ANOCA

Prepared by **Dr. Sidhartha Mullapudi**, DrNB (Cardiology), MD (General Medicine)
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I DEFINITION AND CLINICAL SIGNIFICANCE (ESC 2024 CCS GUIDELINES)

- **Definition: Angina with Non-Obstructive Coronary Arteries (ANOCA)** refers to patients presenting with chronic anginal symptoms (and when accompanied by objective evidence of myocardial ischemia on non-invasive testing, termed **INOCA**) who have either normal epicardial coronary arteries or non-obstructive atherosclerosis (**less than 50 percent luminal diameter stenosis** and physiologically non-flow-limiting FFR greater than 0.80) on coronary angiography.
- **Epidemiology:** Present in **40 to 50 percent** of patients undergoing elective diagnostic coronary angiography for suspected stable angina, with a strong **female predominance** (particularly peri- and post-menopausal women).
- **The Paradigm Shift:** Historically dismissed as benign "Cardiac Syndrome X," contemporary guidelines recognize ANOCA/INOCA as a pathophysiological condition associated with recurrent hospitalizations, impaired quality of life, increased risk of **Major Adverse Cardiovascular Events (MACE)**, and progression to **Heart Failure with Preserved Ejection Fraction (HFpEF)**.

II PATHOPHYSIOLOGICAL ENDOTYPES OF ANOCA

- **Microvascular Angina (MVA — Structural and/or Functional Microvascular Dysfunction):**
  - **Mechanism:** Structural remodeling (**capillary rarefaction, arteriolar medial hypertrophy, and perivascular fibrosis**) and/or functional impairment (**endothelial nitric oxide deficiency** or impaired smooth muscle relaxation) of the coronary microcirculation (pre-arterioles and arterioles **less than 500 micrometers** in diameter).
  - **Hemodynamic Consequence:** Inability of the coronary microvascular bed to vasodilate and augment myocardial blood flow in response to increased myocardial oxygen demand during exertion.
  - **Epicardial Vasospastic Angina (VSA / Prinzmetal Variant Angina):**
  - **Mechanism:** Vascular smooth muscle hyper-reactivity (mediated by Rho-kinase upregulation and autonomic/endothelial dysfunction) causing transient, severe focal or diffuse vasoconstriction of a large epicardial coronary artery, classically occurring **at rest** (especially between midnight and early morning) with transient ST-segment elevation.
  - **Microvascular Vasospasm:**
  - **Mechanism:** Intense vasoconstriction localized exclusively to the coronary microvasculature, producing anginal chest pain and ischemic ECG changes without epicardial vessel narrowing exceeding 90 percent.
  - **Mixed / Combined Endotype (MVA + VSA):**
  - **Mechanism:** Coexistence of both impaired microvascular vasodilatory reserve/elevated microvascular resistance and epicardial or microvascular vasospasm, which carries a worse symptomatic prognosis if both mechanisms are not simultaneously targeted.

III DIAGNOSTIC PATHWAY (NON-INVASIVE AND INVASIVE CORONARY FUNCTION TESTING)

- **The CorMicA Trial Mandate:** The landmark **CorMicA Trial** proved that performing invasive **Coronary Function Testing (CFT)** at the time of diagnostic angiography to stratify ANOCA patients into their specific endotype and tailor medical therapy significantly improves angina severity (Seattle Angina Questionnaire) and quality of life compared with standard empirical care.

A Non-Invasive Functional Imaging (Class IIa)

- **Positron Emission Tomography (Cardiac PET-CT):** The non-invasive reference standard for quantifying absolute resting and stress **Myocardial Blood Flow (MBF in mL/min/g)** and global **Coronary Flow Reserve (CFR)**.
- **Stress Perfusion Cardiac MRI (Stress CMR):** Quantifies the **Myocardial Perfusion Reserve Index (MPRI)** and detects circumferential subendocardial hypoperfusion after ruling out epicardial stenosis.

B Invasive Coronary Function Testing (CFT — ESC 2024 Class I)

- **Step 1 — Endothelium-Independent Microvascular Assessment (Intravenous Adenosine Hyperemia):** Using a **pressure-temperature sensor guidewire (thermodilution)** or **Doppler flow velocity wire** in the LAD during maximal hyperemia with intravenous Adenosine:
- **Coronary Flow Reserve (CFR):** Ratio of hyperemic blood flow to resting blood flow; **abnormal CFR is less than 2.0** (or less than 2.5 in recent consensus), indicating impaired microvascular vasodilatory reserve.
- **Index of Microcirculatory Resistance (IMR):** Product of distal coronary pressure and mean transit time during maximal hyperemia; **abnormal IMR is 25 units or greater**, indicating structural microvascular disease.
- **Step 2 — Intracoronary Provocative Vasoreactivity Testing (Acetylcholine or Ergonovine):** Incremental intracoronary infusions of **Acetylcholine (ACh)** to test endothelial nitric oxide function and smooth muscle hyper-reactivity:
- **Diagnostic of Epicardial Vasospastic Angina (COVADIS Criteria): Reproduction of usual chest pain + ischemic ECG changes (ST-elevation or ST-depression >=0.1 mV) + severe epicardial vasoconstriction (90 percent or greater lumen diameter reduction)** on angiography.
- **Diagnostic of Microvascular Spasm: Reproduction of usual chest pain + ischemic ECG changes** during intracoronary ACh infusion, in the **absence of severe epicardial vasoconstriction (less than 90 percent narrowing)**.

ANOCA Endotype	Intracoronary Adenosine (CFR & IMR)	Intracoronary Acetylcholine (ACh) Provocation	First-Line Targeted Pharmacotherapy (ESC 2024)
Microvascular Angina (MVA)	**CFR < 2.0** and/or **IMR >= 25**	Negative for epicardial spasm	**Beta-Blockers (Nebivolol/Carvedilol)** or CCBs; **Ranolazine / Ivabradine / Trimetazidine**; **ACEi + Statin**
Epicardial Vasospastic Angina (VSA)	Normal CFR (>=2.0) & Normal IMR (<25)	**>=90% epicardial constriction** + Angina + Ischemic ECG shifts	**Calcium Channel Blockers (Diltiazem, Verapamil, Amlodipine)** + **Long-Acting Nitrates / Nicorandil**; **Avoid Beta-Blockers**
Microvascular Spasm	Normal or reduced CFR	**Angina + Ischemic ECG shifts WITHOUT >=90% epicardial constriction**	**Calcium Channel Blockers** + **Nicorandil / Ranolazine**; **ACEi + Statin**
Mixed Endotype (MVA + VSA)	**CFR < 2.0** and/or **IMR >= 25**	Positive for epicardial or microvascular spasm	**Calcium Channel Blockers + Nicorandil / Ranolazine + ACEi + Statin** (avoid non-selective beta-blockers)

IV ENDOTYPE-DRIVEN PHARMACOTHERAPY (ESC 2024 GUIDELINES)

A Management of Microvascular Angina (Impaired CFR / Elevated IMR)

- **First-Line Anti-Ischemic Therapy: Beta-Blockers** (particularly vasodilating beta-blockers with nitric-oxide-donating properties such as **Nebivolol**, or **Carvedilol**) to reduce myocardial oxygen demand and prolong diastolic perfusion time, or **Calcium Channel Blockers (CCBs)**.
- **Second-Line / Adjunctive Anti-Anginals: Ranolazine** (inhibits the late inward sodium current [INa], reducing intracellular calcium overload and improving left ventricular diastolic microvascular compliance), **Ivabradine**, **Trimetazidine**, or **Nicorandil**.
- **Endothelial Disease Modification: ACE Inhibitors (or ARBs)** and **High-Intensity Statins** are recommended in all patients with endothelial dysfunction or non-obstructive atherosclerosis to improve microvascular function, alongside structured weight loss, smoking cessation, and aerobic exercise rehabilitation.

B Management of Vasospastic Angina (Epicardial or Microvascular Spasm)

- **First-Line Therapy: Non-Dihydropyridine CCBs (Diltiazem or Verapamil)** or **Dihydropyridine CCBs (Amlodipine or Nifedipine)**, often titrated to high doses or used in dual CCB combination for refractory spasm.
- **Second-Line Vasodilators: Long-Acting Nitrates** (with a nitrate-free interval to prevent tolerance) and **Nicorandil** (dual nitrate-like donor and ATP-sensitive potassium channel opener that dilates both epicardial and microvascular resistance vessels).
- **Avoid Beta-Blockers in Isolated Spasm: Beta-blockers (especially non-selective agents like Propranolol) should be avoided in isolated Vasospastic Angina** because blockade of vasodilatory vascular beta-2 receptors leaves alpha-1 adrenergic vasoconstrictor receptors unopposed, aggravating and prolonging severe coronary vasospasm.

KEY REFERENCES

- **Vrints C, Andreotti F, Koskinas KC, et al.:** 2024 ESC Guidelines for the management of chronic coronary syndromes, *European Heart Journal*, 2024.
- **Libby P, Bonow RO, Mann DL, Tomaselli GF, Bhatt DL, Solomon SD:** *Braunwald's Heart Disease: A Textbook of Cardiovascular Medicine*, 12th Ed., Elsevier, 2022.