What is New from the 2024 European Society of Cardiology Congress on the Management of Chronic Coronary Syndromes? Updated Guidelines and Trials

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The 2024 European Society of Cardiology (ESC) congress introduced key advancements in the management of chronic coronary syndrome (CCS). Updated guidelines incorporated new evidence in the diagnosis and treatment of CCS, and few Late-breaking Clinical Trials dealt with CCS.[1]

New Recommendations from 2024 European Society of Cardiology Guidelines

Definition and Diagnostic Approach

The task force provided a more comprehensive definition of CCS, encompassing all clinical conditions characterised by transient, reversible imbalances between myocardial oxygen demand and blood supply, leading to myocardial ischaemia.

A four-step, stepwise diagnostic approach is recommended for individuals with suspected CCS. The task force endorses the use of the risk factor-weighted clinical likelihood model to estimate the pretest likelihood of obstructive epicardial coronary artery disease (CAD). This scoring system incorporates several variables, including sex, age, angina symptoms and cardiovascular (CV) risk factors, with adjustments based on individual specific features (e.g. peripheral artery disease, resting ECG, echocardiography or vascular calcifications).[2] This tailored approach tripled the number of individuals classified as having a very low likelihood (≤5%) of obstructive CAD, which should defer further diagnostic testing, while enhancing the precision of estimated annualised event rates of MI and mortality.[1]

Pathophysiology of Chronic Coronary Syndrome and Identification of Chronic Coronary Syndrome Endotype

The current ESC guidelines also reappraise the pathophysiology of CCS, including both structural and functional abnormalities of the epicardial and microvascular districts.

Coronary vasomotor disorders and coronary microvascular dysfunction have emerged as significant contributors to CCS, accounting for 41% and 40%, respectively, of non-obstructive CAD.[3] Notably, coronary microvascular dysfunction has been associated with increased rates of major adverse cardiac events over a 5-year follow-up period.[4] Coronary vasomotor disorders have been similarly linked to sudden cardiac death and MI.[5]

A significant update is the recommendation (class 1, level of evidence b) for invasive coronary functional testing in the catheterisation laboratory to confirm or rule out the diagnosis of obstructive CAD or angina with non-obstructive coronary arteries.[1] Doppler flow velocity and thermodilution-based methods are used to assess coronary flow reserve and microvascular resistance,[6] while acetylcholine coronary provocative testing is the gold standard for evaluating coronary vasomotor disorders.[7] These diagnostic techniques allow for the identification of specific CCS endotypes, facilitating personalised therapies with potential prognostic benefits.[8]

Lifestyle Interventions

The 2024 ESC guidelines emphasise the importance of shared decision-making between clinicians and patients. Clinicians are encouraged to tailor treatment plans to the individual's preferences, capabilities and healthcare costs, while striving to simplify medication regimens where feasible. Additionally, the guidelines recommend lifelong education programmes, to enhance long-term adherence to healthy lifestyles and medications.

Psychological support and exercise-based cardiac rehabilitation are key pillars of secondary prevention of CCS, with robust evidence showing a reduction in mortality rates compared with placebo.[9,10] Of interest, achieving and maintaining a healthy weight is a primary objective for patients with CCS, as it positively impacts clinical outcomes, improves risk-factor control and enhances quality of life. For patients who fail to meet weight targets, pharmacological intervention with glucagon-like peptide-1 receptor agonists may be considered. These agents have demonstrated efficacy in promoting weight loss and reducing the incidence of major adverse cardiac events, both in patients with and without type 2 diabetes.[11,12]

Medical Therapy

The updated guidelines integrate new evidence regarding optimal antiplatelet therapy secondary prevention in CCS. Specifically, clopidogrel monotherapy is now recommended as a safe alternative to aspirin monotherapy.[1] This recommendation is substantiated by recent large-scale randomised clinical trials (RCTs), which have demonstrated a potential reduction in the composite ischaemic/haemorrhagic endpoint with clopidogrel compared with aspirin.[13–15]

A precise assessment of the individual's ischaemic and haemorrhagic risk profile is crucial for guiding antiplatelet therapy in patients with CCS after percutaneous coronary intervention (PCI). For patients at high ischaemic risk and low bleeding risk, ticagrelor monotherapy may be considered as an alternative strategy.[1] Conversely, a short duration of dual antiplatelet therapy (1–3 months) is recommended for patients at high bleeding risk and low ischaemic risk, compared with the conventional 6-month regimen. This recommendation, which was introduced in previous guidelines, has been further reinforced by the recent Master-DAPT trial.[16]

Strong evidence supports the use of sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists, as these agents offer CV benefits beyond their glucose-lowering effects.[17,18] Both sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists are now recommended as first-line therapies for patients with type 2 diabetes and CCS to reduce major adverse cardiac events, regardless of glycaemic control and glucose-lowering medications.[1]

Additionally, low-dose colchicine should be considered in CCS patients with atherosclerotic CAD. This recommendation is supported by the results of the LODOCO2 trial, which demonstrated a significant reduction of adverse events in 5,550 patients with CCS over a median follow-up of 2.4 years.[19]

Myocardial Revascularisation

The prognostic role of myocardial revascularisation in CCS remains unclear. The large ischaemia trial, which included 5,179 patients with CAD and moderate to severe inducible myocardial ischaemia (excluding those with left main disease and reduced [<35%] left ventricular ejection fraction [LVEF]) found that invasive and conservative strategies led to comparable outcomes. Notably, at 7 years of follow-up, the invasive strategy was associated with lower rates of spontaneous MI and non-cardiac mortality, while the conservative strategy was linked to a reduced occurrence of CV mortality.[20] Current guidelines recommend myocardial revascularisation for CCS patients with LVEF >35% and functionally significant lumen disease, three-vessel disease or significant single- or two-vessel disease involving the proximal left anterior descending artery.[1]

The prognostic impact of myocardial revascularisation in patients with impaired LVEF (≤35%) is still debated. The landmark STICH trial demonstrated that coronary artery bypass grafting (CABG) was superior to medical therapy in reducing all-cause and CV mortality at a median follow-up of 9.8 years.[21] Conversely, the REVIVED-BCIS2 trial found that PCI did not significantly reduce the composite primary endpoint of all-cause death or heart failure rehospitalisation compared with optimal medical therapy at a 3.4-year follow-up.[22]

Based on these findings, current guidelines suggest that the decision between revascularisation and medical therapy should be made through a Heart Team discussion. For surgically eligible CCS patients with multivessel CAD and LVEF ≤35%, CABG is recommended over medical therapy. PCI may be considered as an alternative to CABG for patients who are at high surgical risk or not operable.[1]

In patients with lumen disease, CABG is recommended over medical therapy alone to improve survival according to recent RCTs.[23] However, PCI is recommended for patients with low anatomical CAD complexity and should be considered for those with moderate anatomical CAD complexity.[1]

For symptomatic patients with functionally significant obstructive CAD despite guideline-directed medical treatment, PCI is recommended to alleviate symptoms, as supported by the recent ORBITA-2 trial.[24]

Recent observational evidence has highlighted the importance of Heart Team discussions in the decision-making process for revascularisation.[25] These findings have been integrated into the current guidelines (class 1 recommendation, level of evidence C).[1]

Of interest, current guidelines for the first time recommend the use of intracoronary imaging, either intravascular ultrasound or optical coherence tomography, for guiding PCI in complex lesions, such as lumen lesions, true bifurcations, and long lesions. The landmark RENOVATE-COMPLEX PCI and OCTOBER trials demonstrated better outcomes with intravascular ultrasound-guided PCI compared to angiography-guided PCI.[26,27]

Finally, based on recent RCTs, drug-eluting stents are recommended over drug-coated balloons for the treatment of in-stent restenosis.[28]

Late-breaking Clinical Trials

The EPIC-CAD trial randomised 1,040 patients with stable CAD (≥6 months after revascularisation for CCS or ≥12 months for acute coronary syndrome; or medical therapy alone) and high-risk AF to edoxaban, or edoxaban plus a single antiplatelet agent. At 12 months, edoxaban monotherapy was associated with a lower risk of clinical events, mainly driven by a reduction of major bleedings.[29]

The Rec-CAGEFREE I trial enrolled 2,272 with *de novo* non-complex CAD. Notably, paclitaxel-coated balloons did not achieve expected non-inferiority versus drug-eluting stents in regard to a 2-year device-oriented composite endpoint.[30]

Gaps in Knowledge

From a pathological perspective, the reasons why patients with common risk factors progress differently to CAD or coronary microvascular dysfunction are not fully understood. Identifying additional pathological mechanisms could be crucial for a better understanding of these conditions.

Currently, there is a lack of a precise diagnostic work-up for patients with angina with non-obstructive coronary arteries, and RCTs are needed to evaluate whether tailored medications can improve clinical outcomes in these patients.

The prognostic impact of myocardial revascularisation in patients with CCS also requires further investigation: future RCTs should focus on high-risk patients with anatomically complex CAD to close the gap between current randomised evidence and real-world clinical practice.

Finally, implementing strategies to enhance patient adherence to healthy lifestyles and medications is essential for improving patients' quality of life and clinical outcomes.

Conclusion

The ESC Congress 2024 represents a significant advance for CCS patients, moving towards a precise diagnosis of CCS endotype and patient-tailored management. The guidelines also broaden the armamentarium of recommended medical treatments and advocate for the routine use of imaging guidance in complex PCI. Nevertheless, improving outcomes for CCS patients is a lengthy process that requires extensive research. ❑

1. Vrints C, Andreotti F, Koskinas KC, et al. 2024 ESC Guidelines for the management of chronic coronary syndromes. *Eur Heart J* 2024;45:3415–537. https://doi.org/10.1093/eurheartj/ehae177; PMID: 39210710.
2. Winther S, Schmidt SE, Mayrhofer T, et al. Incorporating coronary calcification into pre-test assessment of the likelihood of coronary artery disease. *J Am Coll Cardiol* 2020;76:2421–32. https://doi.org/10.1016/j.jacc.2020.09.585; PMID: 33213720.
3. Mileva N, Nagumo S, Mizukami T, et al. Prevalence of coronary microvascular disease and coronary vasospasm in patients with nonobstructive coronary artery disease: systematic review and meta-analysis. *J Am Heart Assoc* 2022;11:e023207. https://doi.org/10.1161/jaha.121.023207; PMID: 35301851.
4. Boerhout CKM, de Waard GA, Lee JM, et al. Prognostic value of structural and functional coronary microvascular dysfunction in patients with non-obstructive coronary artery disease; from the multicentre international ILIAS registry. *EuroIntervention* 2022;18:719–28. https://doi.org/10.4244/eij-d-22-00043; PMID: 35694826.
5. Montone RA, Niccoli G, Fracassi F, et al. Patients with acute myocardial infarction and non-obstructive coronary arteries: safety and prognostic relevance of invasive coronary provocative tests. *Eur Heart J* 2018;39:91–8. https://doi.org/10.1093/eurheartj/ehx667; PMID: 29228159.
6. Kunadian V, Chieffo A, Camici PG, et al. An EAPCI Expert consensus document on ischaemia with non-obstructive coronary arteries in collaboration with European Society of Cardiology working group on coronary pathophysiology & microcirculation endorsed by coronary vasomotor disorders international study group. *Eur Heart J* 2020;41:3504–20. https://doi.org/10.1093/eurheartj/ehaa503; PMID: 32626906.
7. Montone RA, Rinaldi R, Del Buono MG, et al. Safety and prognostic relevance of acetylcholine testing in patients with stable myocardial ischaemia or myocardial infarction and non-obstructive coronary arteries. *EuroIntervention* 2022;18:e666–76. https://DOI.ORG/10.4244/EIJ-D-21-00971; PMID: 35377315.
8. Ford TJ, Stanley B, Good R, et al. Stratified medical therapy using invasive coronary function testing in angina: the CorMicA trial. *J Am Coll Cardiol* 2018;72:2841–55. https://doi.org/10.1016/j.jacc.2018.09.006; PMID: 30266608.
9. Tully PJ, Ang SY, Lee EJ, et al. Psychological and pharmacological interventions for depression in patients with coronary artery disease. *Cochrane Database Syst Rev* 2021;12:CD008012. https://doi.org/10.1002/14651858.CD008012.pub4; PMID: 34910821.
10. Salzwedel A, Jensen K, Rauch B, et al. Effectiveness of comprehensive cardiac rehabilitation in coronary artery disease patients treated according to contemporary evidence based medicine: update of the Cardiac Rehabilitation Outcome Study (CROS-II). *Eur J Prev Cardiol* 2020;27:1756–74. https://doi.org/10.1177/2047487320905719; PMID: 32089005.
11. Garvey WT, Frias JP, Jastreboff AM, et al. Tirzepatide once weekly for the treatment of obesity in people with type 2 diabetes (SURMOUNT-2): a double-blind, randomised, multicentre, placebo-controlled, phase 3 trial. *Lancet* 2023;402:613–26. https://doi.org/10.1016/s0140-6736(23)01200-x; PMID: 37385275.
12. Lincoff AM, Brown-Frandsen K, Colhoun HM, et al. Semaglutide and cardiovascular outcomes in obesity without diabetes. *N Engl J Med* 2023;389:2221–32. https://doi.org/10.1056/NEJMoa2307563; PMID: 37952131.
13. Gragnano F, Cao D, Pirondini L, et al. $P2Y_{12}$ inhibitor or aspirin monotherapy for secondary prevention of coronary events. *J Am Coll Cardiol* 2023;82:89–105. https://doi.org/10.1016/j.jacc.2023.04.051; PMID: 37407118.
14. Chiarito M, Sanz-Sánchez J, Cannata F, et al. Monotherapy with a $P2Y_{12}$ inhibitor or aspirin for secondary prevention in patients with established atherosclerosis: a systematic review and meta-analysis. *Lancet* 2020;395:1487–95. https://doi.org/10.1016/S0140-6736(20)30315-9; PMID: 32386592.
15. Koo BK, Kang J, Park KW, et al. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. *Lancet* 2021;397:2487–96. https://doi.org/10.1016/S0140-6736(21)01063-1; PMID: 34010616.
16. Valgimigli M, Frigoli E, Heg D, et al. Dual antiplatelet therapy after PCI in patients at high bleeding risk. *N Engl J Med* 2021;385:1643–55. https://doi.org/10.1056/NEJMoa2108749; PMID: 34449185.
17. McGuire DK, Shih WJ, Cosentino F, et al. Association of SGLT2 inhibitors with cardiovascular and kidney outcomes in patients with type 2 diabetes: a meta-analysis. *JAMA Cardiol* 2021;6:148–58. https://doi.org/10.1001/jamacardio.2020.4511; PMID: 33031522.
18. Sattar N, Lee MMY, Kristensen SL, et al. Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of randomised trials. *Lancet Diabetes Endocrinol* 2021;9:653–62. https://doi.org/10.1016/S2213-8587(21)00203-5; PMID: 34425083.
19. Nidorf SM, Fiolet ATL, Mosterd A, et al. Colchicine in patients with chronic coronary disease. *N Engl J Med* 2020;383:1838–47. https://doi.org/10.1056/NEJMoa2021372; PMID: 32865380.
20. Hochman JS, Anthopolos R, Reynolds HR, et al. Survival after invasive or conservative management of stable coronary disease. *Circulation* 2023;147:8–19. https://doi.org/10.1161/circulationaha.122.062714; PMID: 36335918.
21. Velazquez EJ, Lee KL, Jones RH, et al. Coronary-artery bypass surgery in patients with ischemic cardiomyopathy. *N Engl J Med* 2016;374:1511–20. https://doi.org/10.1056/NEJMoa1602001; PMID: 27040723.
22. Perera D, Clayton T, O'Kane PD, et al. Percutaneous revascularization for ischemic left ventricular dysfunction. *N Engl J Med* 2022;387:1351–60. https://doi.org/10.1056/NEJMoa2206606; PMID: 36027563.
23. Ahmad Y, Howard JP, Arnold AD, et al. Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials. *Eur Heart J* 2020;41:3228–35. https://doi.org/10.1093/eurheartj/ehaa135; PMID: 32118272.
24. Rajkumar CA, Foley MJ, Ahmed-Jushuf F, et al. A placebo-controlled trial of percutaneous coronary intervention for stable angina. *N Engl J Med* 2023;389:2319–30. https://doi.org/10.1056/NEJMoa2310610; PMID: 38015442.
25. Witberg G, Segev A, Barac YD, et al. Heart team/guidelines discordance is associated with increased mortality: data from a national survey of revascularization in patients with complex coronary artery disease. *Circ Cardiovasc Interv* 2021;14:e009686. https://doi.org/10.1161/circinterventions.120.009686; PMID: 33423541.
26. Lee JM, Choi KH, Song YB, et al. Intravascular imaging-guided or angiography-guided complex PCI. *N Engl J Med* 2023;388:1668–79. https://doi.org/10.1056/NEJMoa2216607; PMID: 36876735.
27. Holm NR, Andreasen LN, Neghabat O, et al. OCT or angiography guidance for PCI in complex bifurcation lesions. *N Engl J Med* 2023;389:1477–87. https://doi.org/10.1056/NEJMoa2307770; PMID: 37634149.
28. Elgendy IY, Mahmoud AN, Elgendy AY, et al. Drug-eluting balloons versus everolimus-eluting stents for in-stent restenosis: a meta-analysis of randomized trials. *Cardiovasc Revasc Med* 2019;20:612–8. https://doi.org/10.1016/j.carrev.2018.08.010; PMID: 30126824.
29. Cho MS, Kang DY, Ahn JM, et al. Edoxaban antithrombotic therapy for atrial fibrillation and stable coronary artery disease. *N Engl J Med*. 2024. https://doi.org/10.1056/NEJMoa2407362; PMID: 39225258; epub ahead of press.
30. Gao C, He X, Ouyang F, et al. Drug-coated balloon angioplasty with rescue stenting versus intended stenting for the treatment of patients with de novo coronary artery lesions (REC-CAGEFREE I): an open-label, randomised, non-inferiority trial. *Lancet* 2024;404:1040–50. https://doi.org/10.1016/S0140-6736(24)01594-0; PMID: 39236727.