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Chapter

Drug-Related Problems in Coronary Artery Diseases

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Abstract

Coronary artery disease (CAD) remains the leading cause of mortality among cardiovascular diseases, responsible for 16% of the world's total deaths. According to a statistical report published in 2020, the global prevalence of CAD was estimated at 1655 per 100,000 people and is predicted to exceed 1845 by 2030. Annually, in the United States, CAD accounts for approximately 610,000 deaths and costs more than 200 billion dollars for healthcare services. Most patients with CAD need to be treated over long periods with a combination of drugs. Therefore, the inappropriate use of drugs, or drug-related problems (DRPs), can lead to many consequences that affect these patients' health, including decreased quality of life, increased hospitalization rates, prolonged hospital stays, increased overall health care costs, and even increased risk of morbidity and mortality. DRPs are common in CAD patients, with a prevalence of over 60%. DRPs must therefore be noticed and recognized by healthcare professionals. This chapter describes common types and determinants of DRPs in CAD patients and recommends interventions to limit their prevalence.

Keywords: cardiovascular diseases, ischemic heart disease, coronary artery disease, drug-related problems, interventions

1. Introduction

Worldwide, cardiovascular diseases (CVDs) are leading morbidity and mortality burdens. It has been estimated that 17.9 million people die from CVDs each year, representing 32% of all global deaths. The World Health Organization (WHO) defines CVDs as a group of disorders that include coronary artery disease (CAD), cerebrovascular disease, peripheral arterial disease, rheumatic heart disease, congenital heart disease, deep vein thrombosis, and pulmonary embolisms [1]. The world’s biggest killer of all is ischemic heart disease, or CAD, responsible for 16% of the world’s total deaths [2]. According to a statistical report published in 2020, the global prevalence...
of CAD was estimated at 1655 per 100,000 people and is predicted to exceed 1845 by 2030 [3]. In the United States, CAD accounts annually for approximately 610,000 deaths and costs more than 200 billion dollars for healthcare [4].

As most CAD patients are elderly and have multiple comorbidities, they need to use medication combinations over long periods, either for treatment or prophylaxis [5, 6]. One of the major strategies used for preventing CAD is antiplatelet therapy, and the most widely used antiplatelet agent tested is aspirin [6]. However, the therapeutic window of CAD drugs is very small, and inappropriate use can lead to many consequences that affect patients’ health. For instance, aspirin plays a role in reducing the risk of cardiovascular events, but it also increases the risk of bleeding, the most common risk being gastrointestinal bleeding [7, 8]. Therefore, despite the benefit of the drug, it also causes problems that adversely affect health. Old age, polypharmacy, and comorbidities are significant risk factors for developing drug-related problems (DRPs) [9, 10].

A drug-related problem (DRP) has been defined as “an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes” [11]. DRPs can have many negative consequences for patients and society, such as decreased quality of life for patients, increased hospitalization rates, prolonged hospital stays, increased overall healthcare costs, and even increased risk of morbidity and mortality [12–14]. For example, warfarin and oral antiplatelet agents have been reported to be implicated in nearly 50% of emergency hospital admissions of elderly Americans [15].

A further serious consequence of DRPs is the economic burden. DRPs accounted for a waste of $528.4 billion, equivalent to 16% of total US healthcare expenditures [16]. In studies of CVDs, the prevalence of patients with at least one DRP varied from nearly 30% to more than 90% [17–19]. A systematic review of DRPs concluded that the drugs most commonly involved were cardiovascular drugs [12]. In CAD patients, the drugs most implicated in DRPs were beta-blockers (BBs) (34.4%), followed by angiotensin-converting enzyme inhibitors (ACEI) (24.8%), statins (16.5%), and antithrombotics (13.1%) [20]. Different drugs are often associated with several different common DRPs. To illustrate, BBs were frequently involved in ineffective drug therapy, too low dosage, and the need for additional drug therapy, while ACEIs were commonly associated with too low dosage [20]. Studies in Ethiopia, Vietnam, and Spain have estimated that the mean numbers of DRPs for each patient with CAD were about 0.75, 0.92, and 1.51, respectively [17, 18, 21]. The prevalence of CAD patients with at least one DRP was 61.1% [21]. These statistics are relatively high and represent an alarming frequency of DRPs in patients with CAD. DRPs must therefore be noticed and recognized by healthcare professionals.

This chapter separates DRPs in CAD patients into 5 common subtypes: drug selection, dose selection, adverse drug-drug interactions (DDI), patient adherence, and cost issues. We also discuss determinants that increase the ratio of DRPs, and list interventions to limit their prevalence. Our goal is to provide health care providers with an overview of the extent of DRPs and their common types; these must be considered to ensure the safety and effectiveness of drug therapy.

2. Drug-related problems

2.1 Drug selection

Inappropriate drug selection is a common type of DRP in patients with CAD; it mainly includes ineffective drug therapy, a need for additional drug therapy, and
prescription of drugs with contraindications. In an Ethiopian study, O.A. Abdela et al. found that, globally, the most common category of DRPs was inappropriate drug selection for CVDs (36.1%), and in particular for CAD (46.6%) [17]. Studies in Spain and Vietnam showed the prevalence of inappropriate drug selection of 19.4% and 3.5% for CAD patients [18, 21]. Inappropriate drug selection can have several causes. A study in Indonesia found that clinicians’ critical factor influencing statin prescribing was their lack of awareness of specific details in current guideline recommendations. Although clinicians generally know the guidelines, they remain uncertain about how to determine the level of total cholesterol in combination with other cardiovascular risk factors like diabetes and hypertension [22].

Ineffective drug therapy occurs when the drug product used is not effective for the treatment of the medical condition [23]. A need for additional drug therapy exists when the medical condition requires additional drugs to achieve synergistic or additive effects [23]. A study by A.W. Tsige et al. in Ethiopia showed that among DRPs, the prevalence of need for additional drug therapy was 30.53%, and ineffective drug therapy was 26.9% [24]. In the Netherlands, J. Tra et al. conducted a study of prescriptions for patients discharged after CADs. They found that the angiotensin-converting enzyme inhibitor, one of the most important drugs in the prescribing guideline, was often missing (21.2%) [25]. In patients who have had acute coronary syndromes, it is vital to follow prescribing guidelines for secondary prevention to avoid further serious cardiovascular events. For example, according to a study on the prescription of secondary preventative cardiovascular therapies for non-ST elevation myocardial infarction (NSTEMI), adenosine-diphosphate receptor antagonist prescribing rates had significantly increased (76%) [26]. On the other hand, a study evaluating patient adherence to prescription guidelines after acute coronary syndrome indicated that adherence to lipid-lowering therapy was the lowest. The percentage of adherence to the criterion: ‘Patient regardless of lipid level is prescribed a high-intensity statin either atorvastatin 40–80 mg or rosuvastatin 20–40 mg’, was only 16.7% in the post-ST elevation myocardial infarction group, and 33.3% in the post-non-ST elevation acute coronary syndrome group [27]. A Canadian study found that only 61% of patients with stable coronary artery disease received optimal drug therapy involving concurrent use of β-blockers, ACE inhibitor/angiotensin receptor blockers, and statins [28]. Failure to prescribe drugs that should be indicated for treatment or prevention reduces the effectiveness of treatment. For example, after myocardial infarction, patients who have conditions like heart failure, pulmonary disease, and older age are often prescribed beta-blockade therapy, which is ineffective. However, patients without these conditions benefit from such therapy [29]. Ineffective drug therapy and a need for additional drugs can lead to increased medical costs, potential drug interactions, and decreased patient adherence [30].

Medicines that cause harm to the patient or negative interaction with a combination drug are called contraindicated medicines [31]. In a multicenter study in France, research on physicians’ acceptance of pharmacists’ daily routine interventions revealed that contraindication was the most identified DRP (21.3%) [32]. However, studies on CAD patients in Vietnam and Ethiopia showed that the prevalence of contraindicated medicines leading to DRPs was only approximately 0% and 2%, respectively [17, 21]. Therefore, in the latter two countries, among CAD patients, this issue is less common than in other DRPs.

Increasing the role of clinical pharmacists and the application of prescription management software in the prescribing process to check contraindication and interaction could be effective interventions to minimize such problems. For patients
to be treated with appropriate drugs, clinicians should follow treatment guidelines and update their recommendations. In addition, the patient’s response to treatment should be monitored by clinical examination and tests, and if necessary, a change of drug to suit the patient’s condition.

2.2 Dose selection

Inappropriate dose selection includes both too high and too low [23]. A study in Spain by P. Gastelurrutia et al. found that inappropriate dose selection was one of the most frequently identified DRPs, with a prevalence of 22% [33], and a study in Turkey by Urbina, Olatz et al. found inappropriate dose selection in CAD patients to have a prevalence of 41% [18]. In a Vietnamese study by T.T.A. Truong et al., this prevalence was 22.2% [21]. Inappropriate dose selection can take place for several reasons. For example, ignoring comorbidities that affect the pharmacodynamics of a drug, such as hepatic or renal failure, can lead to inappropriate dose selection. Patients with renal and hepatic dysfunction require lower doses; otherwise, failure of excretion or breakdown of the drug can cause toxicity [34]. Furthermore, differing characteristics of patients, such as weight and body mass index, can make a prescribed dose too low or high for the patient’s needs.

Sometimes high dosage prescription was considered when the duration of drug therapy was regarded as too long, possibly leading to unwanted side-effects for the patient [23]. In Spain and Vietnam, patients with CAD had a prevalence of high dose prescriptions of 8.6% and 0.1%, respectively [18, 21]. A study by Simon B. Dimmitt et al. had found that statin doses around an estimated effective dose of 50 (ED50) could reduce myocardial infarction (25%) and mortality (10%). However, the high dosage can also increase adverse events: myopathy was shown to increase 29-fold, and liver dysfunction as much as 9-fold [35]. A national study in America reported that overdoses led to nearly two-thirds of emergency hospitalizations [15]. Because the therapeutic window of CVD drugs in general, and CAD drugs in particular, is very small, an overdose is very severe and can lead to death. For example, an indirect sympathomimetic overdose can result in tachycardia, hypertension, stroke, and acute myocardial infarction [36]. Furthermore, in patients with renal dysfunction or renal failure, drugs that are eliminated by the kidney should be dosed proportionally according to creatinine clearance [37].

In contrast, a too low dosage means that the dose is not sufficient to produce the desired response [23]. In Spain and Vietnam, DRPs of patients with CAD occurring due to low dosage prescriptions were 7.9% and 22.3%, respectively [18, 21]. Taking too low a dose fails to achieve the desired therapeutic goal, increasing the possibility of cardiovascular events [23]. A systematic overview of randomized trial studies in patients with risk of cardiovascular disease found that a dose of aspirin between 75 and 150 mg daily gives adequate prophylaxis; doses lower than 75 mg daily are less effective [38]. A study was conducted in patients with acute coronary syndrome after stent implantation to compare the efficacy of different doses of rosuvastatin [39]. This study concluded that high doses of rosuvastatin could postpone ventricular remodeling, decrease the prevalence of adverse events, and significantly improve long-term prognosis.

To limit problems related to dose selection, doctors need to pay attention to each patient’s condition, comorbidities, and characteristics affecting drug pharmacokinetics and monitor and adjust drug dose depending on the tolerance of the individual patient. In addition, the clinical pharmacist can help to calculate the appropriate drug dose for each patient. Furthermore, the application software should be developed to
assist in dose calculation for special populations like elderly patients or liver and/or kidney disease patients.

2.3 Adverse drug-drug interaction

Adverse drug-drug interactions (DDIs) occur when drug interaction leads to undesirable reactions that are not dose-related [23]. In patients with heart failure in Ethiopia, DDIs were the most common cause of DRPs, with a prevalence of 27.3% in 2020 and 33.4% in 2021 [24, 40]. However, a study in Taiwan found DDIs to be the second most common DRP (29.6%) [41]. In patients with CAD in Ethiopia and Vietnam, DDIs had prevalences of 21.2% and 19.3%, respectively [21, 40]. Often, patients with CAD have to take multiple medications for a long time [5], and other drugs must frequently be used to treat co-morbidities. However, the greater the number of drugs, the greater the risk of drug-drug interactions [5].

The most common DDI found in patients with heart failure was the combined use of spironolactone and digoxin, possibly resulting in increased digoxin toxicity [40]. A systematic review of secondary prevention of adverse ischemic events found that a regimen including aspirin plus clopidogrel led to a significantly higher rate of hemorrhagic events than other regimens (aspirin alone, plus ticlopidine or cilostazol, etc.) [6]. Another common drug-drug interaction between clopidogrel and proton pump inhibitors (PPIs) in patients with CAD. Clopidogrel is a P2Y12 receptor inhibitor and one of the two components of dual antiplatelet therapy [42]. PPIs are recommended for patients on dual antiplatelet therapy with a history or high risk of gastrointestinal bleeding [43]. Adverse drug interactions reduce the effectiveness of treatment. For example, some PPIs, such as omeprazole and esomeprazole, reduce the antiplatelet effect of clopidogrel by inhibiting the CYP2C19-mediated conversion of clopidogrel to the active metabolite in the liver [44]. In addition, concomitant clopidogrel-PPI therapy appears to increase the risk of major adverse cardiovascular events [45]. Meanwhile, PPIs such as lansoprazole and dexlansoprazole have been found to have less effect, and pantoprazole and rabeprazole do not affect the metabolism of clopidogrel [46, 47]. Therefore, one of the four PPIs: pantoprazole, rabeprazole, lansoprazole, or dexlansoprazole, should be chosen, and omeprazole and esomeprazole should be avoided in patients requiring a combination of clopidogrel and PPI.

To limit adverse drug-drug interactions, clinicians can use drug interaction testing tools with the assistance of a clinical pharmacist. If a severe drug-drug interaction occurs, an alternative drug should be considered. Furthermore, an online drug interaction checker (Drug.com, Medscape, etc.) should be used for checking before prescribing to patients.

2.4 Patient nonadherence

Poor patient adherence is another common DRP in coronary artery disease. Nonadherence involves the failure of a patient to take medications appropriately due to personal factors [23]. Several studies have indicated that roughly 20% and more than 50% of CAD patients are non-adherent to prescribed medications [48–50]. Many factors can affect patient adherence to treatment: lack of motivation, failure to understand instructions, forgetfulness, the complexity of the regimen, polypharmacy, multiple daily doses, adverse side effects, high cost, failure to initiate treatment before discharge, and the physician’s lack of knowledge of clinical indicators for the use of medications [51, 52]. In addition, older people have many unique difficulties
that contribute to poor adherence [52], one of the main factors being forgetfulness [53]. Some studies indicate that long-term therapy involving CAD prophylaxis may decrease adherence. A Swedish study reported that the adherence rate in CAD patients after discharge rapidly decreased within 2 years. Statin, aspirin, and clopidogrel adherence rates decreased from 91.7% to 56.1%, 93.2% to 61.5%, and 81.9% to 39.4% respectively, 2 years after discharge [54].

Patient adherence greatly contributes to the success of treatment and secondary prevention strategies in CAD patients. Good adherence to evidence-based medication regimens, including β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, antiplatelet drugs, and statins, has been shown to be associated with decreased risk of all-cause mortality (risk ratio 0.56; 95% confidence interval: 0.45–0.69), cardiovascular mortality (risk ratio 0.66; 95% confidence interval: 0.51–0.87), and cardiovascular hospitalization/myocardial infarction (risk ratio 0.61; 95% confidence interval: 0.45–0.82) [55]. In contrast, poor adherence can lead to major cardiovascular events, including death [56]. In Turkey, during one-year follow-up treatment, patients with acute coronary syndrome were found to have low adherence to statin therapy (17.8%) [57]. According to a study by C.A. Jackevicius et al. in the Canadian population, patients who did not use all of their discharge medications after acute coronary syndrome had an increased risk of death at 1 year [56]. The death rates among high-adherence and low-adherence were respectively 2310/14,345 (16%), and 261/1071 (24%) (adjusted hazard ratio, 1.25; 95% confidence interval, 1.09–1.42; \( p = 0.001 \)). The study also found a similar but less pronounced dose-response-type adherence-mortality association for beta-blockers [58]. However, the harmful consequence of nonadherence depends on the type of medication. For example, the mortality rate was not associated with adherence to calcium channel blockers [58]. However, patients must adhere to the prescribed regimens to achieve treatment goals.

Drug counseling upon discharge and post-discharge follow-up may increase adherence [56]. When patients know their medical condition and the benefits of prescription medications, they are more motivated to take them exactly as recommended [59]. Moreover, appropriate prescribing upon discharge should be encouraged to improve patient adherence [52]. Prescribing fixed-dose combination pills instead of using multiple single drugs also helps to enhance adherence [60, 61]. A systematic review in low- and middle-income countries demonstrated considerable variation in nonadherence to antihypertensive medication [62]. Due to the overload of healthcare systems, especially in these low- and middle-income countries and during the COVID-19 pandemic, clinicians have too little time to educate patients [63]. A systematic review of 67 countries found that about half of the world’s population spends 5 min or less with their primary care physicians [64]. Therefore, more attention should be paid to the role of the clinical pharmacist. Clinical pharmacists can help patients understand the benefits of each medication they take, the timing and frequency of administration, and signs of side effects; they can also encourage and monitor patient adherence. A systematic review of medication adherence interventions showed significant reductions in mortality risk among heart failure patients (relative risk, 0.89; 95% CI, 0.81, 0.99). A bulk of these interventions utilized medication education (\( s = 50 \)) and disease education (\( s = 48 \)) [65].

2.5 Cost issue

Medical costs for CAD have increased dramatically in recent years and are expected to rise even more [66]. The result is an increased economic burden for
patients themselves and countries. For example, hospital admission for acute myocardial infarction requiring percutaneous coronary intervention costs an average of $20,000 [67]. In the USA, it has been calculated that in 2016 DRPs wasted $528.4 billion, equivalent to 16% of the total US healthcare expenditure for that year [16]. Furthermore, the cost of informal healthcare for CAD alone was estimated at $1 billion and projected to increase to $1.9 billion by 2035 [68]. According to M. Guerro-Prado et al., cost issues accounted for up to 6.5% of all DRPs. Unnecessary and unnecessarily expensive treatments were the main reasons for such problems [69]. Furthermore, cost issues are also related to physicians’ prescriptions. A Chinese national study among 3362 primary healthcare sites showed that expensive medications were more likely to be prescribed than less costly alternatives, thus contributing to high medication costs [70]. Increased medication costs may likely reduce patient adherence and negatively affect their healthcare [51, 71]. Patients’ discontinuation of medication therapies affects their treatment outcomes and increases the occurrence of adverse cardiovascular events [56]. To treat these events, the costs of treatment become even greater.

WHO has listed some interventions that may reduce costs. Such interventions include providing information; government communication is vital to raise public awareness of the importance of reducing cardiovascular risk factors. Further efforts to reduce medical costs include early disease detection, optimal treatment according to recommendations, and close patient management to limit complications, hospitalization, and death. Also recommended for patients with coronary artery disease are lifestyle changes that enhance the effectiveness of treatment, thereby reducing the number of drugs needed [72]. To further avoid adding to treatment costs, clinicians should avoid prescribing unnecessary extra drugs [70]. Finally, it is necessary to encourage individuals to participate in health insurance to reduce the financial burden of illness [72].

3. Conclusions

DRPs are a global problem, causing adverse consequences in cardiology in particular and medicine in general. Drug selection, dose selection, adverse drug-drug interactions, and patient adherence are the most common categories involved in DRPs. Inability to control DRPs can diminish healthcare outcomes and increase the prevalence of adverse cardiovascular events, and DRPs can also inhibit economic growth due to medication costs. To minimize the negative impacts of DRPs we propose several key solutions: (1) appropriate prescribing according to guidelines, (2) enhancing the role of clinical pharmacists in the identification and intervention of DRPs, and (3) developing tools to check for drug interactions and contraindications. More effective definition and recognition of DRPs and application of relevant interventions can help to limit these global problems.
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