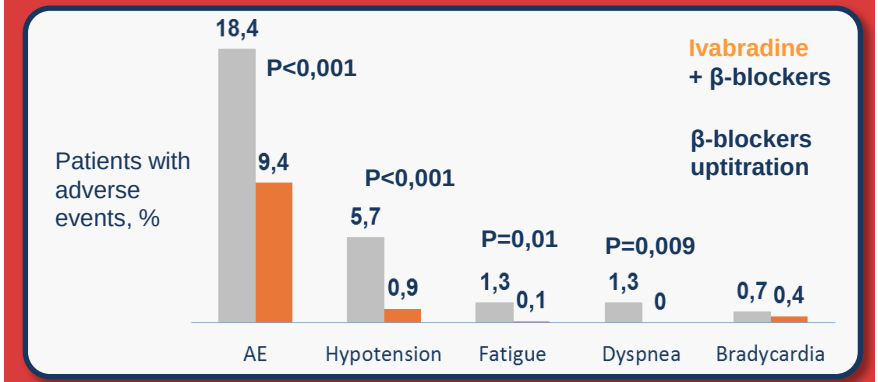
Synergistic anginal efficacy for Coralan plus BBs vs BB uptitration alone and Ivabradine is recommended as the preferred agent for angina patients with high HR, LVD and/or HF right after BBs by the new ESC CCS guideline

ESC European Society of Cardiology

3.3.1.2.4 Ivabradine. Ivabradine has been reported to be non-inferior to atenolol or amlodipine in the treatment of angina and ischaemia in patients with CCS.[235,236] Adding ivabradine 7.5 mg b.i.d. [bis in die (twice a day)] to atenolol therapy gave better control of heart rate and anginal symptoms.[237] In 10 917 patients with limiting previous







2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

Myth 5

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

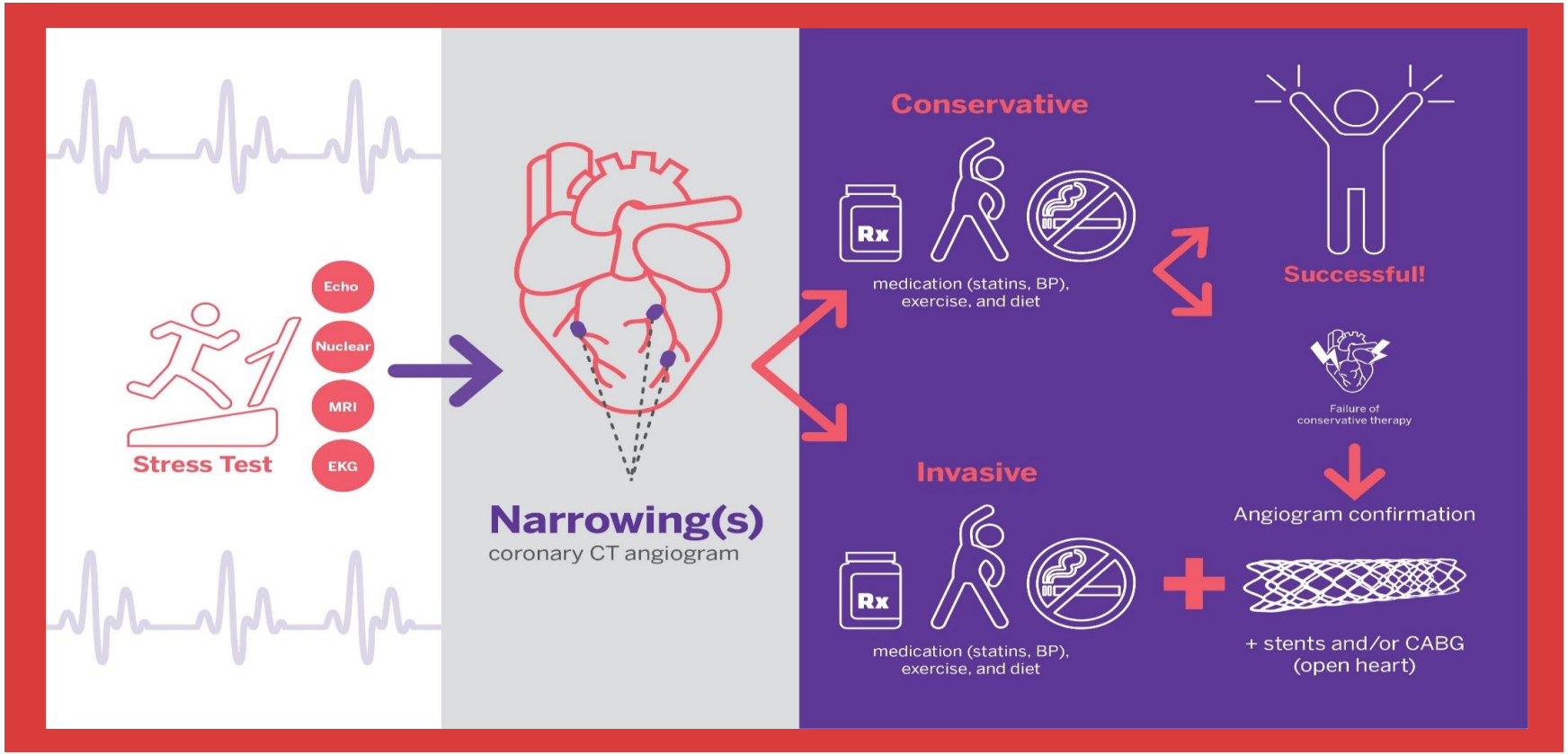
For stable coronary disease patients, is revascularization plus medical therapy better than medical therapy alone?

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



N Engl J Med 2020;382:1395-407. DOI: 10.1056/NEJMoa1915922

ISCHEMIA trial – who are included and excluded?

Clinical and Stress Test Eligibility Criteria

Inclusion Criteria

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

CCTA Eligibility Criteria

Inclusion Criteria

- ≥50% stenosis in a major epicardial vessel (stress imaging participants)
- ≥70% stenosis in a proximal or mid vessel (ETT participants)

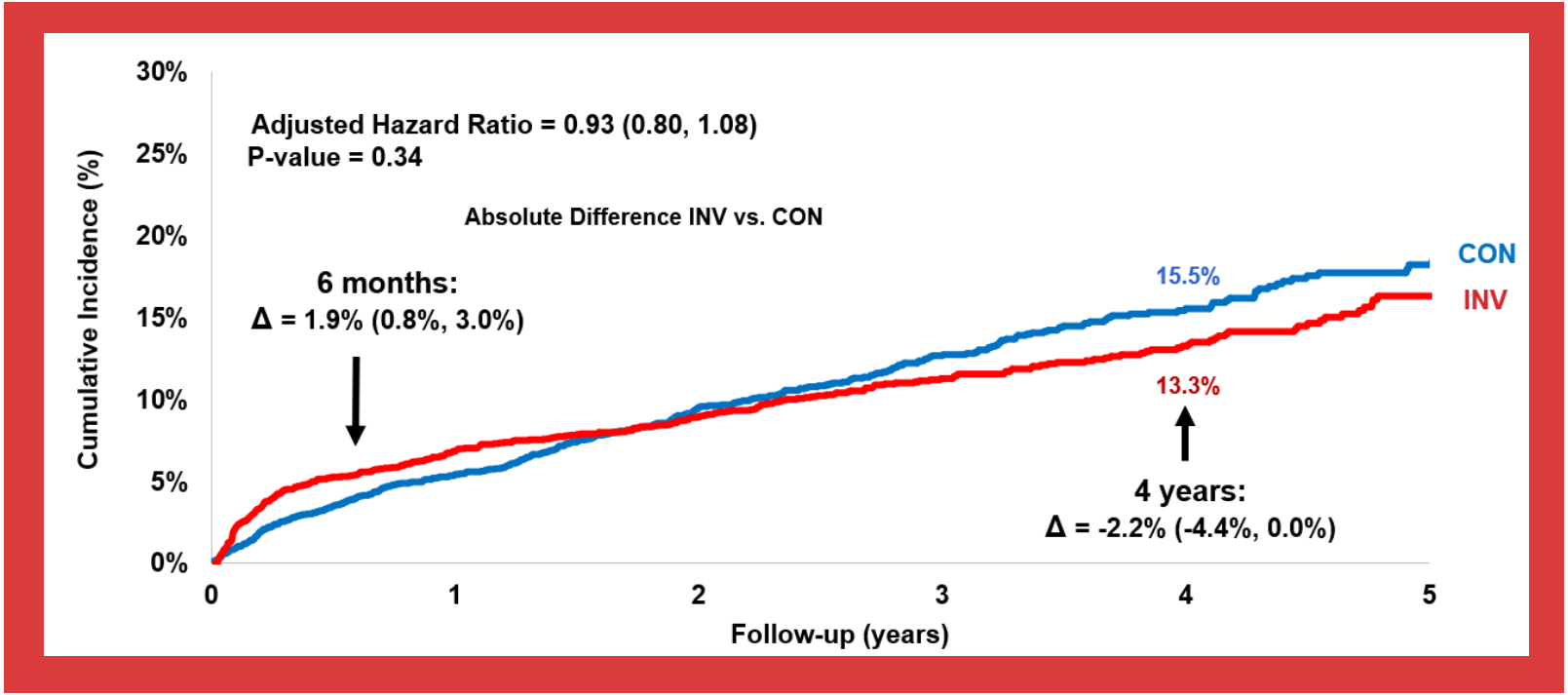
Major Exclusion Criteria

- ≥50% stenosis in unprotected left main

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

N Engl J Med 2020;382:1395-407. DOI: 10.1056/NEJMoa1915922

Primary Outcome: CV Death, MI, hospitalization for UA, HF or resuscitated cardiac arrest



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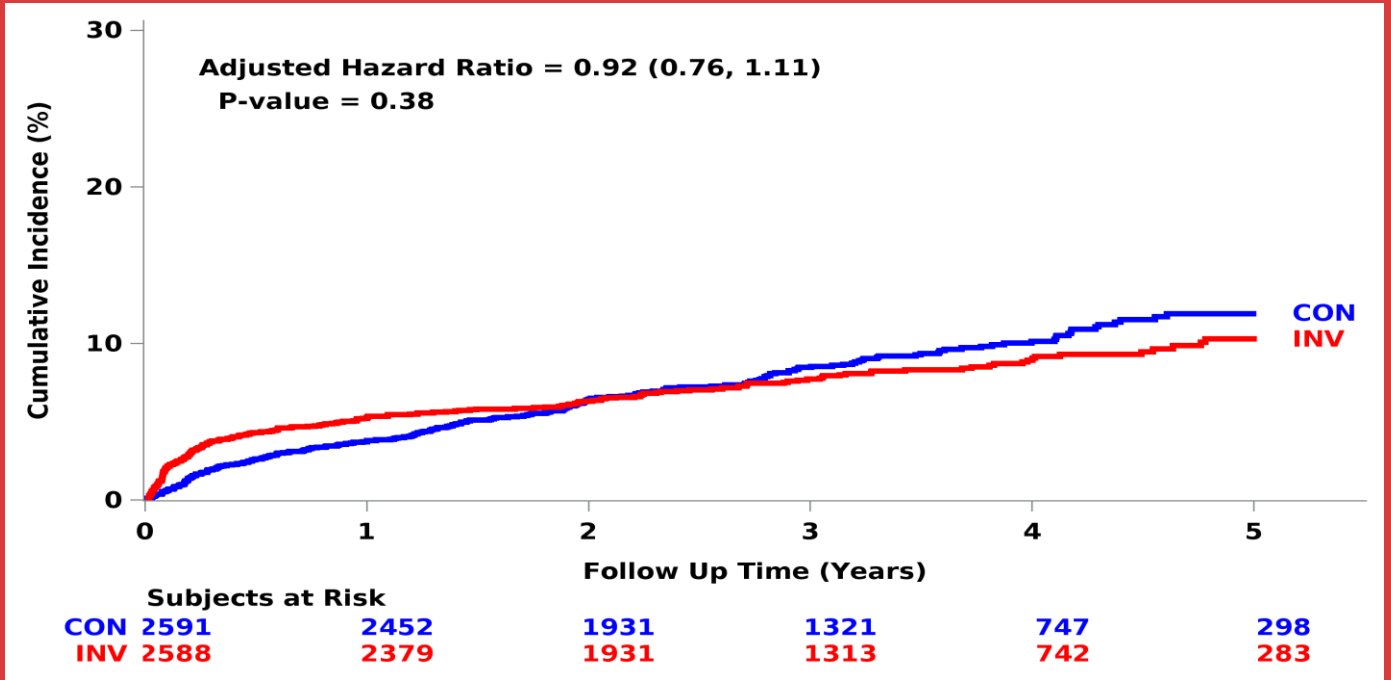
Myocardial Infarction



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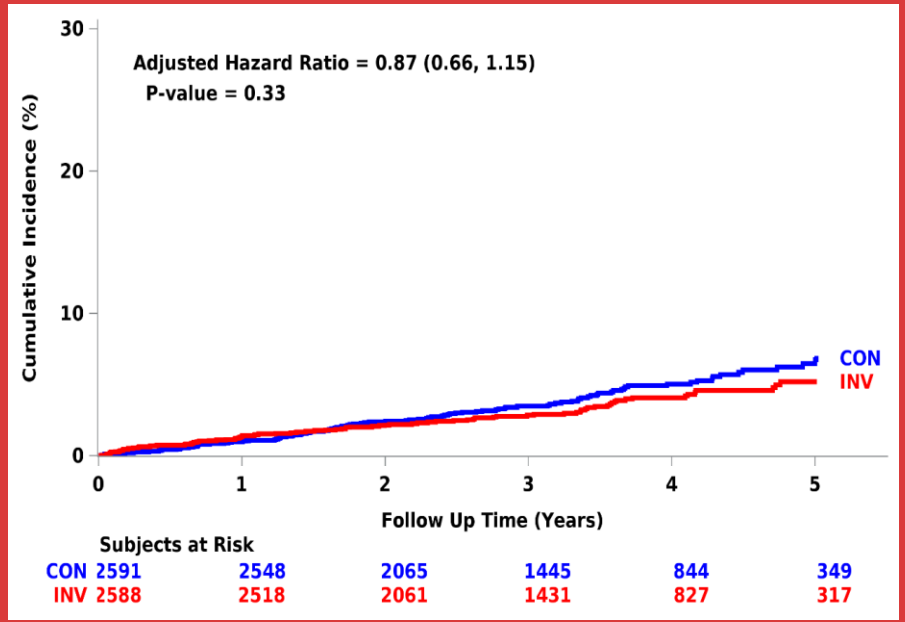
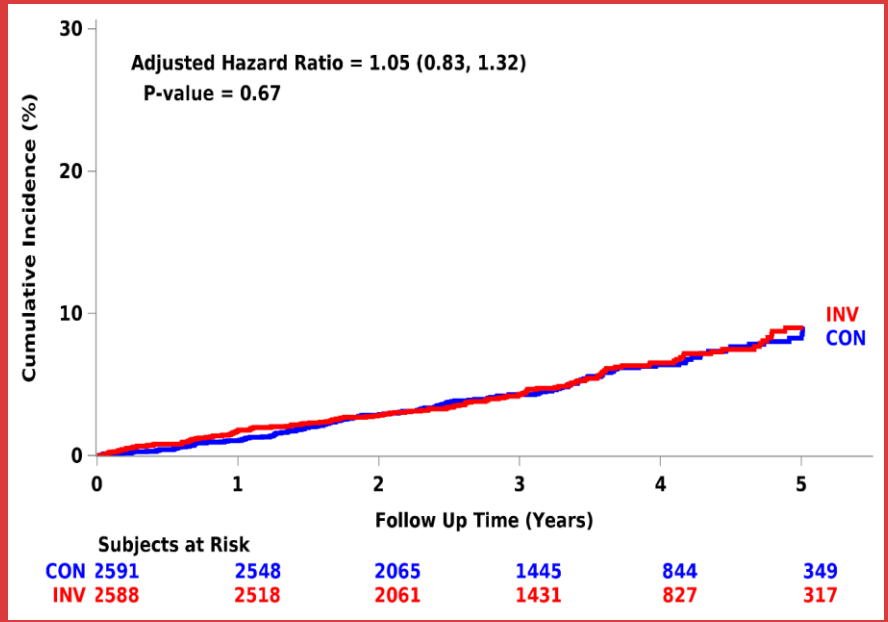
Cardiovascular death and all-cause death



CV death



All-cause death

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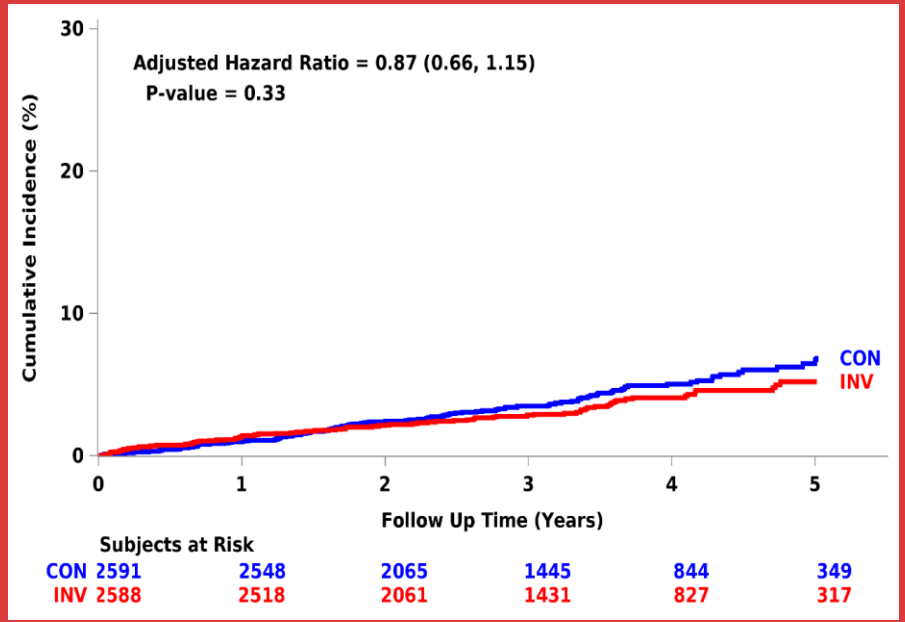
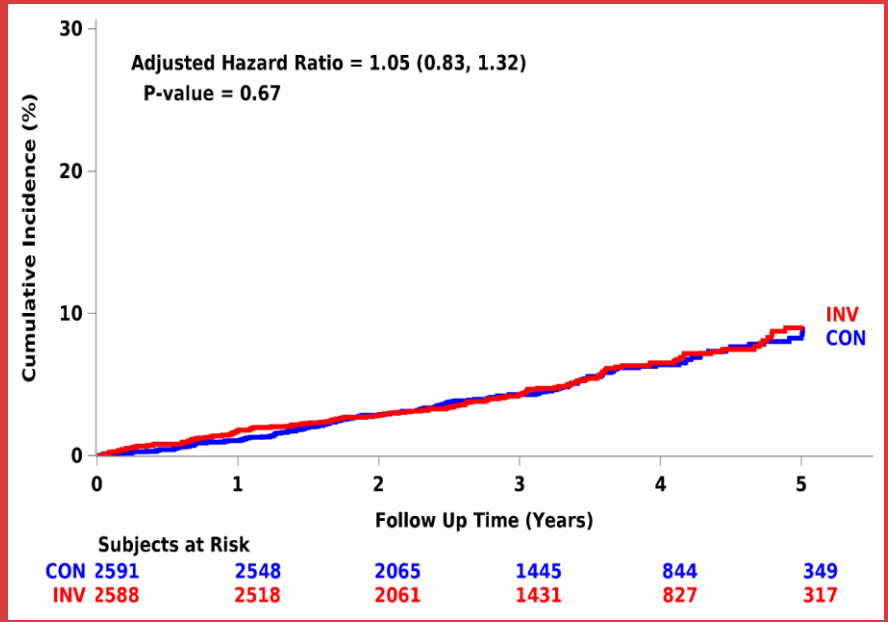
Cardiovascular death and all-cause death



CV death



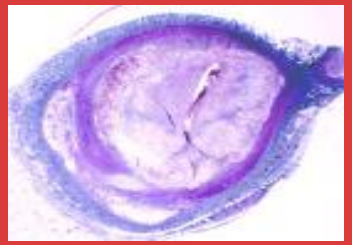
All-cause death

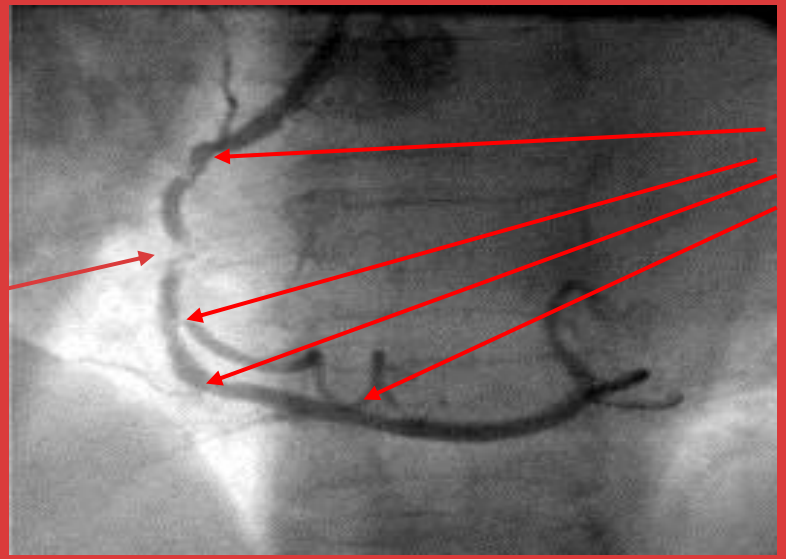
N Engl J Med 2020;382:1395-407. DOI: 10.1056/NEJMoa1915922

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

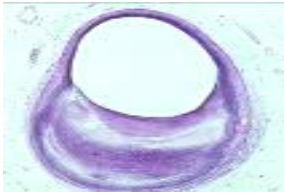
Severe Obstruction (angina, no rupture) vs Mild Obstruction (no angina, likely to rupture)

Severe fibrotic plaque
- **Severe obstruction**
- **No lipid**
- **Fibrosis, Ca^{2+}**





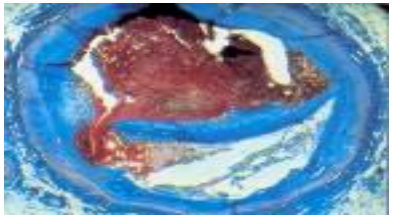
Vulnerable plaque
- **Minor obstruction**
- **Eccentric plaque**
- **Lipid pool**
- **Thin cap**



Exertional angina
- **(+) ETT**

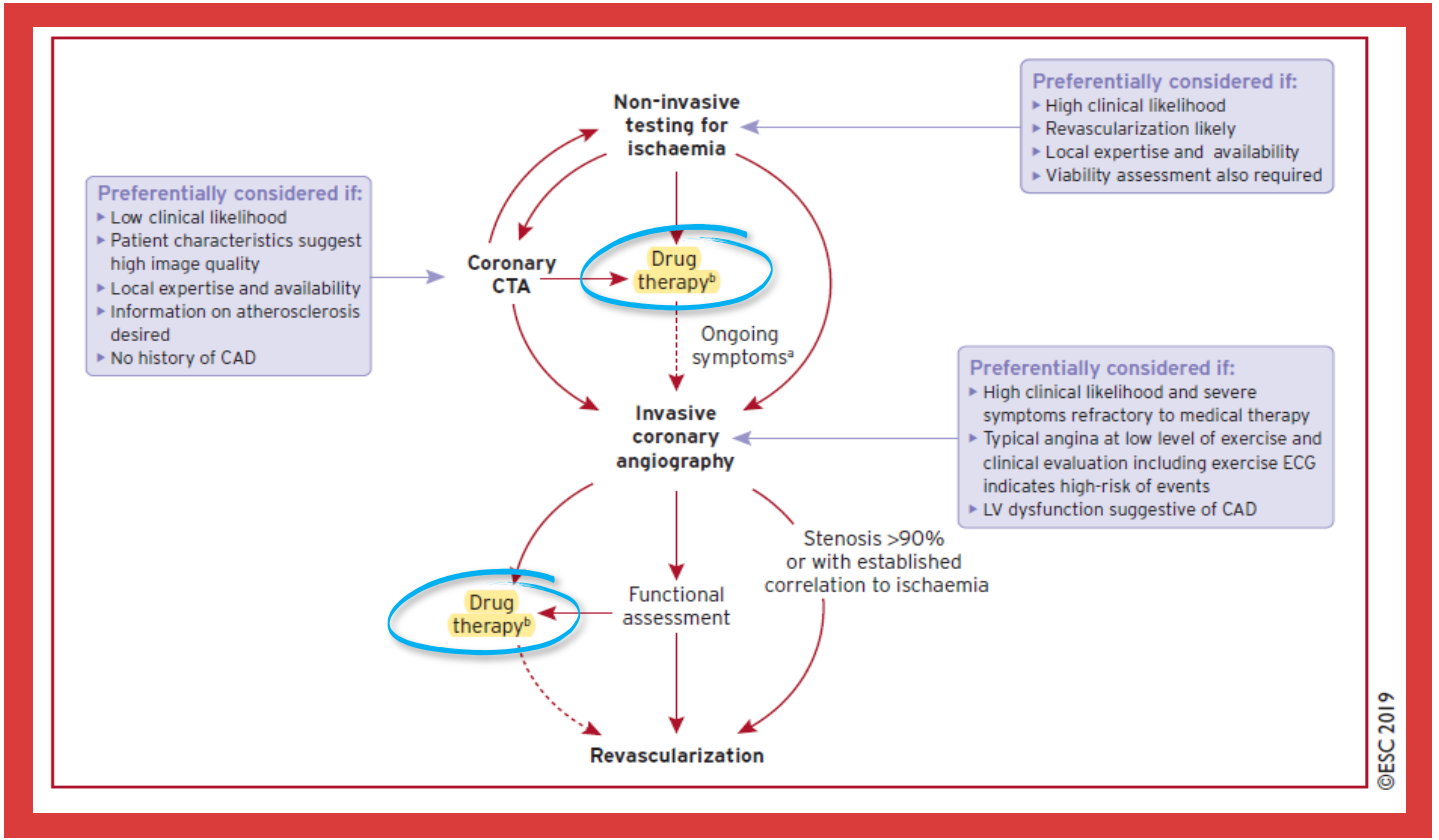
Revascularization
Anti-anginal Rx

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

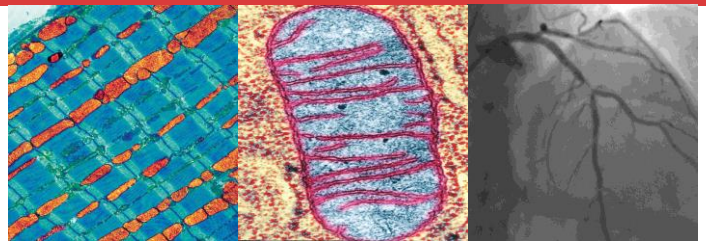


2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. The Task Force for the diagnosis and management of chronic coronary syndromes of the European Society of Cardiology (ESC). European Heart Journal (2019) 00, 1-71 doi:10.1093/eurheartj/ehz425

ATPCI study – the landmark trial of trimetazidine for angina patients after PCI

ATPCI

*The effic**A**cy and safety of **T**rimetazidine in **P**atients with angina pectoris having been treated by percutaneous **C**oronary **I**ntervention.*



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

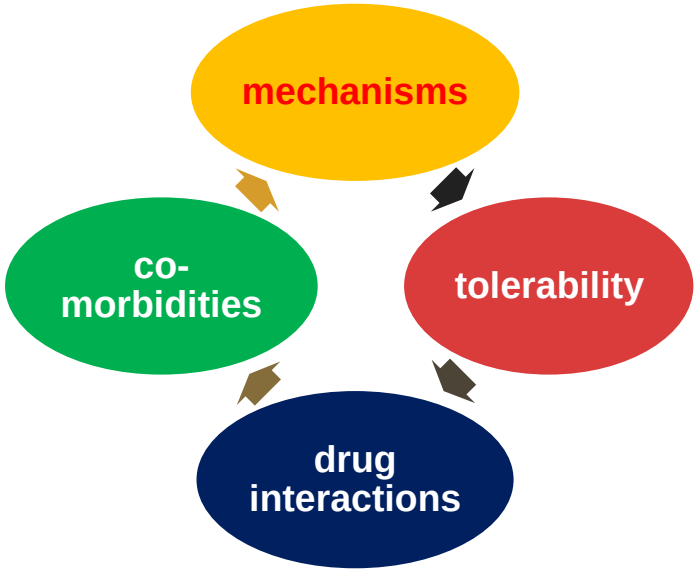
- ESC 2020 (late Aug to early Sept)

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)**

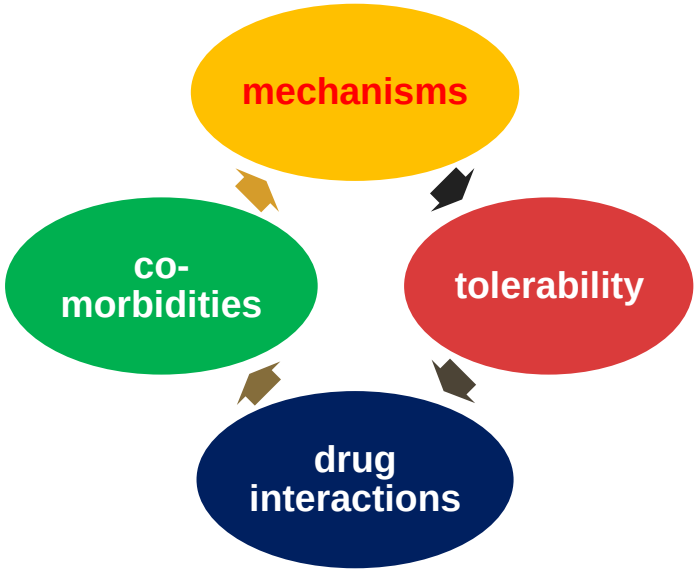
- Personalized angina management – to be or not to be? **YES, because “NOT all angina are the same and NOT all patients are the same”, both life-long follow-up and tailored medical treatment from the very beginning of diagnosis are essential**



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