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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

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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 22.1%, 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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References

[1] World Health Organization, Cardiovascular diseases (CVDs). 2021 . Available from: https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) [Accessed: June 11, 2021]

[2] World Health Organization, The Top 10 Causes of Death. 2020 . Available from: https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death [Accessed: December 9, 2020]

[3] Khan MA et al. Global epidemiology of ischemic heart disease: Results from the Global Burden of Disease Study. Cureus. 2020;**12**(7):e9349

[4] Brown JC, Gerhardt TE, Kwon E. Risk factors for coronary artery disease. In: StatPearls. 2022, StatPearls Publishing Copyright ©. Treasure Island (FL): StatPearls Publishing LLC; 2022

[5] InformedHealth.org. Medication for the Long-Term Treatment of Coronary Artery Disease. 2006 . Available from: https://www.ncbi.nlm.nih.gov/books/NBK355311/ [Accessed: July 27, 2017]

[6] Niu PP et al. Antiplatelet regimens in the long-term secondary prevention of transient ischaemic attack and ischaemic stroke: An updated network meta-analysis. BMJ Open. 2016;**6**(3):e009013

[7] Zhao B et al. Pros and cons of aspirin for the primary prevention of cardiovascular events: A secondary study of trial sequential analysis. Frontiers in Pharmacology. 2020;**11**:592116

[8] Weisman SM, Brunton S. Primary prevention of CVD with aspirin: Benefits vs risks. The Journal of Family Practice. 2021;**70**(6s):S41-s46

[9] Nivya K et al. Systemic review on drug related hospital admissions—A pubmed based search. Saudi Pharmaceutical Journal. 2015;**23**(1):1-8

[10] Al Hamid A et al. A systematic review of hospitalization resulting from medicine-related problems in adult patients. British Journal of Clinical Pharmacology. 2014;**78**(2):202-217

[11] Association. P.C.N.E. Pharmaceutical Care Network Europe Classification for Drug Related Problem V9.1. 2020 . Available from: https://www.pcne.org/upload/files/417_PCNE_classification_V9-1_final.pdf

[12] Gayathri B et al. Drug related problems: A systemic literature review. International Journal of Clinical Pharmacology and Therapeutics. 2018;**9**(1):1409-1415

[13] Ayalew MB, Tegegn HG, Abdela OA. Drug related hospital admissions; a systematic review of the recent literatures. Bulletin of Emergency And Trauma. 2019;**7**(4):339-346

[14] Abraham RR. Drug related problems and reactive pharmacist interventions for inpatients receiving cardiovascular drugs. International Journal of Basic Medical Sciences and Pharmacy (IJBMSP). 2014;**3**(2):42-48

[15] Budnitz DS et al. Emergency hospitalizations for adverse drug events in older Americans. The New England Journal of Medicine. 2011;**365**(21):2002-2012

[16] Watanabe JH, McInnis T, Hirsch JD. Cost of prescription drug-related morbidity and mortality. The Annals of Pharmacotherapy. 2018;**52**(9):829-837

[17] Abdela OA et al. Risk factors for developing drug-related problems in

patients with cardiovascular diseases attending Gondar University Hospital, Ethiopia. Journal of Pharmacy and Bioallied Sciences. 2016;**8**(4):289-295

[18] Urbina O et al. Patient risk factors for developing a drug-related problem in a cardiology ward. Therapeutics and Clinical Risk Management. 2015;**11**:9-15

[19] Niquille A, Bugnon O. Relationship between drug-related problems and health outcomes: A cross-sectional study among cardiovascular patients. Pharmacy World & Science. 2010;**32**(4): 512-519

[20] Niriayo YL et al. Drug therapy problems and contributing factors in the management of heart failure patients in Jimma University Specialized Hospital, Southwest Ethiopia. PLoS One. 2018;**13**(10):e0206120

[21] Truong TTA et al. Drug-related problems in prescribing for coronary artery diseases in Vietnam: Cross-sectional study. Tropical Medicine & International Health. 2019;**24**(11):1335-1340

[22] Irawati S et al. Key factors influencing the prescribing of statins: A qualitative study among physicians working in primary healthcare facilities in Indonesia. BMJ Open. 2020;**10**(6):e035098

[23] Cipolle RJ et al. Pharmaceutical Care Practice: The Clinician's Guide: The Clinician's Guide. Americas New York City, United States: McGraw-Hill Medical; 2004

[24] Tsige AW, Yikna BB, Altaye BM. Drug-related problems among ambulatory heart failure patients on follow-up at Debre Berhan comprehensive specialized hospital, Ethiopia. Therapeutics and Clinical Risk Management. 2021;**17**:1165-1175

[25] Tra J et al. Adherence to guidelines for the prescription of secondary prevention medication at hospital discharge after acute coronary syndrome: A multicentre study. Netherlands Heart Journal. 2015;**23**(4):214-221

[26] Venkatason P et al. Trends and variations in the prescribing of secondary preventative cardiovascular therapies for non-ST elevation myocardial infarction (NSTEMI) in Malaysia. European Journal of Clinical Pharmacology. 2018;**74**(7):953-960

[27] Al-Taweel D, Awad A. Development and validation of medication assessment tools to evaluate prescribing adherence to evidence-based guidelines for secondary prevention of coronary heart disease in post-acute coronary syndromes patients in Kuwait. PLoS One. 2020;**15**(11):e02416 33-e0241633

[28] Chun S et al. Predictors and outcomes of routine versus optimal medical therapy in stable coronary heart disease. The American Journal of Cardiology. 2015;**116**(5):671-677

[29] Gottlieb SS, McCarter RJ, Vogel RA. Effect of beta-blockade on mortality among high-risk and low-risk patients after myocardial infarction. The New England Journal of Medicine. 1998;**339**(8):489-497

[30] By J. Mark Ruscin, S.A.L. Drug-Related Problems in Older Adults. 2021. Available from: https://www.msdmanuals.com/professional/geriatrics/drug-therapy-in-older-adults/drug-related-problems-in-older-adults

[31] Company, F.A.D. Contraindication. 2004. Available from: https://www.tabers.com/tabersonline/view/Tabers-Dictionary/754565/all/contraindication

[32] Bedouch P et al. Assessment of clinical pharmacists' interventions in French hospitals: Results of a multicenter study. The Annals of Pharmacotherapy. 2008;**42**(7):1095-1103

[33] Gastelurrutia P et al. Negative clinical outcomes associated with drug-related problems in heart failure (HF) outpatients: Impact of a pharmacist in a multidisciplinary HF clinic. Journal of Cardiac Failure. 2011;**17**(3):217-223

[34] Tariq RA et al. Medication Dispensing Errors and Prevention. In: StatPearls. Treasure Island (FL), United States: StatPearls Publishing; 2022

[35] Dimmitt SB, Stampfer HG, Warren JB. The pharmacodynamic and clinical trial evidence for statin dose. British Journal of Clinical Pharmacology. 2018;**84**(6):1128-1135

[36] Mladěnka P et al. Comprehensive review of cardiovascular toxicity of drugs and related agents. Medicinal Research Reviews. 2018;**38**(4):1332-1403

[37] Doogue MP, Polasek TM. Drug dosing in renal disease. Clinical Biochemist Reviews. 2011;**32**(2):69-73

[38] Antithrombotic Trialist's Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;**324**(7329):71-86

[39] Guo J et al. Study on the effect of different doses of rosuvastatin on ventricular remodeling in patients with acute coronary syndrome after emergency percutaneous coronary intervention. European Review for Medical and Pharmacological Sciences. 2017;**21**(19):4457-4463

[40] Seid E et al. Evaluation of drug therapy problems, medication adherence and treatment satisfaction among heart failure patients on follow-up at a tertiary care hospital in Ethiopia. PLoS One. 2020;**15**(8):e0237781

[41] Hsu WT, Shen LJ, Lee CM. Drug-related problems vary with medication category and treatment duration in Taiwanese heart failure outpatients receiving case management. Journal of the Formosan Medical Association. 2016;**115**(5):335-342

[42] Ferri N, Corsini A, Bellosta S. Pharmacology of the new P2Y12 receptor inhibitors: Insights on pharmacokinetic and pharmacodynamic properties. Drugs. 2013;**73**(15):1681-1709

[43] Levine GN et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non–ST-Elevation Acute Coronary Syndromes, and 2014 ACC/AHA Guideline on Perioperative cardiovascular evaluation and management of patients undergoing noncardiac surgery. Circulation. 2016;**134**(10):e123-e155

[44] Norgard NB, Mathews KD, Wall GC. *Drug-drug interaction between clopidogrel and the proton pump inhibitors*. The Annals of Pharmacotherapy. 2009;**43**(7):1266-1274

[45] Serbin MA, Guzauskas GF, Veenstra DL. Clopidogrel-proton pump inhibitor drug-drug interaction and risk of adverse clinical outcomes among PCI-treated ACS patients: A meta-analysis. Journal of Managed Care & Specialty Pharmacy. 2016;**22**(8):939-947

[46] Frelinger AL 3rd et al. A randomized, 2-period, crossover design study to assess the effects of dexlansoprazole, lansoprazole, esomeprazole, and omeprazole on the steady-state pharmacokinetics and pharmacodynamics of clopidogrel in healthy volunteers. Journal of the American College of Cardiology. 2012;**59**(14):1304-1311

[47] Wang ZY et al. Pharmacokinetic drug interactions with clopidogrel: Updated review and risk management in combination therapy. Therapeutics and Clinical Risk Management. 2015;**11**:449-467

[48] Molloy GJ et al. Intentional and unintentional non-adherence to medications following an acute coronary syndrome: A longitudinal study. Journal of Psychosomatic Research. 2014;**76**(5):430-432

[49] Ali MA et al. Frequency and predictors of non-adherence to lifestyle modifications and medications after coronary artery bypass grafting: A cross-sectional study. Indian Heart Journal. 2017;**69**(4):469-473

[50] Padilha JC et al. Prevalence of pharmacological adherence in patients with coronary artery disease and associated factors. Revista Latino-Americana de Enfermagem. 2021;**29**:e3464

[51] Cheng K et al. Evidence of poor adherence to secondary prevention after acute coronary syndromes: Possible remedies through the application of new technologies. Open Heart. 2015;**2**(1):e000166

[52] Sengstock D et al. Under-prescribing and non-adherence to medications after coronary bypass surgery in older adults: Strategies to improve adherence. Drugs & Aging. 2012;**29**(2):93-103

[53] Bastani P et al. Determinants affecting medication adherence in the elderly: A qualitative study. Aging Medicine. 2021;**4**(1):35-41

[54] Glader EL et al. Persistent use of secondary preventive drugs declines rapidly during the first 2 years after stroke. Stroke. 2010;**41**(2):397-401

[55] Du L et al. The impact of medication adherence on clinical outcomes of coronary artery disease: A meta-analysis. European Journal of Preventive Cardiology. 2017;**24**(9):962-970

[56] Jackevicius CA, Li P, Tu JV. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. Circulation. 2008;**117**(8):1028-1036

[57] Şimşek B et al. In-hospital statin initiation characteristics and one-year statin adherence rates in patients hospitalised for acute coronary syndrome. Acta Cardiologica. 2021;**76**(8):852-858

[58] Rasmussen JN, Chong A, Alter DA. Relationship between adherence to evidence-based pharmacotherapy and long-term mortality after acute myocardial infarction. JAMA. 2007;**297**(2):177-186

[59] Jimmy B, Jose J. Patient medication adherence: Measures in daily practice. Oman Medical Journal. 2011;**26**(3):155-159

[60] Lauffenburger JC, Landon JE, Fischer MA. Effect of combination

therapy on adherence among US patients initiating therapy for hypertension: A cohort study. Journal of General Internal Medicine. 2017;**32**(6):619-625

[61] Yusuf S et al. Combination pharmacotherapy to prevent cardiovascular disease: Present status and challenges. European Heart Journal. 2014;**35**(6):353-364

[62] Nielsen J et al. Non-adherence to anti-hypertensive medication in low- and middle-income countries: A systematic review and meta-analysis of 92443 subjects. Journal of Human Hypertension. 2017;**31**(1):14-21

[63] Hamid H, Abid Z, Amir A, Rehman TU, Akram W, Mehboob T. Current burden on healthcare systems in low- and middle-income countries: Recommendations for emergency care of COVID-19 [published online ahead of print, 2020 Aug 9]. Drugs Ther Perspect. 2020:1-3. DOI: 10.1007/s40267-020-00766-2

[64] Irving G et al. International variations in primary care physician consultation time: A systematic review of 67 countries. BMJ Open. 2017;**7**(10):e017902

[65] Ruppar TM et al. Medication adherence interventions improve heart failure mortality and readmission rates: Systematic review and meta-analysis of controlled trials. Journal of the American Heart Association. 2016;**5**(6):1-18

[66] International, R. Cardiovascular Disease Costs Will Exceed $1 Trillion by 2035: Nearly Half of Americans Will Develop Pre-Existing Cardiovascular Disease Conditions, Analysis Shows. 2017. Available from: www.sciencedaily.com/releases/2017/02/170214162750.htm

[67] Cowper PA et al. Acute and 1-year hospitalization costs for acute myocardial infarction treated with percutaneous coronary intervention: Results from the TRANSLATE-ACS registry. Journal of the American Heart Association. 2019;**8**(8):e011322-e011322

[68] Dunbar SB et al. Projected costs of informal caregiving for cardiovascular disease: 2015 to 2035: A policy statement from the American Heart Association. Circulation. 2018;**137**(19):e558-e577

[69] Guerro-Prado M, Olmo-Revuelto MA, Catalá-Pindado M. Prevalence of medication-related problems in complex chronic patients and opportunities for improvement. Farmacia Hospitalaria. 2018;**42**(5):197-199

[70] Su M et al. Availability, cost, and prescription patterns of antihypertensive medications in primary health care in China: A nationwide cross-sectional survey. Lancet. 2017;**390**(10112):2559-2568

[71] McIntyre D et al. What are the economic consequences for households of illness and of paying for health care in low- and middle-income country contexts? Social Science & Medicine. 2006;**62**(4):858-865

[72] Essue BM et al. The effectiveness of interventions to reduce the household economic burden of illness and injury: A systematic review. Bulletin of the World Health Organization. 2015;**93**(2):102-12b