Evidence-to-Recommendation Framework

This document outlines the underpinning evidence and rationale for the recommendation statements in the ACE Clinical Guideline (ACG) 'Management of chronic coronary syndrome'.

In ACGs, the strength of recommendation reflects the confidence that the desirable effects of the recommended practice outweigh undesirable effects across the range of patients for whom the recommendation applies, based on the best available evidence:

- A strong recommendation is usually made when benefits clearly outweigh the risks, based on at least moderate-certainty evidence.
- A weak or conditional recommendation may be needed when there is a closer balance between benefits and harms, evidence is of low certainty, there is significant variability in patients' values and preferences, or important concerns with resourcing and feasibility of the recommended practice.[1]

Recommendation 1	**a. Use long-term low-dose aspirin monotherapy for secondary prevention of cardiovascular events.** **b. Consider long-term clopidogrel monotherapy as an alternative to aspirin.**

Strength of recommendation (1a): **Strong** | Weak/conditional

Strength of recommendation (1b): Strong | **Weak/conditional**

Summary:
Recommendations 1a and 1b highlight the antiplatelet therapy options for chronic coronary syndrome (CCS). While both aspirin and clopidogrel have a favourable benefit-harm balance, certainty of evidence is stronger for aspirin compared to clopidogrel. Furthermore, use of clopidogrel requires greater practical considerations. Based on these factors, the Expert Group (EG) agreed with a strong recommendation for aspirin and a weak/conditional recommendation for clopidogrel as alternative.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Aspirin vs placebo/other antiplatelet regimes: In patients with documented cardiovascular disease (CVD), long-term antiplatelet monotherapy with aspirin provides net clinical benefits compared to placebo or other antiplatelet regimes, especially at low dose, and it is considered the first choice in those with coronary artery disease (CAD).[2,3] The findings from systematic reviews (SRs) and meta-analyses (MAs) of randomised controlled trials (RCTs) indicated that low-dose aspirin (75 to 150 mg daily) was associated with significant reduction in serious vascular events, non-fatal myocardial infarction (MI), non-fatal stroke, and vascular mortality compared to placebo or different antiplatelet regimes.[3-9] Aspirin was associated with increased risk of gastrointestinal side effects at higher doses (i.e. 500-1500 mg/day), and current evidence supports a daily dose of 75 to 100 mg for the prevention of ischaemic events in patients with CAD, with or without a history of MI. Clopidogrel vs placebo: The efficacy and safety of clopidogrel compared to placebo in patients who received aspirin as background treatment indicated that clopidogrel is associated with a 7.7% reduction in the risk of hospitalisation for ischaemic events compared to the placebo group. Significant differences were found in non-fatal stroke (clopidogrel 1.9% vs placebo 2.4%, P=0.03) and hospitalisation (clopidogrel 11.1% vs placebo 12.3%, P=0.02) rates.[10] The primary safety outcomes including fatal bleeding and intracranial bleeding outcomes were found to be similar between the two groups.[10] Aspirin vs clopidogrel: The efficacy and safety of clopidogrel monotherapy compared to aspirin monotherapy was first reported in the CAPRIE trial (clopidogrel versus aspirin in patients at risk of ischaemic events)[11] where clopidogrel was found to be marginally superior to aspirin in terms of efficacy (8.7% relative risk reduction), with a similar safety profile compared to medium-dose aspirin (i.e. 160-325 mg/day) in patients with atherosclerotic vascular disease manifested as either recent ischaemic stroke, recent MI, or symptomatic peripheral arterial disease (PAD). Recent SR and MAs reported by Liu et al (including the findings from CAPRIE) indicated that clopidogrel monotherapy was associated with improved efficacy and safety outcomes compared to aspirin monotherapy in patients with CCS who had PCI, coronary artery bypass grafting or MI.[12, 13] Compared to aspirin monotherapy, clopidogrel monotherapy is associated with a 32% reduction in the risk of major adverse cardiac and cerebrovascular events, 43% reduction in the risk of MI, 45% reduction in the risk of stroke and 27% reduction in the risk of Bleeding Academic Research Consortium (BARC) major bleeding post intervention.[13]	No significant concerns or variability identified.

Certainty of evidence	Resources and feasibility
Recommendation 1a: Low dose aspirin (75 to 150 mg) was associated with significant reduction in serious vascular events, non-fatal myocardial infarction (MI), non-fatal stroke, and vascular mortality compared to placebo or different antiplatelet regimes.[3-9] The certainty of evidence was assessed to be moderate for most of the reported outcomes. Recommendation 1b: The findings from MAs of trials comparing aspirin to clopidogrel monotherapy favoured clopidogrel.[13] However, the quality of evidence was assessed to be low for most outcomes, thereby limiting the generalisability and applicability of the reported findings. Also, there are less studies on the efficacy and safety of clopidogrel monotherapy in patients with CCS compared to aspirin.	Both aspirin and clopidogrel are included in the local Standard Drug List and Healthier SG whitelisted drugs. The use of clopidogrel monotherapy in CCS management is associated with some practical considerations. Patients may need to switch temporarily to aspirin before elective procedures. For those with aspirin intolerance or allergy, aspirin desensitisation under specialist guidance is an option. Alternatively, in patients with low thrombotic risk, stopping clopidogrel temporarily without aspirin cover may be considered after consulting a cardiologist. These factors necessitate careful planning, coordination and may influence the use of clopidogrel monotherapy in CCS management.
Expert Group deliberation of above factors	
The EG concurred with the indications for low-dose aspirin monotherapy for secondary prevention in patients with CCS due to its efficacy and long-term safety profile. The EG also acknowledged the findings from the MAs indicating improved efficacy and safety of clopidogrel compared to aspirin, noting the low-quality evidence for most outcomes. The EG also noted that the overall evidence base on the efficacy and safety of clopidogrel monotherapy is limited compared to aspirin monotherapy, and suggested that the overall effectiveness of clopidogrel monotherapy still needs to be further assessed clinically for long-term management of patients with CCS. As such, the EG agreed with positioning clopidogrel as an alternative to aspirin for secondary prevention in patients with CCS.	

Recommendation 2	**Review patients following PCI to confirm that there is a specified treatment duration for their dual antiplatelet therapy and check with the referring cardiologist if treatment duration is unclear.**

Strength of recommendation (2): **Strong** Weak/conditional

Summary:
Most patients with CCS post-PCI receive dual antiplatelet therapy (DAPT) for a specified period, followed by single antiplatelet therapy. Recent evidence suggests that shorter DAPT durations (1-3 months) may offer net clinical benefits over longer durations (12 months). However, the optimal DAPT duration is influenced by various factors, including the individual patient's risk of bleeding versus thrombosis, procedure-related considerations, and the involvement of multiple stents. As DAPT duration is usually recommended by the cardiologist performing PCI, a strong recommendation was made to emphasise the role of primary care physicians in continuing patient review after hospital discharge. If the DAPT duration is not provided or is unclear, primary care physicians should confirm this with the cardiologist. This approach balances the benefits of DAPT in preventing thrombotic events with the risks of prolonged therapy, while emphasising the importance of clear communication between specialists and primary care providers to ensure optimal patient management.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
In patients with CCS, the optimal duration of DAPT differs depending on its net clinical benefit, which is based on individual patient's ischaemic and bleeding risks. In general, prolonged DAPT increases bleeding risk regardless of clinical presentation and recent trial evidence indicated that compared to 12-months of DAPT, short-term DAPT (i.e. 1-3 months) followed by P2Y12 (purinergic receptor P2Y, G-protein coupled, 12 protein) inhibitors (i.e. clopidogrel or ticagrelor) could significantly reduce the risk of major bleeding by 40% (hazard ratio [HR], 0.60 [95% CI, 0.45–0.79], I^2=64.6%), with no difference in the risk of major adverse cardiovascular events (MACE) (HR, 0.88, 95% CI: 0.77–1.02, I^2=11.8%), MI (HR, 0.85, 95% CI: 0.69–1.06, I^2=0%), or death (HR, 0.85, 95% CI: 0.70–1.03, I^2=3.5%).[14] However, other factors beyond clinical effectiveness also affect the type and duration of DAPT, especially where drug-eluting stents are involved, such as procedure-related considerations, and multiple stents or stent sites.	No significant concerns or variability identified.
Certainty of evidence	**Resources and feasibility**
The overall risk of bias assessed for five trials included in the MAs[14] is assessed to be low, and the certainty of evidence for most reported outcomes mentioned above is assessed to be moderate.	Additional consultation time and follow up may be required as part of collaborative care with cardiologist for some patients.

Expert Group deliberation of above factors
While the EG acknowledged that DAPT is typically initiated by cardiologists following a procedure, they agreed that it was important for the ACG to outline the treatment principles and indications for DAPT in patients with CCS, emphasising the typical treatment duration (i.e., less than 6 months or no more than 12 months) and the primary care physician's role in following up patients who are initiated on DAPT after a PCI. This recommendation aims to prompt primary care clinicians to consider the need for shared care if patients remain on DAPT beyond the recommended duration or if there is lack of clarity on the treatment duration for DAPT.

Recommendation 3	**a. For patients with new-onset AF with no recent stent (within the past 12 months), consider oral anticoagulant monotherapy based on *modified* CHA_2DS_2VASc score and patient factors such as comorbidities and bleeding risk.** **b. For patients with new-onset AF and a stent within the past 12 months, consult a cardiologist to reassess and optimise the current antithrombotic therapy.**

Strength of recommendation (3a): Strong **Weak/conditional**

Strength of recommendation (3b): **Strong** Weak/conditional

Summary:
For patients with new-onset atrial fibrillation (AF) with no stent within the past 12 months, the need for oral anticoagulant (OAC) therapy should be based on the *modified* CHA_2DS_2VASc ($mCHA_2DS_2VASc$) score. In the literature, the benefit of OAC in reducing thromboembolic stroke has been reported for patients with new-onset AF. However, the suitability of OAC therapy in patients with new-onset AF is also highly dependent on additional patient-specific factors, hence the conditional recommendation. These patient-specific factors include underlying comorbid conditions and bleeding risk, especially in elderly patients who have a higher bleeding risk. For detailed management of OAC therapy, clinicians may follow the published ACG on 'Oral anticoagulation for AF'.

For patients with a stent and new-onset AF within the past 12 months, the EG acknowledged that the current medication regimen may need to be re-evaluated given that AF further increases the risk of thromboembolic stroke, potentially necessitating adjustments to the patient's post-PCI antithrombotic therapy. The type and duration of antithrombotic therapy will vary depending on the individual patient's risk of ischaemia and thrombosis versus the risk of bleeding. Therefore, the EG recommended consulting a cardiologist for collaborative care to individualise and optimise medication therapy for such patients.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Recommendation 3a: OAC therapy is primarily indicated for patients with AF to prevent thromboembolic events.[8, 9] Generally, direct oral anticoagulants (DOACs) are favoured over warfarin due to improved efficacy and safety outcomes.[6, 8, 9] The evidence on the efficacy and safety of OACs are mainly derived from post-PCI patients with existing AF. A recently published SR and network MA, based on the findings from five RCTs indicated that a DOAC plus a P2Y12 inhibitor regime was associated with less bleeding and improved safety outcomes compared with vitamin K antagonists (e.g. warfarin) plus DAPT.[15, 16] The duration of OAC therapy (+/- antiplatelet	No significant concerns or variability identified.

therapy) depends on the individual patient's risk of thrombosis versus the risk of bleeding. In post-PCI patients with drug-eluting stents, the literature indicated that the duration of dual pathway inhibition (i.e., OAC therapy plus antiplatelet therapy) may vary from 1-6 months (up to 12 months if needed), followed by OAC monotherapy.[15, 16] Dual pathway inhibition beyond 12 months is associated with higher risk of bleeding and therefore not recommended in general. (Also see summary above and EG deliberation below for patient-specific considerations in relation to benefits and harms.) Recommendation 3b: In patients with new-onset AF who had a stent placed within the past 12 months, additional management considerations arise due to AF further increasing the risk of thromboembolic stroke, and possible bleeding risk associated with potential changes to existing antithrombotic treatment regimen. Additionally, thromboembolic risk may vary based on individual patient circumstances, including the timing of new-onset AF relative to stent placement and the patient's comorbidities. Therefore, consultation with a cardiologist is recommended for these patients.	
Certainty of evidence	**Resources and feasibility**
Recommendation 3a: The risk of bias for the RCTs reported in the SR by Lopes et al 2019[15] and 2020[16] were assessed to be low, and the certainty of evidence assessed to be moderate for most reported outcomes. The certainty of evidence was rated down because outcomes were mainly based on post-PCI patients with existing AF, and due to inconsistencies of reported outcomes. Recommendation 3b: Not applicable.	Recommendation 3a: Some DOACs are included in the local Standard Drug List and Healthier SG whitelisted drugs. Recommendation 3b: No significant concerns identified.
Expert Group deliberation of above factors	
The EG concurred with the evidence findings and agreed that primary care physicians should consider OAC therapy based on $mCHA_2DS_2VASc$ score in patients with no recent stents (within the last 12 months), factoring in existing comorbidities and bleeding risk, especially in older people who are at higher risk of bleeding. Notwithstanding the evidence reporting benefits of OAC therapy in patients with AF, Recommendation 3a was positioned as a conditional recommendation due to the varying risk of bleeding for each patient which must be accounted for when considering OAC therapy. For patients with new-onset AF following a stent within the past 12 months, the EG highlighted that there is a need to reassess their thromboembolic risk as AF further increases the risk of thromboembolic stroke, potentially necessitating adjustments to the patient's post-PCI antithrombotic therapy. Overall, the EG concurred that the type and duration of antithrombotic therapy will vary depending on the individual patient's risk of ischaemia and thrombosis versus the risk of bleeding. The precise medication regimen and duration (triple, dual, or single antithrombotic therapy) will also depend on the timing of the new-onset AF relative to the stent placement. Despite limited direct evidence and acknowledging the risks of complications, consultation with a cardiologist for collaborative care is recommended to individualise and optimise medication therapy.	

Recommendation 4	**Optimise management of comorbid or associated conditions in patients with CCS to reduce overall cardiovascular risk and complications.**

Strength of recommendation (4): **Strong** Weak/conditional

Summary: In patients with CCS, managing other associated conditions such as dyslipidaemia, hypertension, diabetes mellitus and angina (symptomatic or asymptomatic) plays a crucial role in reducing or preventing overall cardiovascular risk and complications.[17, 18] This involves assessing overall CV risk factor s and providing a personalised management plan to reduce the overall CV risk and associated complications. The EG agreed on the importance of managing comorbid conditions as well as optimising CV risk factors as part of overall management. They concurred on providing a strong recommendation even though associated evidence may vary depending on the outcomes as well as the type of comorbid conditions.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
Patients with CCS are at increased risk of CV complications.[17] Often, patients with CCS have more than one comorbid condition such as dyslipidaemia, diabetes mellitus, and hypertension. The overall CV risk varies depending on individual patients' underlying comorbid conditions and baseline characteristics. Management of these comorbid conditions includes both non-pharmacological and pharmacological interventions; and associated evidence will vary depending on types of intervention versus reported outcomes.[19] Overall, evidence from the literature supports addressing overall CV risk, optimising CV risk factors, and reducing CV complications as part of managing patients with CCS.	Patient preferences and adherence to managing comorbid conditions may vary depending on the types of interventions. Patients' values and preferences should be taken into account to improve outcomes.
Certainty of evidence	**Resources and feasibility**
The certainty of evidence varies depending on types of outcomes, study design, and nature of comorbid conditions.	No significant concerns identified.
Expert Group deliberation of above factors	
The EG highlighted the need to optimise management of comorbid conditions and CV risk factors given its importance in reducing overall CV risks and complications in patients with CCS. Additionally, the group agreed with the plan for the ACG to summarise key management principles for the main comorbid conditions associated with CCS in Singapore.	

Recommendation 5	**Encourage sustained lifestyle interventions, including regular physical activity tailored to the patient's capabilities and preferences.**

Strength of recommendation (5): **Strong** Weak/conditional

Summary: Lifestyle management plays a pivotal role in the non-pharmacological treatment of CCS, mainly encompassing three key areas: physical activity, smoking cessation, and diet. Regular exercise, smoking cessation, and healthy dietary habits are crucial for reducing cardiovascular disease risk in patients with CCS. Moderate-to-vigorous physical activity correlates with lower mortality risk. Quitting smoking significantly reduces heart attack risk and overall mortalit y. Diets rich in whole grains, fruits, and dairy may lower cardiovascular risk, especially in Asian populations.[20] The successful implementation of these lifestyle interventions hinges on patient involvement and shared decision-making. While the strength of evidence varies across these interventions, the EG recommend ed the inclusion of lifestyle management principles in the overall care plan for patients with CCS, recognising their potential to significantly improve outcomes a nd reduce cardiovascular risk.

Evidence-to-recommendation considerations

Balance of benefits and harms	Values and preferences
Physical activity: Regular physical activity is recommended for patients with CCS as it reduces atherosclerotic risk factors and mortality.[21] A pooled analysis of observational studies showed a dose-response relationship of physical activity with mortality, indicating moderate-to-vigorous physical activity lowered the risk of mortality by 31-37%.[22] A MA of patients with previous MI, angina pectoris or CAD demonstrated that exercise-based cardiac rehabilitation could reduce cardiac mortality.[23] Since there is no evidence of harm associated with regular physical activity in people with CCS (except for people with contraindications to physical activity, e.g. patients with angina symptoms or uncontrolled hypertension), they are encouraged to participate in routine physical activity, including activities to reduce sitting time and to increase aerobic and resistance exercise. Smoking cessation: Tobacco smoke exposure, particularly from cigarette smoking, is a leading cause of CVD and cardiovascular events in individuals with CCS.[24-26] Prospective cohort studies of patients with CCS demonstrate that smoking cessation is associated with a 32% reduction in MI,[27] and 36% risk reduction in mortality.[27] Therefore, patients with CCS who smoke tobacco should be advised to quit at every visit.[28] Diet: Dietary intake plays a significant role in reducing the risk of CVD in patients with CCS. The findings based on observational trials and RCTs have suggested that a healthy dietary pattern is associated with a lower CVD risk.[29, 30] A local study reported that adherence to the 'ethnic breads, legumes and nuts' and 'whole grains, fruit and dairy' patterns was associated with a lower predicted CVD risk in an Asian population.[20] Unhealthy diets are a leading contributor to CAD and its progression, and improvements in eating patterns in patients with	Successful implementation of lifestyle interventions requires patient involvement and shared decision-making. There are limited local studies evaluating the effect of lifestyle interventions in patients with CCS. Patient preferences should be considered when recommending lifestyle interventions.

CCS have resulted in a reduction in mortality and CV events.[31]	
Certainty of evidence	**Resources and feasibility**
There is moderate certainty evidence supporting regular physical activities in patients with CCS, mainly due to its beneficial effects on the cardiovascular system, including reducing atherosclerotic risk factors and mortality.[21] Regarding diet, the evidence on the association between nutrition and ASCVD outcomes is generally limited due to the lack of large-scale prospective RCTs. The findings are mainly based on observational studies which have shown the effect of dietary patterns on CVD mortality.[32] The certainty of evidence for the reported outcomes from the above study[27] varies from low to moderate. However, evidence from long-term prospective studies have consistently suggested smoking cessation is a recognised risk factors for CV disease and a single greatest preventable cause of mortality in general population.[33, 34]	No significant concerns identified.
Expert Group deliberation of above factors	
The EG agreed with the plan to include principles highlighting the importance of lifestyle interventions as part of the overall management plan for patients with CCS.	

Recommendation 6	**Schedule regular follow-up visits for all patients with CCS to monitor symptoms, assess medication adherence, and adjust treatment plans as needed.**

Strength of recommendation (6): **Strong** Weak/conditional

Summary: The EG acknowledged the importance of regular follow-up for patients with CCS who are on antithrombotic therapy. Given the potential risk of thrombosis or ischaemia related to undertreatment versus the risk of bleeding due to over-treatment, the EG concurred with providing a strong recommendation to encourage timely assessment and management of the patients based on individual patients' risk. Even when the condition is stable and asymptomatic, regular follow-up helps to assess overall CV risk factors, especially in patients with comorbid conditions such as dyslipidaemia and type 2 diabetes mellitus. The frequency of follow-up will vary depending on the severity of the condition, comorbidities, optimisation of risk factors, changes in symptoms, and availability of resources.

Evidence-to-recommendation considerations

Balance of benefits and harms	**Values and preferences**
Patients with CCS who are on antithrombotic therapy should be reviewed regularly for optimal management, including symptom monitoring and adherence checks, even if their condition is stable and asymptomatic. The type and nature of assessments and testing at follow-up visits vary depending on individual patient risk. Clinical judgement is required to determine the need for testing or repeated testing for optimal management. There is limited evidence to guide the frequency of review for patients with CCS.	No significant concerns or variability identified.
Certainty of evidence	**Resources and feasibility**
Not applicable.	The availability of resources, including required tests, may depend on the healthcare setting and should be taken into account when scheduling follow-ups.
Expert Group deliberation of above factors	
The EG agreed with the recommendation that regular follow-up and monitoring are important aspects of managing patients with CCS who are on antithrombotic therapy, acknowledging that the frequency of follow-up may vary depending on individual patient circumstances. Feasibility and resource utilisation should be considered alongside clinical concerns when scheduling follow-ups for patients with CCS.	

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