

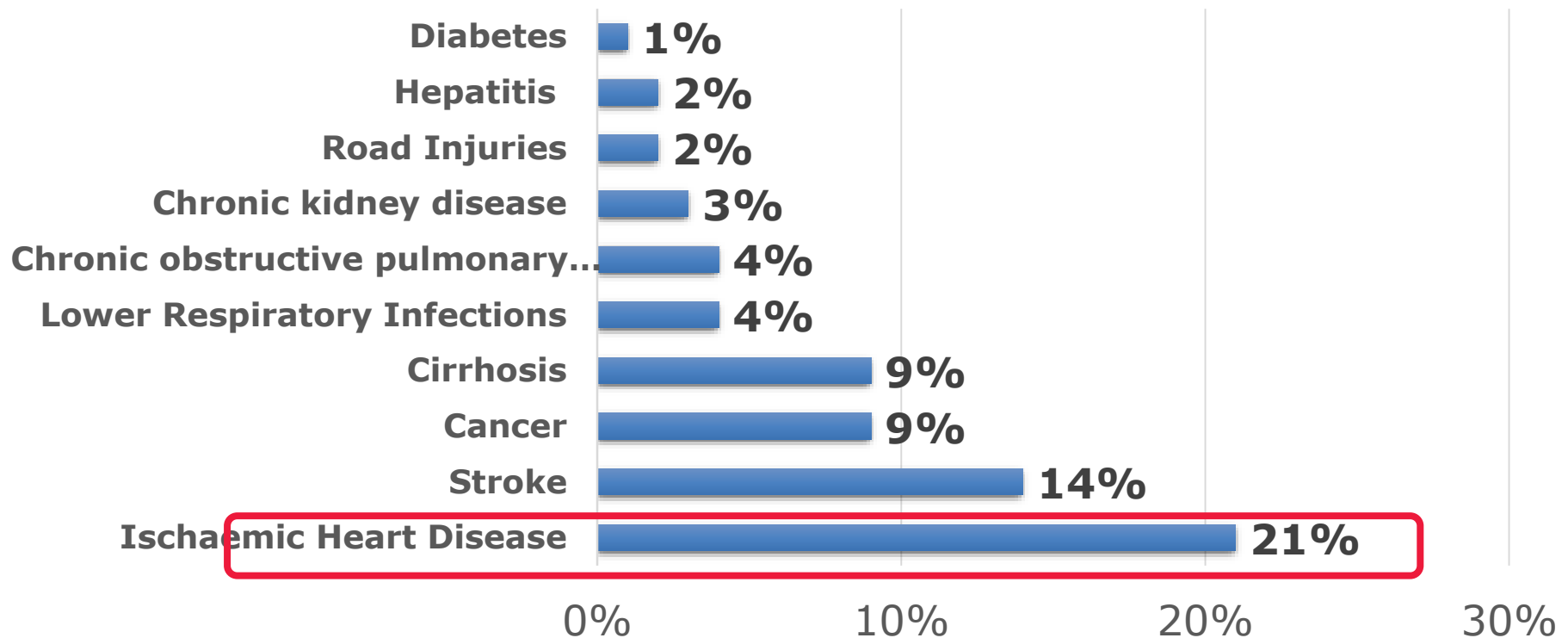
Chronic coronary syndrome

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IHD in Egypt – CDC Data

Top 10 Causes of Death



Chronic coronary syndrome (CCS)

Why new name for stable CAD:

Stable CAD term may give some false reassurance which is not always true (as some pt have progressive disease despite a stable symptoms, so the name changed to chronic coronary syndrome.

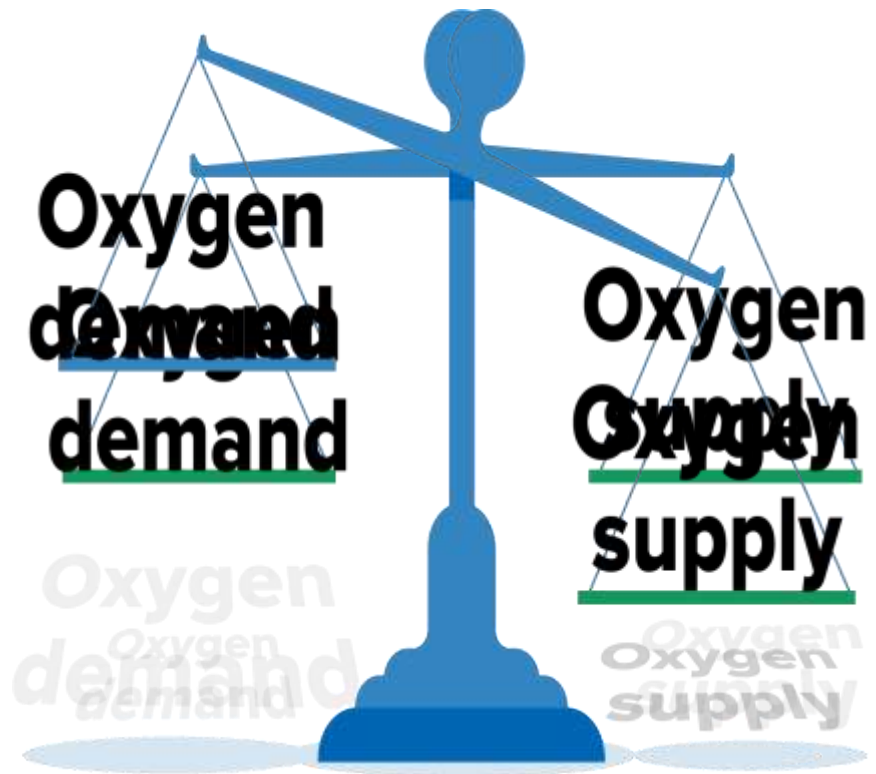
Chronic coronary syndrome (CCS)

The spectrum of CCS include 6 categories:

- 1- pt with angina and suspected CAD
- 2- Pt with angina and HF or EF less than 50%
- 3- Pt underwent revascularization less than 1 y or less than 1 y post ACS
- 4 - Pt underwent revascularization more than 1 y or more than 1 y post ACS.
- 5- angina with on obstructive CAD (vasospastic angina or microvascular angina.
- 6- Screening for CAD in asymptomatic pts

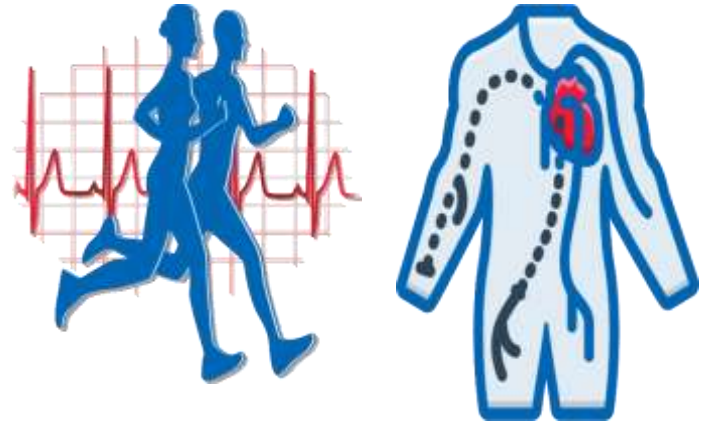
Pathophysiology of IHD

- Normal Metabolism requires oxygen supply
- In Myocardial Ischemia, the oxygen supply is insufficient.



Clinical Presentation & Diagnostic tests for Ischemic patients

- History and Symptoms
- Investigations such as:
 - ECG
 - Biochemistry
 - Exercise testing
 - Angiography



Initial diagnostic testing - Resting ECG

Recommendations	Class ^a	Level ^b
A resting 12 lead ECG is recommended in all patients with chest pain without an obvious non-cardiac cause.	I	C
A resting 12 lead ECG is recommended in all patients during or immediately after an episode of angina suspected to be indicative of clinical instability of CAD.	I	C
ST-segment alterations recorded during supraventricular tachyarrhythmias should not be used as evidence of CAD.	III	C

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Initial diagnostic testing - Chest X-Ray

Recommendation	Class ^a	Level ^b
Chest X-ray is recommended for patients with atypical presentation, signs and symptoms of HF, or suspicion of pulmonary disease.	I	C

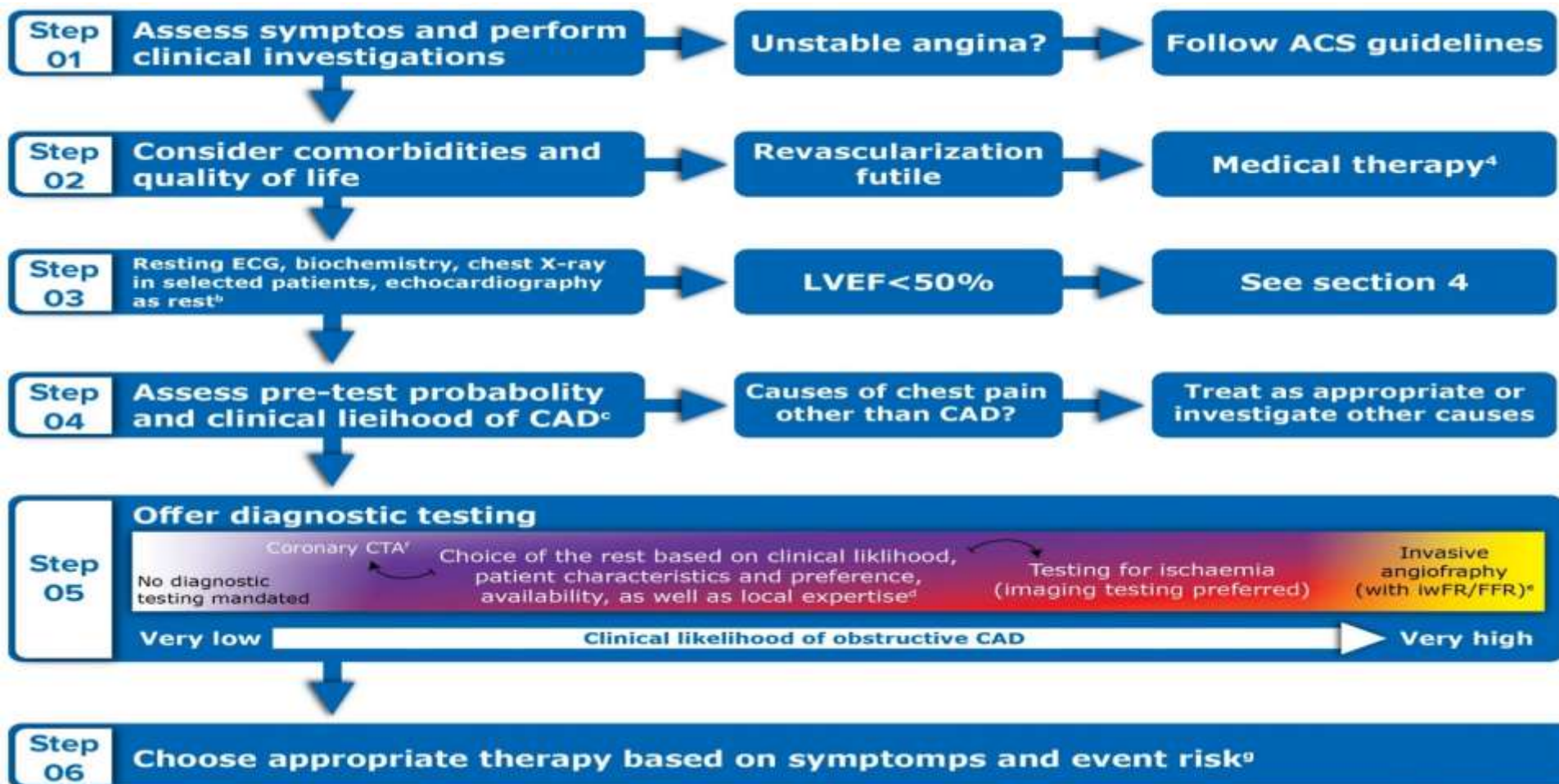
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Initial diagnostic testing - Basic biochemistry

Recommendations	Class ^a	Level ^b
If evaluation suggests clinical instability or ACS, repeated measurements of troponin, preferably using high-sensitivity or ultrasensitive assays, are recommended to rule-out myocardial injury associated with ACS.	I	A
The following blood tests are recommended in all patients:		
• Full blood count (including haemoglobin);	I	B
• Creatinine measurement and estimation of renal function;	I	A
• A lipid profile (including LDL-C).	I	A
It is recommended that screening for type 2 diabetes mellitus in patients with suspected and established CCS is implemented with HbA1c and fasting plasma glucose measurements, and that an oral glucose tolerance test is added if HbA1c and fasting plasma glucose results are inconclusive.	I	B
Assessment of thyroid function is recommended in case of clinical suspicion of thyroid disorders.	I	C

?? Exercise ECG

Initial diagnostic management of pts with angina



Basic Diagnostic updates in 2019

Basic testing, diagnostics, and risk assessment

Non-invasive functional imaging or coronary CTA as the initial test for diagnosing CAD.

Initial non-invasive test based on the clinical likelihood of CAD, patient characteristics, local expertise and availability

Functional imaging for myocardial ischaemia if coronary CTA has shown CAD of uncertain functional significance or is not diagnostic.

Invasive angiography to diagnose CAD in patients with

- a high clinical likelihood and severe symptoms refractory to medical therapy
- typical angina at low level of exercise and clinical evaluation that indicates high event risk.

Invasive functional assessment must be available and used to evaluate stenoses before revascularization, unless very high grade (>90% diameter stenosis).

Invasive coronary angiography with availability of invasive functional evaluation for confirmation of CAD diagnosis in patients with uncertain diagnosis on non-invasive testing.

Coronary CTA as an alternative to invasive angiography if another non-invasive test is equivocal or non-diagnostic.

Coronary CTA when any conditions make good image quality unlikely.

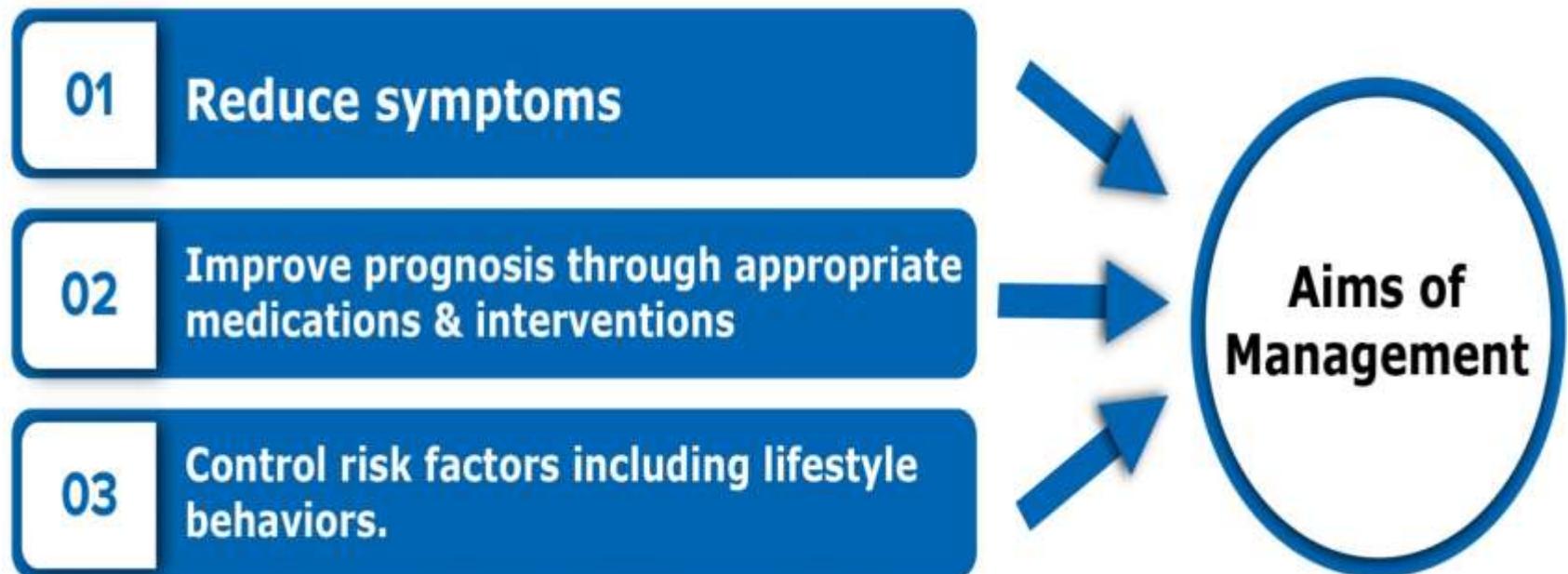
■ Class I

■ Class IIa

■ Class IIb

■ Class III

Aims of Management



Management Strategies

I. Risk factor reduction And Lifestyle modification

- Changeable risk factors: Smoking, Exercise, Diet
- Controllable risk factors: Hypertension, Diabetes



II. Coronary intervention and surgery

- Angioplasty \pm stent (PTCA)
- Coronary Artery Bypass Grafts (CABG)



III. Drug therapy

I - Risk factor reduction and Lifestyle modification



Smoking cessation

Use pharmacological and behavioural strategies to help patients quit smoking. Avoid passive smoking.



Healthy diet

Diet high in vegetables, fruit, and wholegrains
Limit saturated fat to <10% of total intake.
Limit alcohol to <100 g/week or 15 g/day.



Physical activity

30 - 60 min moderate physical activity most days, but even irregular activity is beneficial.



Healthy weight

Obtain and maintain a healthy weight (<25 kg/m²), or reduce weight through recommended energy intake and increased physical activity.



Other

Take medications as prescribed.
Sexual activity is low risk for stable patients not symptomatic at low-to-moderate activity levels.

II - Coronary intervention and surgery

Indication for revascularization:

- 1- EF less than 35%
- 2- Reversible ischemia in SPECT with defect size 10%
- 3- FFR less than 0.8
- 4- IFR less than 0.89
- 5- Epicardial stenosis 90%

II - Coronary intervention and surgery

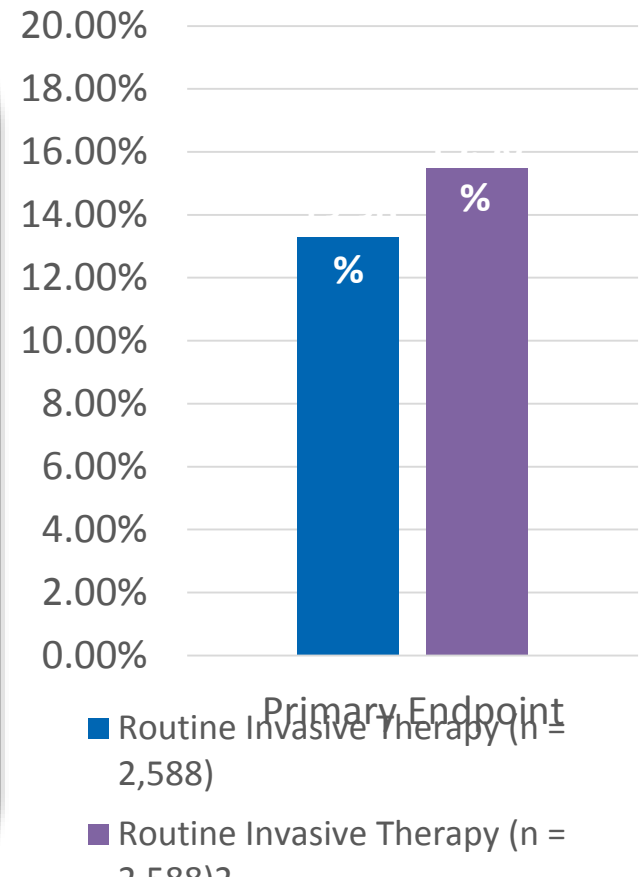
- ISCHEMIA Trial #AHA19
- **Trial Description:** Pts with stable CAD and moderate to severe ischemia were randomized to routine invasive therapy vs. medical therapy.

II - Coronary intervention and surgery

CONCLUSIONS

pts with stable CAD and moderate to severe ischemia on stress testing,
invasive therapy failed to reduce major adverse cardiac events vs. medical therapy.

Invasive therapy associated with increase in periprocedural MI at 6 m and reduction in spontaneous MI at 4 y.



III - Therapeutic management of Angina

III - Therapeutic management of Angina

Recommendations	Class ^a	Level ^b
Angina/ischaemia^c relief		
Short-acting nitrates are recommended for immediate relief of effort angina.	I	B
First-line treatment is indicated with beta-blockers and/or CCBs to control heart rate and symptoms.	I	A
If angina symptoms are not successfully controlled on a beta-blocker or a CCB, the combination of a beta-blocker with a DHP-CCB should be considered.	IIa	C
Initial first-line treatment with the combination of a beta-blocker and a DHP-CCB should be considered.	IIa	B
Long-acting nitrates should be considered as a second-line treatment option when initial therapy with a beta-blocker and/or a non-DHP-CCB is contraindicated, poorly tolerated, or inadequate to control angina symptoms.	IIa	B
When long-acting nitrates are prescribed, a nitrate-free or low-nitrate interval should be considered to reduce tolerance.	IIa	B
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	B
In subjects with baseline low heart rate and low BP, ranolazine or trimetazidine may be considered as a first-line drug to reduce angina frequency and improve exercise tolerance.	IIb	C
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	B
Nitrates are not recommended in patients with hypertrophic obstructive cardiomyopathy or co-administration of phosphodiesterase inhibitors.	III	B

III - Therapeutic management of Angina

Recommendations for Event Prevention	Class ^a	Level ^b
Antithrombotic therapy in patients with CCS and in sinus rhythm		
Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.	I	A
Clopidogrel 75 mg daily is recommended as an alternative to aspirin in patients with aspirin intolerance.	I	B
Clopidogrel 75 mg daily may be considered in preference to aspirin in symptomatic or asymptomatic patients, with either PAD or a history of ischaemic stroke or transient ischaemic attack.	IIb	B
Aspirin 75–100 mg daily may be considered in patients without a history of MI or revascularization, but with definitive evidence of CAD on imaging.	IIb	C
Adding a second antithrombotic drug to aspirin for long-term secondary prevention should be considered in patients with a high risk of ischaemic events ^c and without high bleeding risk ^d .	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 ^e and without high bleeding risk ^d .	IIb	A

III - Therapeutic management of Angina

Recommendations for Event Prevention

Class^a Level^b

Lipid-lowering drugs

Statins are recommended in all patients with CCS.^c

Aspirin 75–100 mg daily is recommended in patients with a previous MI or revascularization.

I

A

If a patient's goal^c is not achieved with the maximum tolerated dose of statin, combination with ezetimibe is recommended.

I

B

For patients at very high risk who do not achieve their goal^c on a maximum tolerated dose of statin and ezetimibe, combination with a PCSK9 inhibitor is recommended.

I

A

ACE inhibitors

ACE inhibitors (or ARBs) are recommended if a patient has other conditions (e.g. heart failure, hypertension, or diabetes).

IIa

A

ACE inhibitors should be considered in CCS patients at very high risk of cardiovascular events.

I

A

Other drugs

Beta-blockers are recommended in patients with LV dysfunction or systolic HF.

IIa

B

In patients with a previous STEMI, long-term oral treatment with a beta-blocker should be considered.

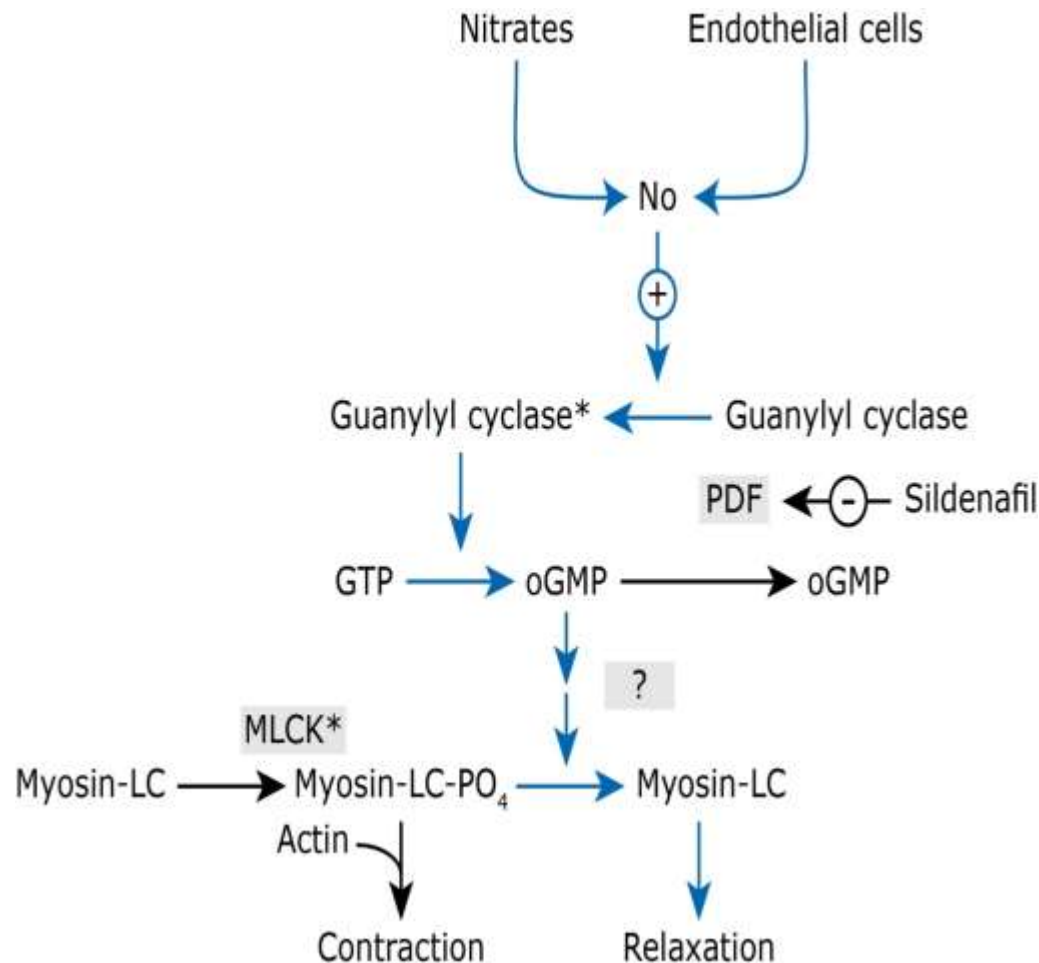
Limitations of angina treatments

ADVERSE EVENTS	CALCIUM CHANNEL BLOCKERS	β BLOCKERS	LONG-ACTING NITRATES
Most common	Constipation Dizziness Leg edema Flushing Headache Hypotension Palpitation Weakness	Bronchospasm Conduction disorders Depression Fatigue GI* disturbance Peripheral vasoconstriction Sexual dysfunction Sleep disturbance Weakness	Dizziness Flushing Headache Postural hypotension Tachycardia
Other significant effects	Myocardial ischemia or infarction due to "coronary steal" hypotension	Bradycardia Heart failure Increased angina on abrupt withdrawal May mask symptoms of hypoglycemia	Tolerance Increased angina during nitrate-free period

*GI=gastrointestinal

Parker, J.O., 2004. Chronic angina pectoris: inadequacies of current therapy. *The American journal of geriatric cardiology*, 13(5), pp.261-266.

Molecular mechanisms of Nitrate Action and Tolerance



Nitrate Treatment Induces Endothelial Dysfunction

- Endothelial dysfunction (ED) can be observed in humans during prolonged GTN therapy.
- GTN treatment reduces basal NO bioavailability and that this may be attributable to abnormalities in NOS function, that NOS generates a vasoconstrictor agent.

This leads to tolerance...

Nitrate-Free Intervals

ESC - 2013

Long-acting nitrates for angina prophylaxis. Long-acting nitrates are not continuously effective if regularly taken over a prolonged period without a nitrate-free or nitrate-low interval of about 8–10 hours (tolerance). Worsening of endothelial dysfunction is a potential complication of long-acting nitrates, hence the common practice of the routine use of long-acting nitrates as first line therapy for patients with effort angina needs re-evaluation.²⁸³

ESC - 2019

draw firm conclusions about their relative efficacies.²⁰⁰ When taken over a prolonged period, long-acting nitrates provoke tolerance with loss of efficacy, which requires prescription of a nitrate-free or nitrate-low interval of ~10–14 h.²⁰¹ Nitroglycerin can be administered orally

Montalescot, G., Sechtem, U., Achenbach, S., Andreotti, F., Arden, C., Budaj, A., Bugiardini, R., Crea, F., Cuisset, T. and Di Mario, C., 2013. Task Force Members. 2013 ESC guidelines on the management of stable coronary artery disease: the Task Force on the management of stable coronary artery disease of the European Society of Cardiology. *Eur Heart J*, 34(38), pp.2949-3003.

Knuuti, J., Wijns, W., Saraste, A., Capodanno, D., Barbato, E., Funck-Brentano, C., Prescott, E., Storey, R.F., Deaton, C., Cuisset, T. and Agewall, S., 2019. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. *European heart journal*.

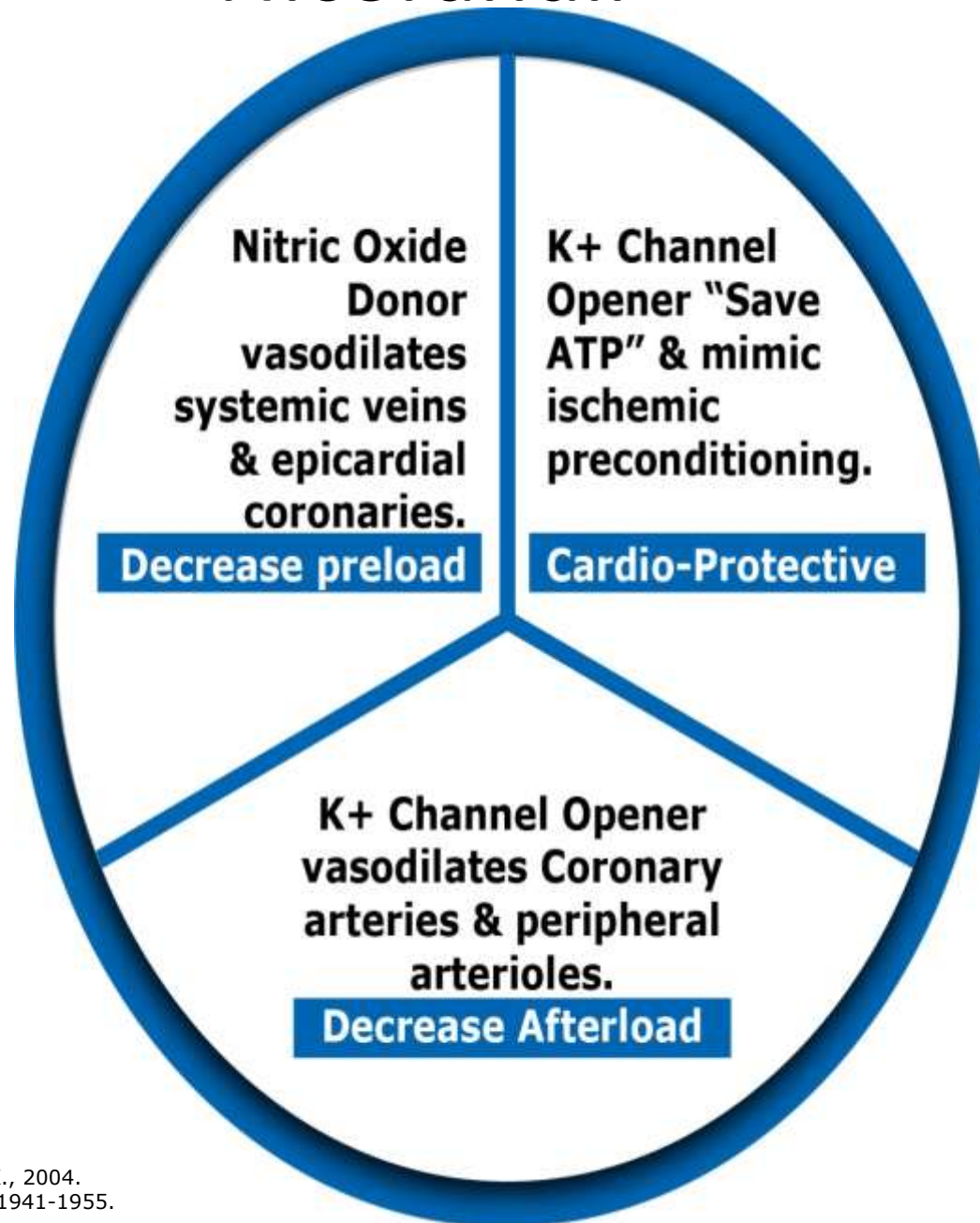
Dangers of Nitrate-Free Intervals

- Can reverse the effects of tolerance; But has many drawbacks!

Drug interactions

Drug class	Side effects ^a	Contraindications	DDIs	Precautions
Short- and long-acting nitrates ^{138,145,146}	<ul style="list-style-type: none"> ● Headache ● Flushing ● Hypotension ● Syncope and postural hypotension ● Reflex tachycardia ● Methaemoglobinaemia 	<ul style="list-style-type: none"> ● Hypertrophic obstructive cardiomyopathy ● Severe aortic stenosis ● PDE5 inhibitors 	<ul style="list-style-type: none"> ● PDE5 inhibitors (sildenafil or similar drugs) ● Alpha-adrenergic blockers ● CCBs 	<ul style="list-style-type: none"> ● Allow a nitrate-free or nitrate-low interval of about 10–14 h with long-acting nitrates

Nicorandil



Nicorandil MOA

- Nicorandil is not associated or rebound angina, and has prognostic benefit due to reduction in oxidative stress during myocardial ischemic reperfusion injury.

- **Overcoming Tolerance and ED:**

Nicorandil, via its nicotinamide component, opens K-ATP channels and activates endothelial NOS, which improves endothelial function and provides cardioprotective effects.

Tarkin JM, Kaski JC. Vasodilator therapy: nitrates and Nicorandil. *Cardiovascular drugs and therapy*. 2016 Aug 1;30(4):367-78.

Jolicœur, E.M. and Henry, T.D., 2017. Refractory angina. *Chronic Coronary Artery Disease: A Companion to Braunwald's Heart Disease*. Philadelphia, PA: Elsevier, pp.p412-432.

Lawrence Kwon, Clive Rosendorff, 20 - The Medical Treatment of Stable Angina, Editor(s): James A. de Lemos, Torbjørn Omland, *Chronic Coronary Artery Disease*, Elsevier, 2018, Pages 280-302, ISBN 9780323428804, <https://doi.org/10.1016/B978-0-323-42880-4.000200>

I – IONA

Study Design

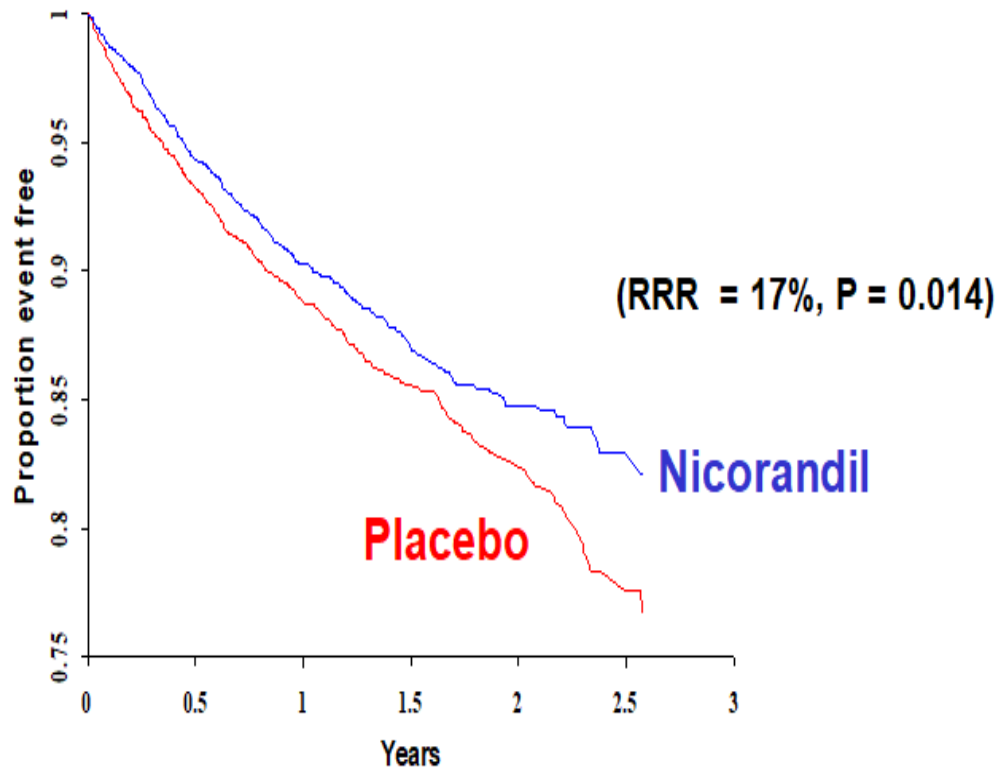
- Randomized trial to Investigate the cardio protective effects of Nicorandil in stable angina.

Methods and Results:

- 5126 patients
- Randomly assigned 20 mg Nicorandil twice daily or placebo.
- The mean follow-up interval was 1.6 years.

I – IONA:

CHD death, non-fatal MI or unplanned hospitalisation for cardiac chest pain



Interaction with other medicinal products

- **Phosphodiesterase 5 inhibitors**

e.g. sildenafil, tadalafil, vardenafil

contraindicated, can lead to serious drop in bl. pr (synergic effect).

- **Antihypertensive agents**

e.g. vasodilators, tricyclic antidepressants, alcohol




- Nicorandil may lower the bl. pr of hypotensive pts.
- If Nicorandil is used with anti HTN agents, the bl. Pr. lowering effect may be increased

- **Medical products that may increase potassium levels.**

- Nicorandil may increase potassium levels

Comparison the different agents used in TTT of Angina

	Diabetes	CKD	Liver	Elderly	Tolerance
Nicorandil					No
Trimetazidine					No
Nitrates					Yes

 No Contraindications
  Caution is advised
  Contraindicated

European Medicines Agency (EMA), 2012. Assessment Report for trimetazidine containing medicinal products.

European Medicines Agency. *Trimetazidine - European Medicines Agency*. [online] Available at: <https://www.ema.europa.eu/en/medicines/human/referrals/trimetazidine> [Accessed 12 Feb. 2020].

Dézsai, C.A., 2016. Trimetazidine in practice: review of the clinical and experimental evidence. *American journal of therapeutics*, 23(3), p.e871.

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Medicines.org.uk. (n.d.). *Isosorbide Mononitrate Tablets 20 mg - Summary of Product Characteristics (SmPC) - (emc)*. [online]. Available at: <https://www.medicines.org.uk/emc/product/2608/emc> [Accessed 12 Feb. 2020].

Thank you