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Review

Therapy response variability in elder cardiac patients

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Cardiovascular drugs are among the most prescribed medications in the world and, despite their proven effectiveness, there is a large variability in the therapeutic response in term of both efficacy and tolerability with remarkable clinical consequences especially in elderly patients. Additionally, cardiovascular patients respond in a changing manner also to non-pharmacological therapeutic approaches, such as antioxidants supplementation and exercise training. This review focuses on factors, including biochemical and molecular variables, comorbidity, polypharmacy and life-style that may influence the response to the common cardiovascular pharmacological and non-pharmacological treatments, paying particular attention to the emergent issue of cardiovascular pharmacogenetics.

Key words: Cardiovascular drugs, Pharmacogenetics, Anticoagulant, Antiplatelet agents, Non-pharmacological treatments

INTRODUCTION

Patients with cardiovascular diseases (CVD) show a large variability in the response to cardiovascular treatments. This is true mainly in elder subjects representing a patient population very complicated to treat and manage [1].

Many and different factors, including molecules in patients' sera and bioavailability of molecules crucial for the maintenance of cardiovascular homeostasis influence onset and progression of chronic diseases as well as the therapeutic response [2].

In elderly population the management of chronic pathologies, i.e. CVD is strongly influenced by the presence of cardiac and noncardiac comorbidities with consequent polypharmacy [3], and it is also conditioned by the frailty [4] and cognitive impairment [5] that are very common in the oldest individuals.

Cardiac patients also vary in the response to non-pharmacological therapeutic approaches, such as Salus Per Aquam (SPA) medicine [6], antioxidants supplementation and exercise training because also the results of non-drug treatments can be determined by the specific metabolic demand and genetic background of each patient [7 8].

Nowadays, it is becoming more and more clear that genetic factors can condition the outcomes of the pharmacological treatments [9 10]. In particular, polymorphisms in genes encoding molecules controlling both pharmacodynamics and pharmacokinetics of cardiac drugs may influence the therapeutic response. This is the basic concept of the cardiovascular pharmacogenetics, which recently is attracting great attention from the scientific community [11].

This review aims to provide a comprehensive overview on the factors influencing the response to both pharmacological and non-pharmacological treatments in elderly cardiac patients, paying particular attention to the emergent issue of cardiovascular pharmacogenetics.

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BIOCHEMICAL AND MOLECULAR CHARACTERISTICS OF PATIENTS

Several molecules concur to the maintenance of cardiovascular homeostasis and their systemic levels often influence cardiovascular drugs response [12].

High serum levels of cholinesterase, total cholesterol and albumin have been associated with residual platelet aggregation rate (RPA) during antiplatelet therapy in patients with CVD [13]. Moreover, Hong et al. have showed that coronary heart patients undergoing percutaneous coronary intervention and treated with a standard antiplatelet agent had higher RPA beside increased levels of inflammatory markers such as E-Selectin, metalloproteinase [9] and molecules involved in the platelet aggregation process, including soluble CD40 ligand [14].

Furthermore, it has been observed that aged cardiac patients with higher magnesium levels showed less probability to survive at a 3-year follow-up than patients with lower levels and a strong relationship between hypermagnesemia and laxative/antacid administration was found [15].

Several studies on the pathways of nitric oxide (NO) have corroborated the idea that the pharmacological treatments are strongly associated to the biochemical and molecular profile of each patient. For instance, the increase of the plasmatic levels of asymmetric dimethyl-arginine (ADMA), a well-known inhibitor of nitric oxide synthase (NOS), may be a predictive factor for cardiovascular events since it contributes to development of the endothelial dysfunction, which is essentially caused by an increase of the oxidant species resulting in oxidative stress and impairment of the NO signalling [16-18]. Hsu et al. demonstrated that ADMA could reduce the capacity of simvastatin to activate endothelial NO synthase (eNOS); notably, the authors subdivided their study population into two tertiles on plasmatic ADMA levels finding that only in patients with lower ADMA the beneficial effects of the statin were preserved [19 20].

On the other hand, high levels of symmetrical dimethylarginine (SDMA) and ADMA in patients with acute congestive heart failure and impaired renal function have been found increased after a standard therapy as a consequence of the reduced expression and activity of eNOS and increased O2- level [21 22]. Furthermore, Angiotensin Converting enzymes inhibitors (ACE-I), especially ramipril, but also statins may improve platelet NO resistance and arterial stiffness, thereby attenuating the risk of coronary events. Such effects are likely to improve therapeutic outcomes and are also helpful to identify patients in whom the pharmacological treatments can be effective [23 24]. The NO pathway has been also referred to explain the reduced response to aspirin (ASA). In this regard, López- Farré have found that patients with coronary artery disease (CAD) showed low response to ASA probably because of a reduction of the eNOS-derived NO levels in mononuclear cells [25]. The suboptimal response to ASA in CAD patients could also depend on homocysteine levels. Actually, high levels of homocysteine acetylated by ASA have been associated with blood platelet refractoriness to low ASA dose and the serum levels of homocysteine have been found significantly lower in good responders compared to the poor ones [26]. Notably, it was showed that in hypertensive patients with high basal levels of homocysteine, β-blockers and ACE-I may reduce such levels, providing an additional therapeutic effect exemplified by an improvement of the endothelial function [27]. Also the treatment with simvastatin has been found able to decrease homocysteine plasma levels in hyperlipidemic patients and, also in this case, in the subjects with higher homocysteine basal levels [28].

COMORBIDITY AND POLYPHARMACY

Patients with CVD are generally elderly subjects and their medical care is often complicated by various, both cardiac and non-cardiac, comorbidities and polypharmacy [29 30]. Braunstein et al. have investigated the relationship between non-cardiac comorbidities and the rates of hospitalizations and total mortality in a large sample of old patients with chronic Heart Failure (HF), finding that chronic disease comorbidities, such as chronic obstructive pulmonary diseases (COPD), renal failure and Alzheimer exerted a huge negative impact on the care of such patients. Of note, the risk of preventable hospitalizations increased with the number of the coexisting diseases [31 32]. These findings are in accordance with those from Muzzarelli and colleagues who have recently reported that a large proportion of early re-hospitalizations in elderly HF patients were due to the presence of non-cardiovascular comorbidities [33].

Unquestionably, the presence of either cardiovascular or non-cardiovascular comorbidities in cardiac patients, especially older ones, invariably leads to polypharmacy that in turn can produce many negative consequences, including the increase of adverse drug reactions and dangerous drug interactions associated with common medications such as thrombolytic, antiplatelet and anticoagulants agents [3 34].

The inappropriate prescribing represents another important problem. Actually, it has been estimated that a large number of aged patients receives one or more unnecessary medical prescriptions and several drugs are often prescribed even when they are contraindicated or ineffective [3 35 36].

Importantly, the inappropriate medication is associated

with an increase of both morbidity and mortality and also contributes in expanding health care costs [37].
Management of the chronic therapies in elderly is complicated also by the presence of frailty that increases the risk of disability, hospitalization, and mortality [4].
For example, diuretic therapy in frail patients with HF is often associated to urinary incontinence, progression of renal dysfunction, delirium, falls, and vasodilators favor orthostatic hypotension [38].
Also adherence to medication is an important issue, especially in the elderly patients in whom, besides the aforementioned variables, also psychological and socioeconomic factors must be taken into account [39 40].
Many and various social barriers contribute to determine the non-adherence to the therapeutic treatments in the elderly. For example, the oldest patients are more likely to be female, often divorced or unmarried and living without caregiver [41].
Non-adherent patients, often with low incomes and without a sufficient level of education, tend to completely break down their social networks [42], easily developing psychological impairments such as depressive mood, anxiety symptoms and cognitive impairment [5].
Campbell et al. found that cognitive decline is one of the most important predictors for poor compliance among the elderly, especially in presence of comorbidity implicating vision and/or hearing impairments. Indeed, the cognitive deficits heavily interfere with all daily activities including the ability to understand and follow physicians' instructions for taking the medications [43]. Cognitive impairment is particularly common in patients affected by CHF with ischemic origin and has been associated with an increased mortality rate [44]. Moreover, the cognitive impairment and dementia appear to increase with the occurrence of atrial fibrillation in elderly regardless of stroke history with a consequent lack of therapy response also to non-pharmacological treatment such as cardiac rehabilitation programs [45].

VARIABILITY IN RESPONSE TO NON-PHARMACOLOGICAL TREATMENTS

Management of elder cardiac patients requires a multidisciplinary approach that includes measures of counseling and education, and life-style modifications in dietary regimen and physical activity.
Physical activity, more specifically, exercise training (ET) is an important component of cardiac rehabilitation programs also in the aged patients [46].
Indeed, sedentary is one of the major risk factors in patients with several chronic diseases, including CVD and the lack of compliance with both physical activity and well-structured ET program is often associated with higher rates of morbidity and mortality of such individuals [47].
Many studies have shown that in elder cardiac patients ET improves generic health-related quality of life (HRQOL) and exercise tolerance assessed by the 6-min walking distance (6MWD) test. However, there is a large variability in response to cardiac rehabilitation programs in dependence on several factors, such as age, gender and CVD severity [48]. Moreover, weight loss represents a good response to the exercise also because it favors the improvement of the exercise tolerance as demonstrated in obese men with coronary artery disease [49]; nonetheless, because of CVD population heterogeneity, a proportion of overweight patients, mainly with HF, may experience an attenuated response to the exercise.
Iellamo et al. have suggested that exercise in elder patients with CVD induced an improvement of heart rate variability and baroreflex sensitivity that correlated to individual volume/intensity training load with a significant increase of functional capacity [50].
Importantly, the effects of ET strongly depend on both type and intensity of the training program [51 52] and, in this framework, great attention has to be payed to worsening of clinical condition possibly associated with an overtraining [52].
Taking together, these data underline the need to administer a personalized cardiac rehabilitation programs for each patient [53].
A multicomponent rehabilitation program especially in geriatric population may be helpful in delaying age-associated frailty also thanks to its ability to improve the capacity of antioxidant system, thereby reducing oxidative stress, which is very high in frail patients [54].
Natural antioxidant compounds, such as vitamins C and E, resveratrol, curcumin and many others have been considered as adjuvant therapy in CVD patients. However, clinical trials involving the use of antioxidants supplementation in several age-associated diseases often show conflicting results and lead to dangerous misconceptions, either too positive or too negative. As a matter of the fact the interplay of both endogenous and exogenous antioxidants with the humans' redox system is very complex and represents an issue that is still under debate [7].
Actually, a certain level of oxidant molecules, namely free radicals, is physiologically necessary and at same time an excess of the antioxidants might be deleterious [55].
Thus, the controversial outcomes of the studies on antioxidants supplementation might partially depend on an underestimation of specific metabolic demand and genetic background of the enrolled patients, mainly in the elderly [7].

CARDIOVASCULAR PHARMACOGENETICS

Pharmacogenetics is the branch of pharmacology, which studies the genetic basis of the variability in drugs response. Many genetic variations, influencing the response to pharmacological treatments, have been identified; among them, particular attention has focused on Single Nucleotide Polymorphisms (SNPs) that can be responsible for the lack of drug efficacy or the occurrence of dangerous side effects. Nowadays, it is possible to provide the right drug and drug dosage to the right person, thereby maximizing drug efficacy and minimizing drug toxicity [56].

The application of pharmacogenetics tests is becoming more and more feasible in several medical areas, including oncology [57 58], immunology [59 60], rheumatology [61], endocrinology [62 63], and many others.

The pharmacogenetics of CVD is of great research interest [11] and, indeed, polymorphisms in genes encoding molecular targets, transport proteins and metabolizing enzymes may influence the response to cardiac drugs encompassing their pharmacodynamics and/or pharmacokinetics [64-66].

Important pharmacogenetics findings for cardiovascular drugs, such as statins, β-blockers, antiplatelet agents and both old (i.e. warfarin) and new (i.e. dabigatran) oral anticoagulants have been identified [64].

Several in vitro and *in vivo* studies suggest that polymophisms in genes encoding adrenergic receptors, such as the SNPs resulting in nonsynonymous substitutions Ser49Gly and Arg389Gly in the β1 adrenergic receptor (ADRB1) gene may influence the therapy response to β-blockers with remarkable clinical consequences in patients with both HF and hypertension [67-69].

In addition, individuals carrying loss of function variant in gene encoding for CYP2D6 P450 enzyme are poor metabolizers for several drugs including β-blockers metoprolol and timolol but this does not result in clinically relevant toxicity. Nevertheless, it has been suggested that in poor metabolizers metoprolol cardioselectivity could be lost [70].

The most important pharmacogenetics findings and the relative tests currently recommended and entered the clinical practice in the area of CVD concern the anticoagulant warfarin and the antiplatelet clopidogrel [64].

Warfarin pharmacogenetics

Warfarin is the most commonly prescribed oral anticoagulant worldwide for prevention and treatment of thromboembolic events in patients with mechanical heart valves or non-valvular atrial fibrillation (AF). Despite its effectiveness, this drug is associated with a high risk of both thromboembolism and bleeding especially in elderly patients [71-73].

In particular, bleeding complications depend on a number of concomitant factors, including the reduction of metabolic clearance, the high prevalence of comorbidities, high occurrence of drug interactions and reduced compliance [74].

Efficacy and safety of warfarin are determined through performing a blood test so called International Normalized Ratio (INR), which checks how long it takes for blood to clot.

An INR between 2.0 and 3.0 is generally accepted for non-valvular AF and venous thromboembolism, but for valve replacements a higher INR between 2.5 and 3.5 is usually recommended. INR levels greater or lower than the target range may result in significant bleeding or stroke respectively, particularly during the first weeks of the therapy [75].

Warfarin acts by inhibiting of vitamin K epoxide reductase complex 1 (VKORC1), thereby limiting the availability of reduced vitamin K and decreasing the synthesis of functionally active vitamin K-dependent clotting factors (II, VII, IX and X). It is administered as a racemic mixture of R- and S-enantiomers and the more potent S-enantiomer is mainly metabolized by the isoform CYP2C9 of CYP450 family (Fig. 1, Panel A).

Patients treated with warfarin vary in the response in terms of both efficacy and safety and, among the numerous genetic factors potentially involved, one SNP in the promoter of the gene encoding warfarin's target vitamin K epoxide reductase complex 1(VKORC1), indicated as VKORC1 -1639 G > A and two SNPs in the genes encoding the metabolizing enzyme CYP2C9 (e.g. CYP2C9-*2 and -*3) have been described as major contributors of dose-response variability. Patients carrying polymorphisms in one or both of these genes require lower or higher warfarin doses to obtain an adequate anticoagulant effect when compared with subjects carrying wild type genes (Fig. 1, Panel A and Tables I and II) [76].

A pharmacogenetic algorithm, incorporating both clinical and genetic information, has been developed by the International Warfarin Pharmacogenetics Consortium (IWPC) to get a stable warfarin maintenance dose to lower the bleeding risk by personalizing the anticoagulant therapy. Actually, besides clinical and demographic factor, the IWPC algorithm includes the screening of the three aforementioned SNPs that can help to predict warfarin dose requirements [77].

In 2007 and in 2010, the Food and Drug Administration (FDA) issued guidelines to stress the utility and the importance to analyze CYP2C9-*2 and -*3 and VKORC1 -1639 G > A polymorphisms before starting warfarin therapy [78 79].

Several studies have demonstrated that the pharmacogenetic approach can be considered a feasible and accurate method to establish warfarin dosing and may

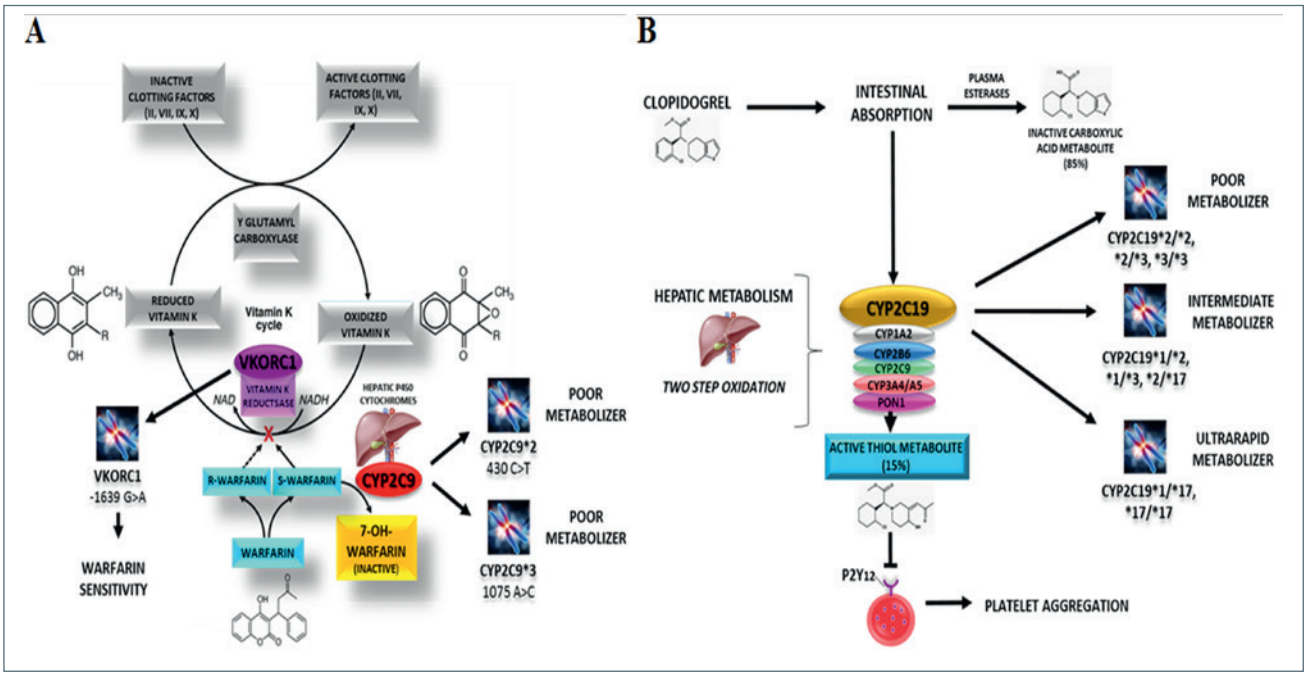

Figure 1. Schematic representation of pharmacodynamics and pharmacokinetics of warfarin and clopidogrel.
Panel A: warfarin produces its pharmacological effect by inhibiting of vitamin K epoxide reductase complex 1 (VKORC1), thereby limiting the availability of reduced vitamin K and decreasing the synthesis of functionally active vitamin K-dependent clotting factors (II, VII, IX and X). It is administered as a racemic mixture of R- and S-enantiomers. The more potent S-enantiomer is metabolized into inactive metabolite, 7-hydroxyl warfarin, by cytochrome *CYP2C9*. The variability in warfarin response depends on the presence of SNPs *VKORC1* -1639 G > A, resulting to a reduced activation of vit. K- dependent clotting factors and *CYP2C9*2* (430 C > T) and *CYP2C9*3* (1075A > C), that lead to the synthesis of *CYP2C9* isoforms with reduced enzymatic activity. These polymorphisms are associated to warfarin sensitivity, thus patients carrying such variants may require doses of anticoagulant lower than 5 mg/die to achieve the therapeutic INR.
Panel B: clopidogrel is a pro-drug that requires hepatic biotrasformation to form an active metabolite. When administered, it is largely inactivated (for about 85%) from plasma esterases, while the remaining 15% is activated from several isoforms of cytochrome P450 family. The isoenzymes of the *CYP450* family involved in clopidogrel metabolism are *CYP2C19, CYP3A4/A5, CY2C9, CYP1A2* and *CYP2B6*. The active metabolite selectively and irreversibly inhibits the purinergic P2Y12 receptor and thus platelet aggregation. Several alleles of *CYP2C19* (mainly *CYP2C19*2, CYP2C19*3* and *CYP2C19*17*) have been recognized as responsible of variable clopidogrel response.

Table I. Impact of CYP2C9 and VKORC1 polymorphisms on warfarin pharmacokinetics and pharmacodynamics, respectively.

CYP2C9		
Genotype	**Metabolism**	**Clinical implications**
*1/*1	Extensive metabolizer	Normal anticoagulant activity
*1/*2	Intermediate metabolizer	Reduced warfarin metabolism; increased anticoagulant activity
*1/*3 *2/*2 *2/*3	Poor metabolizer	Reduced warfarin metabolism; increased anticoagulant activity; increased risk for bleeding
*3/*3	Poor metabolizer	Highly reduced warfarin metabolism; increased anticoagulant activity; increased risk for bleeding
VKORC1(-1639 G > A)		
Genotype	**Enzyme expression**	**Clinical implications**
GG	Normal enzyme expression	Normal activation of vit. K- dependent clotting factors
GA	Moderate enzyme expression	Reduced activation of vit. K- dependent clotting factors
AA	Low enzyme expression	Highly reduced activation of vit. K- dependent clotting factors

Table II. Recommended daily dose of warfarin (mg/die) based on *CYP2C9* and *VKORC1* genotypes.

	CYP2C9 Genotype					
***VKORC1* Genotype (-1639 G > A)**	***1/*1**	***1/*2**	***1/*3**	***2/*2**	***2/*3**	***3/*3**
GG	5-7	5-7	3-4	3-4	3-4	0.5-2
GA	5-7	3-4	3-4	3-4	0.5-2	0.5-2
AA	3-4	3-4	0.5-2	0.5-2	0.5-2	0.5-2

Adapted from Clinical Pharmacogenetics Implementation Consortium (CPIC) guidelines and FDA-approved warfarin (Coumadin) product label.

be preferred over fixed-dose regimens based on the administration of a starting dose of 5 mg/die [76-80].

However, it appears that while individuals at the extremes of the dose requirements are undoubtedly advantaged by the application of the genetic-based warfarin treatment regimen, the overall clinical merits of this approach in the entire patient population remain to be assessed in large prospective clinical studies, that indeed are now ongoing [81].

Nevertheless, it has been recently suggested that specific subgroups have not been included in clinical trials performed until now, likely resulting in underestimation of the pharmacogenetic advantage [82].

The recent introduction into clinical practice of the New Oral anticoagulants (NOACs), such as the direct thrombin inhibitor, dabigatran etexilate and the direct inhibitors of factor Xa (e.g. rivaroxaban, apixaban) has partially readdressed the oral anticoagulant therapy.

Trials that have compared NOACs with warfarin have substantially demonstrated the non-inferiority of this drugs whit respect to warfarin mainly for stroke prevention [83].

However, warfarin remains the mainstay of treatment for patients with mechanical heart valves and also in patients with non-valvular AF it is very important to consider both advantages and disadvantages of NOACs in each patient [84].

Moreover, accumulating evidence suggests that a SNP in gene encoding the hepatic carboxylesterase 1, which is responsible for the biotransformation of the pro-drug dabigatran etexilate into active metabolite dabigatran may influence the therapeutic response of this drug, suggesting the existence of a pharmacogenetics also for the new anticoagulant agents [85 86].

Clopidogrel pharmacogenetics

Clopidogrel is an oral antiplatelet agent commonly prescribed to prevent thrombotic events in patients undergoing percutaneous coronary interventions (PCI) and/or after acute coronary syndrome (ACS). It is also largely used in secondary prevention in the subjects intolerant to ASA or with atrial fibrillation having contraindication to warfarin [87].

Clopidogrel is a pro-drug, which requires an activating metabolism mediated by several hepatic cytochrome P450 enzymes, such as *CYP1A2, CYP2B6, CYP2C9, CYP2A4/5* and *CYP2C19*. After intestinal absorption, only 15% of drug is transformed in active thiol metabolite, while remaining 85% is inactivated by plasma esterases. Once activated, it irreversibly inhibits the platelet P2Y12-adenosine diphosphate receptor, thus preventing ADP- dependent IIb/IIIa glycoprotein complex activation [88].

The response to clopidogrel is highly variable depending on drug interactions with metabolic inhibitors and inducers and polymorphisms present in the gene encoding the enzymatic isoform *CP2C19* [89 90]. Nowadays

Table III. *CYP2C19* variants and their relationship to clopidogrel antiplatelet action.

CYP2C19		
Genotype	**Metabolism**	**Metabolism**
*1/*1	Extensive metabolizer	Normal platelet inhibition; normal residual platelet aggregation
*1/*17 *17/*17	Ultrarapid metabolizer	Increased platelet inhibition; decreased residual platelet aggregation
*1/*2 *1/*3 *2/*17	Intermediate metabolizer	Reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events
*2/*2 *2/*3 *3/*3	Poor metabolizer	Highly reduced platelet inhibition; increased residual platelet aggregation; increased risk for adverse cardiovascular events

more than 25 variant alleles in the *CYP2C19* gene have been identified but loss-of-function *CYP2C19*2, *3* and gain-of function *CYP2C19*17* variants appear to be the major responsible for the variable antiplatelet effect of clopidogrel. From a molecular point of view, *2 allele causes a splicing defect and the *3 allele results in the addition of a premature stop codon, while *17 leads to an increase of *CYP2C19* transcription resulting in a modest gain of function [91]. *CYP2C19* genotypes result in different metabolizer phenotypes; individuals can be extensive metabolizers (EM; *1/*1), intermediate metabolizers (IM; *1/*2, *1/*3, *2/*17), poor metabolizer (PM; *2/*2, *2/*3, *3/*3) and ultra-rapid metabolizers (UM; *1/*17, *17/*17).

According to the *CYP2C19* polymorphic status, about one third of Caucasian patients present high or low on-treatment platelet reactivity, leading to a greater frequency of recurrent thrombotic events or an increased bleeding risk, respectively (Fig. 1, Panel B and Table III). In March 2010, FDA added a black box warning to clopidogrel drug label in order to alert patients and physicians on high risk of treatment failure in *CYP2C19*-poor metabolizers representing up to 14% of patients. Indeed, these patients have a 3.58-times greater risk for major adverse cardiovascular events such as death, heart attack, and stroke [92].

In addition, both FDA and European Medical Agency (EMA) have issued an alert concerning the risk of very serious adverse events occurring when clopidogrel is co-administered with Proton Pump Inhibitors (PPIs), mainly omeoprazole. PPIs are commonly prescribed in patients receiving clopidogrel plus ASA but such gastroprotectors are potent inhibitors of *CYP2C19* isoform [93]. Moreover, PPIs are both substrate and inhibitor of the *CYP2C19* thus patients that are *CYP2C19*-poor metabolyzers may have concomitantly low levels of active clopidogrel and high concentration of PPIs and they could be exposed to a doubled risk of therapeutic failure and toxicity, respectively [94].

As amatter of fact, clopidogrel is one of the cardiovascular drugs that justifies the use of the term “high risk pharmacokinetics” and, according to the *CYP2C19* status, patients may require dose adjustment or switching to an alternative antiplatelet agent [95]. The standard dose of clopidogrel is 75 mg once daily that could be changed in patients with different genotypes by lowering to 6 mg or increasing to 215 mg but currently, there is not yet a standardized protocol for dose adjustment in the carriers of *CYP2C19* alleles [96].

The Clinical Pharmacogenetics Implementation Consortium (CPCI) guidelines recommend to switch to alternative antiplatelet agent i.e. prasugrel or ticagrelor in patients who are intermediate or poor metabolizers according to *CYP2C19* genotype [89-91].

Prasugrel is a new-generation antiplatelet agent, which has been found to be superior to clopidogrel as demonstrated during the phase 3 trial entitled Therapeutic Outcomes by Optimizing Platelet Inhibition with Prasugrel – Thrombolysis in Myocardial Infarction (TRITON-TIMI) that has involved patients with ACS undergoing percutaneous coronary intervention (PCI), comparing a regimen of prasugrel with the standard-dose regimen of clopidogrel [97].

Treatment with prasugrel (a 60 mg loading dose, followed by a 10 mg maintenance dose), thanks to a potent inhibition of the platelet P2Y12 receptor, led to a greater reduction of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke with respect to clopidogrel therapy. However, this beneficial effect in preventing the ischemic events has been inevitably accompanied by an increase in the occurrence of major bleeding. Indeed, prasugrel may not represent a substitute for clopidogrel in all patients; in fact, some individuals > 75 years old and/or with history of transient ischemic attack, stroke, or intracranial bleeding had an increased risk of fatal and major bleeding [97].

Importantly, a secondary analysis of the TRITON-TIMI trial have suggested that there was no difference between patients treated with prasugrel or clopidogrel with fully functional *CYP2C19* alleles that are extensive metabolizers [98].

Prasugrel is a pro-drug as well as clopidogrel, and also this activation strictly depends on the polymorphic *CYP2C19* even if it is less susceptible to genetic variation [99].

However, recent evidence suggests that prasugrel response could be influenced by the presence of the *CYP2C19*17* gain-of-function allele that could be associated with the occurrence of bleeding complications [100].

Platelet function testing might allow measuring the platelet reactivity of individuals and adjusting antiplatelet therapy principally in high-risk patients to improve clinical outcome. However, several randomized trials have failed in demonstrating the clinical efficacy of platelet function monitoring to adjust antiplatelet therapy in ACS/PCI patients [101 102].

Given the high potential pharmacokinetics risk linked to clopidogrel and since there is no basis for dose adjustment as in the case of the algorithm used to personalize the therapy with warfarin, it would be very important to develop an analytical system to evaluate pharmacogenetics in parallel with measure of platelet function in patients receiving clopidogrel [87 95].

CONCLUSIONS

Elder cardiac patients show a large variability in the response to both pharmacological and non- pharmacological therapies. Such variability depends on many

and different factors such as molecular and biochemical variables [103], comorbidities [104] and polypharmacy and also frailty and cognitive impairment, conditions that are very common in the oldest individuals. The response to cardiac drugs is strongly influenced by the genetic background of each patient and nowadays, cardiovascular pharmacogenetics has an important role in informing therapeutic decisions into the larger context of individualizing care [105].

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