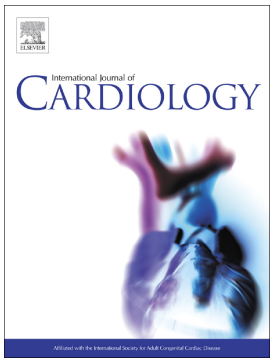

Single-pill combination in the management of chronic coronary syndromes: A strategy to improve treatment adherence and patient outcomes?

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Single-pill combination in the management of chronic coronary syndromes: a strategy to improve treatment adherence and patient outcomes?

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Abstract

Chronic coronary syndrome (CCS) represents a major challenge for physicians, particularly in the context of an increasing ageing population. Additionally, CCS is often underestimated and under-recognised, particularly in female patients. As patients are frequently affected by several chronic comorbidities requiring polypharmacy, this can have a negative impact on patients' adherence to treatment. To overcome this barrier, single-pill combination (SPC), or fixed-dose combination, therapies are already widely used in the management of conditions such as hypertension, dyslipidaemia, and diabetes mellitus. The use of SPC anti-anginal therapy deserves careful consideration, as it has the potential to substantially improve treatment adherence and clinical outcomes, along with reducing the failure of pharmacological treatment before considering other interventions in patients with CCS.

Key words: adherence ● angina ● chronic coronary syndrome ● comorbidities ● single-pill combination ● treatment

1. Introduction

Chronic coronary syndrome (CCS) is the most prevalent symptomatic manifestation of ischaemic heart disease (IHD) [1]. The clinical scenarios encompassed by the term CCS, as proposed by the most recent European Society of Cardiology (ESC) guidelines for the management of chronic IHD [2], include (i) patients with suspected coronary disease (CAD) and 'stable' anginal symptoms, and/or dyspnoea; (ii) patients with new onset of heart failure or left ventricular dysfunction and suspected CAD; (iii) asymptomatic and symptomatic patients with stabilized symptoms <1 year after an acute coronary syndrome, or patients with recent revascularization; (iv) asymptomatic and symptomatic patients >1 year after initial diagnosis or revascularization; (v) patients with angina and suspected vasospastic or microvascular disease; and (vi) asymptomatic subjects in whom CAD is detected at screening. While all of these scenarios are classified as CCS, each have different risks for

future cardiovascular events (e.g. death or myocardial infarction), which may change over time. Thus, CCS encompasses a broad patient population affected by different forms of angina/IHD, with different underlying pathophysiological mechanisms, and who will also be typically affected by a variety of different comorbidities [2].

Treatment of CCS has, until recently, focused almost exclusively on the management of obstructive CAD, with revascularization being largely favoured [2]. However, while atherosclerotic epicardial coronary artery obstruction is a common cause of angina, myocardial ischaemia can be triggered by other mechanisms which are not amenable to revascularization [3]. Such mechanisms include epicardial coronary artery spasm, microvascular dysfunction (leading to reduced vasodilatation of the coronary microvessels or microvascular spasm), and structural abnormalities in the arteriolar/capillary beds and myocardium (leading to increased intramyocardial pressure and reduced microvascular perfusion efficiency). Abnormal metabolic oxygen transport may also play a role in ischaemia [4]. All of these factors can limit coronary blood flow and trigger myocardial ischaemic events [1,3,5,6]. The goals of pharmacological therapy for angina, as recommended by the ESC guidelines, are two-fold: symptom relief and prolonged survival [2]. However, there are many obstacles to the implementation of medical treatment in patients with CCS, including patient adherence and compliance, drug-drug interactions, and polypharmacy [7].

The aim of the present paper is to discuss unmet needs in the management of CCS and the potential role of single-pill combinations (SPC) as suitable therapeutic options to effectively reduce symptoms, and improve both adherence and clinical outcomes.

2. Challenges facing the traditional management strategies for CCS

2.1. The importance of regional differences in the incidence and management of IHD

Globally, IHD affects approximately 126 million individuals, equating to 1.7% of the world's population, and is responsible for nine million deaths annually [8]. In Europe, IHD is the leading single cause of mortality, responsible for 862,000 deaths (19% of all deaths) among men and 877,000 deaths (20%) among women annually [9]. While age-adjusted rates show

a promising decrease in the incidence of IHD, the global prevalence of IHD is rising as healthcare systems are having to manage an increasing number of cases due to an aging population [8]. Of note, men appear more commonly affected than women, with the incidence of IHD related to obstructive coronary disease typically starting in the fourth decade of life and increasing with age.

Regional and national differences in total IHD burden and mortality reflect differences in the prevalence of cardiovascular disease (CVD) risk factors along with access to healthcare [9]. Differences in access to effective primary and secondary prevention strategies may also play a role in differences in total CVD burden, particularly in low- and middle-income countries.

The 'chronic ischaemic CVD' registry has recently investigated the characteristics of a broad spectrum of contemporary patients with CCS in European countries [10]. Evidence-based therapy prescribed for secondary prevention in this at-risk population was suboptimal, with less than two-thirds of patients being prescribed guideline-recommended combination of angiotensin-converting-enzyme inhibitors (ACEI)/angiotensin-II receptor blockers (ARB), beta blockers, aspirin, and statins at ambulatory visit or admission. Following discharge, significantly more patients were prescribed this recommended combination, though the proportion remained low. Age, female sex, and obesity were associated with low rates of prescribed medication. Thus, there is a clear need to develop comprehensive management strategies, such as the simplified use of combination therapy, which may serve to address some of these limitations.

Treatment guidelines for CCS recommend optimizing pharmacological therapy before coronary artery revascularization is considered [2]. The importance of optimal medical therapy in patients with stable angina before referral for revascularization, along with the duration of pharmacotherapy, was recently discussed by Boden et al [6].

Given that a large majority of coronary patients have unhealthy lifestyles in terms of smoking, diet, and sedentary behaviour, all of which adversely impact major cardiovascular risk factors, it makes sense to support lifestyle modification with the goal of disease stabilization or regression [11]. However, data from the ESC-EORP European Action on Secondary and

Primary Prevention through Intervention to Reduce Events (EUROASPIRE) V registry suggest that most coronary patients fail to achieve their blood pressure, low-density lipoprotein cholesterol (LDL-C), and glucose targets, even with the use of cardioprotective medication(s). Nevertheless, positive lifestyle changes by the patient (e.g. smoking cessation) should continue to be encouraged and supported in order to mitigate their cardiovascular risk profile.

The recommendation to optimize pharmacological therapy prior to coronary artery revascularization is based on randomized studies that have shown that after excluding patients with significant obstructive CADs (defined as >50% left main narrowing or proximal 3 vessel disease), revascularization was not superior to medical therapy [2,12–15]. In general, the treatment of CCS has two main goals, namely the alleviation of symptoms and improvement in quality of life, along with the prevention of cardiovascular events, i.e. cardiovascular death and myocardial infarction, via the control of risk factors (dyslipidaemia, diabetes mellitus, hypertension, inflammatory and autoimmune conditions, metabolic syndrome, etc) [2]. These two important treatment goals cannot be achieved with the same class of drugs. Pharmacological interventions to prevent cardiovascular events are based on robust evidence and achieved with the use of treatment such as antiplatelet agents, lipid-lowering agents, ACEIs, or ARBs, sodium-glucose cotransporter-2 inhibitors, and beta blockers [2].

Regarding anti-anginal strategies, recent reports show that pharmacological preventive therapy, when correctly implemented, can also reduce the symptoms of angina [16,17]. Moreover, different classes of anti-anginal drugs are available that have been shown to be effective in controlling angina symptoms. Beta blockers, calcium-channel blockers, ivabradine, nicorandil, nitrates, ranolazine, and trimetazidine, are all recommended by the current ESC guidelines for the management of CCS [2]. While none of these drug classes have consistently been shown to improve prognosis in contemporary cohorts of patients with CCS, all are able to reduce symptoms via different mechanisms. In the absence of any evidence to support a preferred treatment, symptomatic treatment of angina should be

personalized and tailored to the individual patient based upon the pathophysiological mechanisms, along with the patient's characteristics and comorbidities [1].

2.2. Challenges to the implementation of recommended medical therapy for CCS

While patients are now prescribed guideline-based therapies, a reduced cardiovascular risk profile is unfortunately not achieved in many cases [2,6,18–21]. Boden et al. (2022) recently reported that only 33% of patients with stable angina receive optimal pharmacotherapy prior to revascularization [6]. In addition, historical data from the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE), Bypass Angioplasty Revascularization Investigation 2D (BARI 2D), and Bypass Angioplasty Revascularization Investigation (FREEDOM) studies demonstrated low percentages (8–23%) of patients with CCS achieving pre-specified targets for lipids, blood pressure, glucose, and smoking cessation one year after randomization [2,18–20,21]. These findings are disappointing, particularly within the context of randomized clinical studies, given the typical close interaction between study investigators and participants, and structured follow-up process. Several studies have also demonstrated high global prevalence of the undertreatment and poor control of cardiovascular risk factors in CCS [19,22–25]. In the EUROASPIRE IV study >40% remained hypertensive with increased levels of LDL-C and uncontrolled diabetes mellitus even though 67.6% of patients were receiving ≥5 different cardiovascular drugs [26]. More recently, the EUROASPIRE V study has shown that the control of cardiovascular risk factors is substantially worse among women compared with men, despite few gender differences in the prescription of cardiovascular medication [27].

All the above reflect the difficulties observed both in a clinical trial environment and everyday clinical practice regarding the management of CCS.

2.3. The importance of adherence in the management of CCS

Adherence is a multidimensional phenomenon determined by the interplay of several components, but mainly the patient, their healthcare providers, and health system-related

factors [28]. Of note, key reasons for non-adherence include patient demography, socioeconomic factors, health system factors, intensity of follow up, time since last provider visit, adverse effects of therapy, complex medication regimens, and health literacy. Adherence is a particularly important modifier of the efficacy of a long-term therapy [29]. Specific aspects of therapeutic regimens, such as the complexity of the regimen, previous treatment failure(s), fear of side effects, and perceived lack of benefit can all reduce adherence [2,18,20].

Therapy-related factors including poor efficacy, low safety, and dose complexity appear to be particularly important in the development of treatment non-adherence in patients with CAD [7], leading to a substantial worsening of cardiovascular outcomes [30,31]. In contrast, good medication adherence is related to a lower risk of cardiovascular mortality and hospitalization [32]. However, even after myocardial infarction, adherence rate typically fails to rise above 60% [33,34]. While adherence often increases with advancing age, it may also be impaired by comorbidities and polypharmacy in the elderly [35,36]. Different approaches to increase cardiovascular medication adherence in CAD traditionally focus on patient-related and social/economic factors [37–39], although the simplification of the prescribed drug regimen may be an easier option [40]. Of note, use of SPCs has become a real breakthrough in blood pressure control [41,42].

For blood lipid control, the lack of adherence to guidelines-directed therapy with poor attainment of pre-specified LDL-C goals has led to the development of SPCs as an effective strategy to support increasing adherence [43,44]; a statin combined with non-statin lipid-lowering therapies is advised to attain recommended LDL-C targets [45].

2.4. Patient-and physician related barriers to treatment adherence

Some patients with CCS may not have a complete understanding of their disease (along with a considerable proportion of physicians) and perceive themselves as having little control over the course of the disease [46]. Moreover, many do not understand the importance of CVD prevention [47]. Many patients report not having received clear information about their condition and/or encouragement from physicians and other healthcare professionals

regarding how to prevent recurrent cardiovascular events. Other factors, which hinder adherence, include lack of social support, poor psychological wellbeing, inconvenient location with transport difficulties, competing work commitments and financial cost [20]. Inadequacies and time constraints related to education and counselling of patients with CCS before they leave hospital can lead to deficiencies in the implementation of appropriate therapy or prevention [48]. However, patients discharged from hospital with a clear guideline-oriented treatment recommendation, a checklist of measures to ensure risk modification and lifestyle change provided in the discharge letter, and suitable education to allow them to care for themselves and to know how/when to seek follow-up care, can better understand the importance of this information and its potential impact. Indeed, patients with a clear understanding of their after-hospital care instructions are 30% less likely to be readmitted or to visit the emergency department than those who lack this information [49].

A wide variety of supportive techniques to improve medication adherence have been evaluated. A Cochrane review of interventions to improve medication adherence in the general population advised drawing on the support of allied professionals such as nurses and pharmacists to deliver complex interventions, which may include telephone follow-up, interim appointments, and monitoring of repeat prescriptions [50]. Xavier et al. reported on a community health worker-based personalized intervention strategy (patient diaries, unstructured discussions, visual methods) in patients with ACS which improved adherence to evidence-based drugs and significantly improved adherence to healthy lifestyle interventions, resulting in an improvement in clinical risk markers at 12 months [51]. Similarly, a 12-month community-based comprehensive intervention to reduce cardiovascular risk in patients with hypertension (HOPE 4) demonstrated that using non-physician health workers to deliver tablet computer-based simplified management algorithms and counselling programmes, along with the use of a supportive friend or family member, significantly reduced the Framingham Risk Score for 10-year CVD risk by 50% compared with usual care [52].

While drawing on the support of community/non-physician health workers and non-professional people within the social context of the patient, such as spouses, other family

members, carers, or other key figures, and lay groups in the community, may prove to be a useful way of improving adherence, it is important to note that such interventions may be difficult to replicate in everyday clinical care due to cost and availability of personnel.

The development of real or presumed 'drug intolerance' in many patients should be considered, along with how quickly physicians label patients as such, as this may severely disadvantage patients with CCS [50]. Patients with CCS may also present with several comorbidities which require multiple treatments, leading to the possibility of contraindications/drug-drug interactions [50]. Factors supporting adherence are shown in Table 1.

Physician inertia or undertreatment, along with other healthcare system factors, such as associated costs, lack of treatment availability, lack of physician access/communication, and distance/time taken to visit physicians, may contribute to non-adherence [48,53]. Of note, physician inertia means no treatment changes are made in a patient's treatment regimen by the healthcare provider despite clear indication [53].

Given that the physician should aim to simplify any treatment regimen(s) to the lowest effective yet acceptable dose(s), with repetitive monitoring and feedback, the use of combination therapy and SPC to increase adherence to drug therapy may be considered [54].

3. Evidence for the use of SPC approaches for hypertension, diabetes, and dyslipidaemia in CCS

SPC therapies are widely used in the management of conditions such as hypertension, dyslipidaemia, hypertriglyceridemia, and diabetes mellitus, and have been shown to be effective in improving patients' adherence to treatment. SPCs enable the simplification of treatment by rationalizing the therapy, using 'evidence-based medicine' and 'complementary' modes of action to support treatment efficacy and adherence, along with the potential for fewer drug-related side effects [15,41,54–59]. Using diabetes mellitus as an example, current algorithms recommend treatment individualization with most patients requiring ≥2 anti-

hyperglycaemic agents to achieve therapeutic targets [15]. Initial dual-drug combinations are proposed for those patients with CCS and very elevated glycated haemoglobin levels [15,56,59].

Combination therapy may be administered as a SPC or as a combination of oral SPC and/or injectable therapies [15,56,59]. For lipid-lowering therapy, a SPC of ezetimibe with high-intensity statins are prescribed in those patients with CCS not achieving treatment goals with the maximum tolerated dose of statin, while the addition of a proprotein convertase subtilisin/kexin 9 inhibitor can provide a therapeutic solution in selected high-risk cases [15,57,58]. For blood pressure control in patients with CCS, initial low-dose treatment with two or three antihypertensive agents may be more efficacious than the standard dose of each monotherapy [41,54]. In addition, there is evidence that combining drugs from two different classes can provide a reduction in blood pressure approximately five times greater than by simply doubling the dose of a single drug [55].

4. The rationale for the use of SPC anti-anginal therapy in patients with CCS

Over the last few decades, attempts to define the best management strategies for patients with CCS have not been successful, possibly because of the focus on solving the problem of 'significant' flow-limiting atherosclerotic obstructions of the epicardial coronary arteries and the misconception that revascularization was the most appropriate treatment. Available clinical evidence has since demonstrated the limited ability of percutaneous coronary intervention to reduce patient mortality and morbidity, compared with optimal medical therapy (intensive secondary prevention, lifestyle intervention, and the use of anti-anginal agents) [12,13,18].

The management of patients with angina of suspected ischaemic origin requires careful diagnostic testing regardless of whether ischaemic symptoms are due to coronary atherosclerosis or occur in the absence of flow-limiting epicardial stenoses [1,60]; this approach enables prevailing pathogenic mechanism(s) to be identified, along with the subsequent use of anti-anginal agents with suitable modes of action. As with other

cardiovascular conditions, such as hypertension and heart failure, IHD requires a multifaceted pharmacological treatment approach to target the multiple mechanisms that can lead to related symptoms in a given patient [2].

The administration of a single anti-anginal drug is unlikely to be efficacious in patients whose anginal symptoms are triggered by combined mechanisms such as increased coronary vasomotor tone, coronary stenosis, left ventricular hypertrophy, capillary rarefaction, increased intramyocardial pressure or abnormal metabolic oxygen transport [5]. In contrast, combination therapy with agents acting via different mechanisms of action seems to be a logical approach in these patients, albeit with the caveat that clinical studies are still required to provide objective, evidence-based, supportive data for this strategy.

The ongoing challenge that physicians face is the identification of the causes of angina in a selected patient in order to allow a rational pharmacotherapeutic intervention, rather than simply following the concept of 'first-', 'second-' and 'third-line' anti-anginal therapy, which lack robust clinical evidence, yet continue to be endorsed by international guidelines [2].

Considering the multifactorial origin of CCS and the limitations of the classical approach to management, an early combination of a metabolic and a haemodynamically active drug can be considered, with ivabradine being a rational choice and in those patients with elevated heart rate where beta blockers are contraindicated or cannot be up-titrated. Of note, a single pill fixed-dose combination of the beta blocker metoprolol and ivabradine has been recently approved for use in the management of angina in Europe [61].

'Failure of optimal medical therapy' is a notion that requires reconsideration given that if a patient remains symptomatic while receiving one or two anti-anginal drugs, this should simply be an indication that further optimization via treatment up-titration or the use of additional anti-anginal drugs may be appropriate. In this context, it is expected that there will be a considerable number of patients who will require treatment with more than two anti-anginal drugs in order to support/maintain control of symptoms. Thus, this suggests that the use of a SPC may be required in order to support improved treatment adherence.

5. Available SPCs for use in patients with CCS

SPC treatment strategies with ≥2 blood pressure-lowering agents and a statin (with or without aspirin) have been used to reduce CVD risk as both primary and secondary preventative measures [42,54]. The concept of a combination pill was first proposed in the early 2000s as a strategy to substantially reduce CVD in secondary prevention, as well as at the population level [8,62,63]. Early studies demonstrated improved adherence and greater risk factor control with a polypill strategy compared with the use of single drugs, standard care, or placebo [64]. Recent clinical outcome studies have demonstrated that SPC treatments are effective at reducing CVD in primary prevention [65]. A recent meta-analysis of three randomized, controlled trials showed a lower occurrence of cardiovascular events among patients with no known vascular disease who were assigned to receive a polypill than among control patients in primary prevention [65]. This meta-analysis included three large studies (TIPS-3, HOPE-3, and PolyIran) that evaluated a fixed-dose combination strategy of at least two blood pressure lowering agents plus a statin (with or without aspirin), compared with a control strategy (either placebo or usual care). Fixed-dose combination treatment strategies substantially reduced CVD along with risk of myocardial infarction, stroke, revascularization, and cardiovascular death in primary CVD prevention, with consistent benefits irrespective of any cardiometabolic risk factors.

The open-label STYLE study assessed the effectiveness and tolerability of bisoprolol/perindopril SPC in a broad Russian patient population with hypertension and CAD treated in routine clinical practice [66]. Target blood pressure was achieved by 86.7% of patients at 3 months, which was accompanied by significant reductions in the mean number of angina attacks and nitrate consumption, along with improvements in heart rate. These results support the addition of a bisoprolol/perindopril SPC to standard antihypertensive therapy to simultaneously reduce blood pressure and heart rate in patients with hypertension and stable CAD and to allow more patients to achieve blood pressure treatment goals. In addition, these results suggest that physicians should pay more attention to resting HR management in patients with stable angina. Given that angina has an adverse effect on

quality of life because of factors such as pain, limited exercise tolerance, and poor general health status [67], any reduction in the frequency or severity of angina symptoms would therefore be expected to improve patients' quality of life.

The observational IMPLICOR-NOW study demonstrated that treatment with a metoprolol/ivabradine SPC significantly lowered heart rate, angina attack frequency, and short-acting nitrate consumption at 4 months in stable-angina patient subgroups relevant to real-life clinical practice [68]. In addition, SPC use improved self-reported adherence at 4 months, while this was found to decrease in those patients using an increasing number of medications. A relevant improvement in the functional status of patients was also observed, with the proportion of patients in Canadian Cardiovascular Society (CCS) class I (defined as being asymptomatic at normal activity levels) increasing significantly versus baseline. All beneficial effects of the metoprolol/ivabradine SPC were consistently reported across all analyzed subgroups, regardless of age, CAD duration, CCS class, comorbidities, previous myocardial infarction, or history of revascularization.

Data from the randomized SECURE study have demonstrated that the use of a SPC comprising aspirin (100 mg), ramipril (2.5, 5, or 10 mg), and atorvastatin (20 or 40 mg) within 6 months following a myocardial infarction resulted in a significantly lower risk of major adverse cardiovascular events over a 3-year follow-up period compared with usual care [69]. Fewer SPC-treated patients had primary outcome events (cardiovascular death, non-fatal type 1 myocardial infarction, non-fatal ischaemic stroke, or urgent revascularization) compared with usual care (9.5% versus 12.7%; hazard ratio [HR] 0.76; 95% confidence intervals [CI]: 0.60, 0.96; p=0.02). Similarly, fewer patients receiving SPC has secondary endpoint events (composite of all four primary outcome events) compared with usual care (8.2% versus 11.7%; HR 0.70; 95% CI: 0.54, 0.90; p=0.005). Medication adherence as reported by the patients was higher in those receiving SPC compared with usual care, while adverse events were similar between groups. Such findings support the use of a SPC as a simple approach to the secondary prevention of cardiovascular death and complications after myocardial infarction.

For those patients with CCS considered to be a suitable candidate for switching to a SPC, initial therapeutic recommendations will depend on previous pharmacological treatment(s) and whether blood pressure and LDL-C levels are well controlled [2]; in certain circumstances, the addition of a concomitant agent may be required. Indeed, suboptimal cardiovascular risk factor control is common in secondary cardiovascular prevention, as reported by the EUROASPIRE studies [11,26,70].

In addition to the promotion of a healthy lifestyle, an SPC containing ≥2 drugs to control various risk factors associated with IHD might reduce overall healthcare costs, along with improving patient accessibility and adherence to treatment [57]. As discussed above, SPC therapies are widely used in the management of conditions such as hypertension, dyslipidaemia, and diabetes mellitus, yet surprisingly, cardiologists have been 'late' in the adoption of a similar approach for the management of IHD. Thus, the following algorithm to manage patients with CCS is proposed herein based on the use of combined therapy (Figure 1), and a summary of key messages for the cardiologist are also provided (Table 2).

6. Summary and future work

A SPC strategy has been shown to improve medication adherence by virtue of treatment simplification, which may partly explain decreased risk reductions in both primary and secondary prevention of cardiovascular events. In contrast to diabetes, hypertension, and dyslipidaemia, recommendations for the use of SPCs for angina are not available. Thus, work is needed to bridge this knowledge gap. The development of specific SPCs for the management of angina should consider the different pathophysiological mechanisms underlying CCS, risk factors, and comorbidities. To improve cardiovascular outcomes in patients with CCS, strategies need to focus on secondary prevention and levels of modifiable risk factors, encouraging patients to adhere better to lifestyle changes and prescribed treatments. In addition, the use of a SPC as a substitute for several cardiovascular drugs has the potential to be part of an effective secondary prevention strategy in patients with CCS. Given that treatment combinations are required to comprehensively manage CCS and its

associated symptoms, the use of a SPC has the potential to improve adherence, yet allow modification of dosing where symptoms remain or adverse effects arise. Importantly, SPCs combine agents with complementary mechanisms of action and enable the patient to maintain a consistent level of pharmacotherapy, thus supporting secondary prevention of cardiovascular events, such as the incidence of angina attacks. This strategy may represent a significant step forward in the management of patients with CCS.

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Data availability statement

The data underlying this article are available in PubMed at https://pubmed.ncbi.nlm.nih.gov.

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Tables

Table 1. Factors to support adherence.

Adherence factors
• 'Agree' rather than 'dictate' a drug regimen and tailor it to a patient's personal lifestyle and needs • Provide advice regarding the benefits and possible adverse effects of medications, along with the optimal duration and timing of doses • Consider patients' habits and preferences and encourage self-monitoring and the use of cues and technologies to function as treatment reminders • Reduce treatment dosage to the lowest feasible level and simplify the dosing regimen, wherever possible • Take time to ask patients if they are satisfied with their treatment • Back up any verbal instructions with clearly written instructions • Implement repetitive monitoring/feedback and a regular review of medicines to minimize the risk of polypharmacy • If feasible, introduce trained nurses or physician assistants to support adherence, where needed • Promote the active role of the pharmacist in assessing drug adherence by encouraging

patients to discuss their medicines with them, along with any concerns they may have about them • Involve the patient's partner, other family member, or carer in the patient's treatment plan • Offer multisession or combined behavioural intervention for cases of persistently suboptimal adherence

Table 2. Key messages.

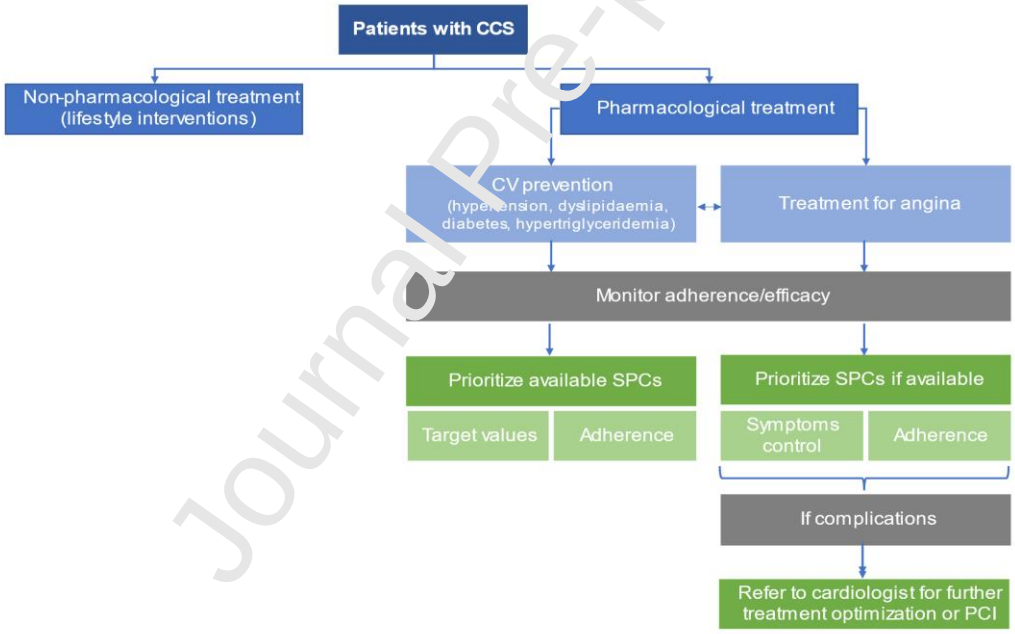
Key messages
• Patients with CCS are treated with non-pharmacological interventions (which aim to promote a healthy lifestyle) and pharmacological treatments (which aim to control symptoms and prevent CV events) • Patients with CCS should be encouraged to follow a healthy lifestyle (healthy diet, increased levels of activity, reduced levels of smoking/smoking cessation, reduced alcohol intake) • For prevention, patients with CCS are treated for hypertension, dyslipidaemia, diabetes, hypertriglyceridemia, etc • For control of CCS symptoms, current guidelines recommend the use of beta blockers, nitrates, calcium-channel blockers, trimetazidine, ranolazine, and ivabradine • Whatever the treatment objective, the main goal is to achieve optimal efficacy/adherence before considering pharmacological treatments to be a failure • As patients with CCS regularly take more than 3–4 drugs, SPCs should be considered in order to improve adherence and, therefore, support efficacy • As far as preventive treatments are concerned, many SPCs are already available, while two fixed-dose combinations exist for symptomatic treatment of patients with CCS (ivabradine/metoprolol and ivabradine/carvedilol) • Availability of new SPCs for the symptomatic treatment of angina may improve efficacy and, therefore, reduce the failure of pharmacological treatment prior to considering/resorting to interventions

CCS, chronic coronary syndrome; CV, cardiovascular; SPC, single-pill combination.

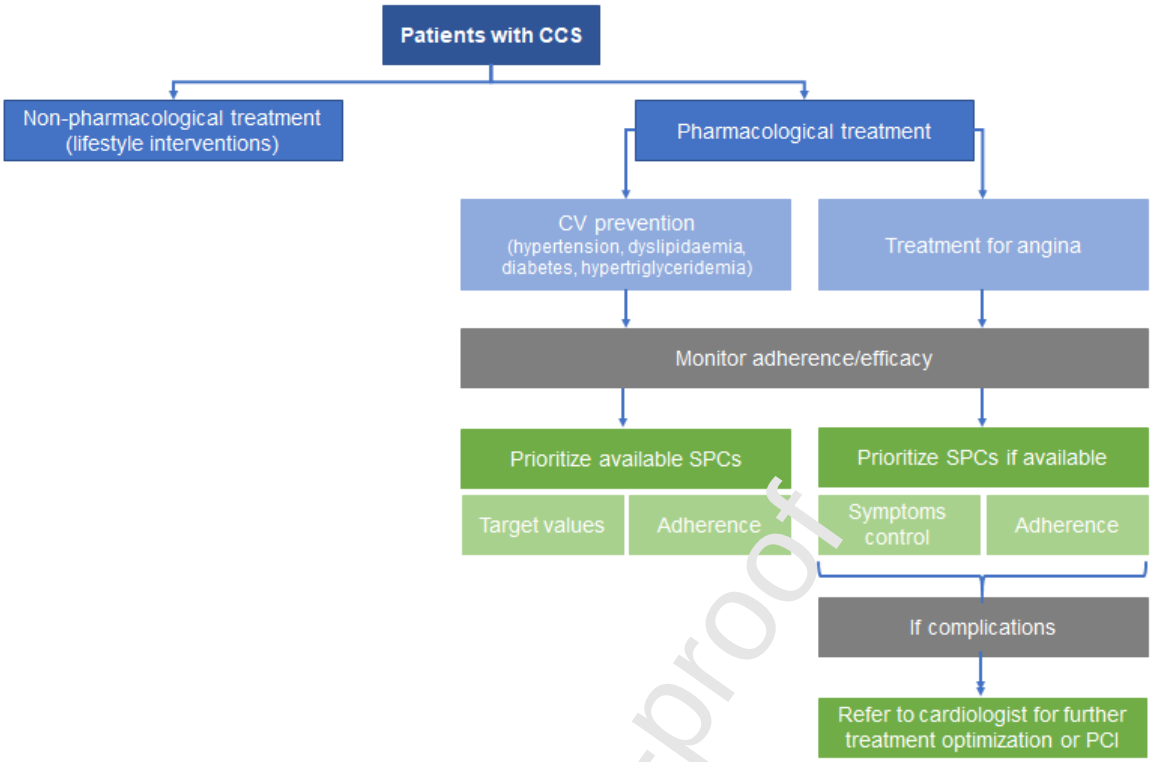
Figures

Figure 1. Management algorithm for patients with CCS based on the use of combined therapy. CCS, chronic coronary syndrome; CV, cardiovascular; HT, hypertension; PCI, percutaneous coronary intervention; SPC, single-pill combination.

Figure 1.



Graphical abstract



Highlights

- Chronic coronary syndrome (CCS) represents a major challenge for physicians, particularly in patients with comorbidities
- Single-pill combination (SPC) anti-anginal therapy has the potential to substantially improve treatment adherence and clinical outcomes in CCS
- SPCs allow modification of dosing where symptoms remain or adverse effects arise
- SPCs combine agents with complementary mechanisms of action
- SPCs support secondary prevention of cardiovascular events by maintaining a consistent level of pharmacotherapy