Adherence to dual antiplatelet therapy after percutaneous coronary artery angioplasty

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Συμμόρφωση με τη διπλή αντιαιμοπεταλιακή αγωγή

Abstract at the end of the article

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Introduction: Percutaneous coronary intervention (PCI) is a treatment option in the management of coronary syndromes, either acute or chronic. Administration of dual antiplatelet therapy (DAPT) is essential in optimizing patients' clinical outcomes after PCI and reducing the risk of stent thrombosis or ischemic events.

The **aim** of the present study was to review the literature regarding adherence to DAPT among patients undergoing PCI.

Methodology: A literature search of scientific articles was conducted in the electronic databases PubMed and Scopus with publication dates during last 5 years. The keywords used for the search were: Percutaneous coronary intervention (PCI), dual antiplatelet therapy (DAPT), adherence as well as synonyms and combinations of the terms.

Results: DAPT involves a combination of aspirin and platelet P2Y12 receptor inhibitors (clopidogrel, prasugrel, ticagrelor). Patients adherence to this therapy tends to decrease with time after PCI, mainly from 6 to 12 months. According to literature, 1 in 3 patients discontinue the P2Y12 inhibitor earlier than the prescribed time. Factors influencing adherence are related to the healthcare system of each country, patients (demographic, economic, social) and comorbidities. Adherence with other medications before PCI is associated with DAPT discontinuation after the procedure. In clinical settings, healthcare professionals either do not have enough time or are not fully familiar with adherence measurements. Also, the short length of hospital stay undermines adherence assessment. Educational interventions that begin in the clinical setting and include post-discharge follow-up are effective in adherence improvement.

Conclusions: A stable therapeutic relationship between patients and healthcare professionals is essential for understanding the factors that determine the degree of DAPT adherence. Given that, adherence is a dynamic and changing process over time, improvement efforts are effective when measurements are repeated.

Keyy-words: *Coronary intervention, dual antiplatelet therapy, adherence*

Introduction

Percutaneous coronary intervention (PCI) is a treatment option for acute or chronic coronary syndromes. This treatment method was introduced to interventional cardiology in 1979 and ever since experienced rapid growth due to the increasingly availability of improved stents and medicines.[1-4] In Greece, the number of PCI procedures performed per year varies geographically. The annual number of patients undergoing PCI in a given geographical area may serve as an indicator of the overall burden of cardiovascular disease.[5]

Recent advances in technology, antiplatelet drugs, and stents, as well as improvements in clinical judgment, physician experience, and laboratory preparedness have provided a meaningful help to optimizing safety outcomes and treatment efficacy. Given the ageing of population, patients present for PCI with more comorbidities (diabetes mellitus, obesity) and complex vascular lesions.[6,7]

Dual antiplatelet therapy (DAPT) after PCI is a "standard" therapeutic approach for secondary prevention of cardiovascular risk and optimal clinical outcomes. Adverse cardiovascular events (nonfatal stroke, nonfatal myocardial infarction, and cardiovascular death) which occur in approximately 20% of patients, within the first year after PCI, exert a negative influence on prognosis and quality of life.[8]

The **aim** of the present study was to review literature regarding adherence to DAPT and associated factors in patients undergoing PCI.

Methodology

A literature search of scientific articles was conducted in the electronic databases Medline (PubMed) and Scopus, during the last 5 years. The following keywords were used during the search: Percutaneous coronary intervention, dual antiplatelet therapy, adherence as well as synonyms and combinations of the terms. Criteria for including an article in the literature review were: a) publication period between 2020-2024, b) availability of full text in electronic databases and d) involving patients undergoing PCI.

Adherence

Adherence is defined as the degree to which a patient's behavior corresponds to recommendations provided by health professionals. Adherence mainly focusses on medication, diet, exercise, monitoring of symptoms and health status reassessment. Furthermore, adherence is influenced by several factors, which are the following: [9,10]

- Patient: personal characteristics, knowledge and beliefs about disease, behavior and skills related to treatment
- Treatment: polypharmacy and duration of treatment
- Comorbidity
- Social and economic factors: cost of diagnostic tests and medication, lack of a supportive network including the National Health System of each country
- Health system: absence of information and education strategies or difficulties in accessibility of health care.

Medication adherence is assessed directly and indirectly. More in detail, direct methods include blood measurement of drug levels or biomarkers, while indirect methods include patients' self-report and clinical response, number of tablets received daily, measurement of physiological markers, and patient diaries. Prescription re-fill rates are considered an accurate measurement of adherence in a "closed pharmacy" system. According to literature, "adherent" patients are those who have medication 80% of time covered, as determined by pharmacy data. In contemporary times, opportuni-

ties for integrating pharmacy data into electronic health systems are increasing. However, it remains unknown whether these technological investments may improve the provided care.[10,11]

In clinical practice, questionnaires are widely used to measure adherence, mainly due to low cost and ease of use. Unfortunately, measuring adherence with questionnaires does not always reflect reality, since patients tend to hide their deviations and present an optimistic assessment of adherence or report adherence rates that do not correspond to their actual behavior.

Dual antiplatelet therapy (DAPT)

Dual antiplatelet therapy (DAPT) is involving two agents. More in detail, a P2Y12 receptor inhibitor such as clopidogrel, prasugrel, ticagrelor added to aspirin are considered the "standard" care for patients undergoing PCI.[12-14] Agents like prasugrel and ticagrelor are preferred in Europe, while clopidogrel retains prominence in USA.[14] Guidelines recommend receiving DAPT for at least 12 months after drug-eluting stent implantation for acute coronary syndrome and at least 6 months for stable ischemic heart disease.[12] Historically, the duration of DAPT has been modified according to stent improvements. First-generation drug-eluting stents increase the risk of late stent thrombosis and DAPT duration is extended to 12 months. In current recommendations DAPT duration is shorter due to new-generation stents, the use of a P2Y12 inhibitor as monotherapy, and the increased prevalence of patients with high risk of bleeding.[13]

There is observed a wide, global variation in DAPT duration according to patients' characteristics (demographic, clinical) including the balance of risk between bleeding and ischemic events, the risk of ischemic events associated with the lesion, and the type of stent. Patients with advanced age are at higher risk of thrombotic events and bleeding complications. Therefore, a careful decision-making is essential when prescribing the antiplatelet regimen. After PCI, elderly patients need an individualized approach to DAPT which evaluates their characteristics (thrombosis, bleeding, fragility) and estimates the invasive technique, stent selection, repair, and secondary prevention.[15]

Literature Review

Non-adherence to DAPT is responsible for revascularization, poor treatment outcomes, elevated healthcare costs, high risk of adverse cardiac events, low quality of life, increased morbidity and mortality.[16,17]

According to estimates, 1 in 5 patients delay to refill their P2Y12 inhibitor prescription after PCI. Furthermore, 1 in 3 patients discontinue the P2Y12 inhibitor before the scheduled duration.[18] Patients receiving their cardiovascular medications before PCI are 2.3 times more likely to receive DAPT after PCI compared to the non-adherent.[11]

Rahhal et al.,[19] studied 1334 patients with ST elevation myocardial infarction who underwent primary PCI. The majority of patients were male (96%) and had a mean age of 51±10.2 years. The adherence rate for all medication was only 28.4%, of which, the rate for aspirin was 50.5%, for P2Y12 inhibitors 49.9%, for statins 48.1%, for β-blockers 39.6% and 42.9% for angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers. Factors that increase the likelihood of treatment adherence were prolonged hospitalization and free medication.

A study in India conducted by Zhang et al.,[20] including 2064 patients, showed discontinuation of DAPT within one year in 470 participants. In addition, younger patients, men and those receiving antihypertensive medication showed higher adherence to DAPT at 1 year. Notably, the same researchers demonstrated a protective effect of DAPT adherence on all-cause mortality in a period of one year after PCI among a low-income population.

In China Xu et al.,[4] in a sample of 901 patients (69.8% male) with implanted drug eluting stents illustrated temporary DAPT discontinuation in 11.1% (n=100), permanent in 8.9% (n=80) and total in 20.0% (n=180). Temporal DAPT discontinuation was associated with non-adherence to medication before PCI, financial difficulties, routine disruption and emotional burden. Permanent discontinuation was associated with living in rural areas or small to medium-sized cities and side effects of medication. The occurrence of adverse cardiovascular events after PCI was associated with prior arterial hypertension and revascularization (two/three stents).

Similarly, in USA LaRosa et al.,[12] in 90.163 individuals who underwent PCI (age 69.0±10.9 years, 33.1% women, 25.1% non-White race) demonstrated an association between antiplatelet adherence and income categories. Individuals with annual income <$40.000 had 1.5-fold higher odds of non-adherence compared to those with income ≥$100.000.

In the field of Cardiology, non-adherence to medicine and the impact of medication costs on adherence fail-

ure, do not represent a new area of interest. A recent study conducted by Oates et al.,[21] showed nonadherence to medication in 106 (7.5%) participants from a total sample of 1506 patients with a mean age of 45.6±3.6 years. The majority of participants were female (69.0%), of white race (55.4%) and married (64.2%). The non-adherent individuals were more likely to be African Americans, single, depressive and with a history of diabetes mellitus but less likely to have a history of malignancy. Regarding social risk factors, those who reported nonadherence had greater financial burden, higher chronic stress, reduced social support, lower education and income (<$25.000). It appears that unmet basic needs, exacerbated by low income, such as food and housing, are associated with difficulties in medication adherence. Individuals with 3-6 social risk factors were 3.3 times more likely to be non-adherent compared to counterparts without social risk factors. These findings provide a framework for interventions aimed to improve medication adherence.

Recognizing the health and economic consequences of nonadherence to medications in cardiovascular disease, the American Heart Association includes the social and economic factors in adherence assessment. It is recommended for social and behavioral factors to be incorporated into patients' electronic medical records because of their well-established contribution to treatment effectiveness. When including these factors in medical record, is more feasible to identify patients at high risk for poor adherence.[12]

Equally important factor associated with adherence failure is symptom relief after myocardial revascularization or lack of time for provision of detailed information and counseling. Adherence failure is accurately assessed only when is considered within the context it occurs. Health related behaviors are shaped by social factors (social status, age, gender, race/ethnicity, religion, living conditions) that indicate the available options in the environment in which each individual lives. It is important to emphasize on the way patients perceive the disease in order to increase their motivation for adherence and illness comprehension.[16,21,22]

Interventions to Enhance Adherence

Though clinicians invest significant resources in patients' education and interventions to promote adherence, however, non-adherence rates remain high.[11]

More in detail, a number of interventions are implemented to improve adherence, including pre-discharge education in clinical setting, post-discharge follow-up, patient motivation, and/or participation in cardiac rehabilitation programs. Incorporating social risk factors such as income into health record might be one of the most effective ways to improve DAPT adherence.[11,17]

Nurse-led interventions to address nonadherence are effective. Interestingly, nurses not only have direct access to patients with coronary artery disease in cardiac rehabilitation, clinics and outpatient settings, but also have skills to promote adherence. Time during hospitalization offers a framework for providing information to patients and their caregivers about secondary prevention, including medication. Interventions that begin in clinical settings (education and medication administration) followed by post-discharge assessment are shown effective in improving medicine adherence.[11,17]

The study conducted by Ho et al.,[18] demonstrated that patients who underwent PCI were less likely to delay refilling their P2Y12 inhibitor prescription at discharge, if they had received an intervention to improve adherence, which included: a) administration of a P2Y12 inhibitor immediately after PCI, b) education about the importance of receiving the P2Y12 inhibitors, c) telephone calls to remind prescription refills, and d) approach at each delay of refilling P2Y12 inhibitor prescriptions.

In the literature is highlighted the need for a multifaceted approach to improve DAPT adherence including early follow-up visits, assessment of medication adherence at 90 days, and education of patients and caregivers.[23] It is widely known that medication nonadherence is complex and costly issue while the ability of healthcare professionals to accurately identify it remains limited for various reasons.[11,17]

Adherence is a dynamic process that changes over time. Therefore, efforts to enhance adherence would be most effective only by repeated measurements. This approach includes screening for social adversities, developing stratification tools to identify high-risk patients and linking patients to resources that address unmet needs.[11,14,17,21]

Last but not least patients are encouraged to actively participate in disease management and express their concerns regarding medical decisions. Absence of involvement in treatment decision-making process or low health literacy contribute to non-adherence.[24,25] Support from patient's environment (family, social) is an important component in chronic disease trajectory.[26] Building a stable therapeutic relationship with health professionals based on trust and optimum informing

sharing permits a deep assessment of patients' health status, such as discomfort, anxiety and depression that may interfere with adherence.[24-25]

Conclusions

Understanding factors associated with DAPT adherence (personal, social, economic) after PCI is fundamental to provide high quality of care. At the same time, the in-depth knowledge of non-adherence related factors is necessary for implementing effective policy change which is anticipated to markedly decrease the economic, medical, individual and social burden of not receiving the prescribed medications.

Additional studies including large samples are needed to identify new strategies to enhance DAPT adherence and clinical outcomes after PCI.

ΠΕΡΙΛΗΨΗ

Συμμόρφωση με τη διπλή αντιαιμοπεταλιακή αγωγή μετά από διαδερμική αγγειοπλαστική στεφανιαίων αρτηριών

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Εισαγωγή: Η διαδερμική αγγειοπλαστική στεφανιαίων αρτηριών αποτελεί θεραπευτική επιλογή στη διαχείριση των οξέων ή χρόνιων στεφανιαίων συνδρόμων. Η λήψη διπλής αντιαιμοπεταλιακής αγωγής είναι απαραίτητη για τη βελτιστοποίηση των κλινικών αποτελεσμάτων των ασθενών μετά από αγγειοπλαστική και τη μείωση του κινδύνου θρόμβωσης της ενδοπρόθεσης ή ισχαιμικών επεισοδίων.

Σκοπός της παρούσας μελέτης ήταν η ανασκόπηση της βιβλιογραφίας αναφορικά με την συμμόρφωση στην λήψη διπλής αντιαιμοπετελιακής αγωγής ασθενών που υποβλήθηκαν σε διαδερμική αγγειοπλαστική στεφανιαίων αρτηριών.

Μεθοδολογία: Διενεργήθηκε βιβλιογραφική αναζήτηση επιστημονικών άρθρων στις ηλεκτρονικές βάσεις δεδομένων PubMed και Scopus, τα οποία δημοσιεύθηκαν τα τελευταία 5 έτη. Οι λέξεις-κλειδιά που χρησιμοποιήθηκαν για την αναζήτηση ήταν: αγγειοπλαστική στεφανιαίων αρτηριών, διπλή αντιαιμοπεταλιακή αγωγή, συμμόρφωση και συνώνυμα και συνδυασμοί των όρων.

Αποτελέσματα: Η λήψη διπλής αντιαιμοπεταλιακής αγωγής περιλαμβάνει συνδυασμό ασπιρίνης και αναστολέων των P2Y12 υποδοχέων των αιμοπεταλίων (κλοπιδογρέλη, πρασουγρέλη, τικαγρελόρη). Η συμμόρφωση των ασθενών προς αυτή τη θεραπεία τείνει να μειώνεται με την παρέλευση του χρόνου μετά την αγγειοπλαστική, κυρίως από 6 έως 12 μήνες. Σύμφωνα με τη βιβλιογραφία, 1 στους 3 ασθενείς διακόπτει τον αναστολέα P2Y12 νωρίτερα από τον προκαθορισμένο χρόνο. Οι παράγοντες που επηρεάζουν τη συμμόρφωση συσχετίζονται με το σύστημα υγειονομικής περίθαλψης κάθε χώρας, με τους ασθενείς (δημογραφικοί, οικονομικοί, κοινωνικοί) και τις συνοσηρότητες. Η συμμόρφωση με τη λήψη άλλων φαρμάκων πριν από την αγγειοπλαστική συνδέεται με διακοπή της διπλής αντιαιμοπεταλιακής αγωγής μετά τη διαδικασία. Σε κλινικά περιβάλλοντα, οι επαγγελματίες υγείας είτε δεν διαθέτουν αρκετό χρόνο ή δεν είναι πλήρως εξοικειωμένοι με τη μέτρηση της συμμόρφωσης. Επίσης, ο σύντομος χρόνος παραμονής στο νοσοκομείο υπονομεύει την αποτελεσματική εκτίμηση της συμμόρφωσης. Οι εκπαιδευτικές παρεμβάσεις που ξεκινούν στο κλινικό περιβάλλον και περιλαμβάνουν παρακολούθηση μετά το εξιτήριο είναι αποτελεσματικές στη βελτίωση της συμμόρφωσης.

Συμπεράσματα: Η σταθερή θεραπευτική σχέση μεταξύ ασθενών και επαγγελματιών υγείας είναι απαραίτητη για την κατανόηση των παραγόντων που καθορίζουν τον βαθμό συμμόρφωσης στη λήψη διπλής αντιαιμοπεταλιακής αγωγής. Δεδομένου ότι, η συμμόρφωση αποτελεί δυναμική και εναλλασσόμενη διαδικασία στην πάροδο του χρόνου, οι προσπάθειες βελτίωσης είναι αποτελεσματικές, όταν οι μετρήσεις είναι επαναλαμβανόμενες.

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