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THROMBOSIS AND BLEEDING COMPLICATIONS AFTER IMPLANTATION OF MECHANICAL CIRCULATORY SUPPORT DEVICES: THE REASONS AND MECHANISMS OF DEVELOPMENT, GENOME-GUIDED CORRECTION. REVIEW.

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Abstract

Introduction. This review is devoted about the development of the thrombosis and bleeding complications after implantation of the mechanical circulatory support (MCS) device in heart failure (HF) patients which could be treated by genotyping test results.

Objective. To analyze literature and clinical investigations about cause of the complications and their prevention by genome-guided antithrombotic therapy according to the genotyping test results for genetic polymorphisms.

Research strategy. Search for scientific publications was carried out in search engines such as Web of Science, ResearchGate, PubMed, Google Academy and e-Library.ru. Criteria for inclusion of publications in the literature review are defined as publications with the full text, in Russian and English, with statistically verified conclusions.

Results. Complications develop due to the presence of the high non-physiological shear stress at the blade region of the MCS device's rotary. The shear stress causes platelet dysfunction which affects to normal hemostatic function. On the other hand, complications development occurs due to the antithrombotic therapy which could be prescribed with incorrect dosage for HF patients after device implantation. Nowadays, complications could be reduced by genome-guided antithrombotic therapy according to the genotyping test results for genetic polymorphisms of *VKORC1, CYP2C9* and *UGT1A6* genes which cause variability of drug dosage approximately for 50%.

Conclusions. The genotype polymorphisms of genes encoding enzymes which influence to the mechanism and activation of the antithrombotic drugs are necessary to be determined in HF patients as it will help to identify appropriate dosage of the drugs. The identified genome-guided antithrombotic therapy will help to reduce and predict thrombosis/bleeding complications at pre and post-MCS device implantation period which will give opportunity for patients to survive and live longer life.

Key words: *heart failure, antithrombotic therapy, warfarin, aspirin, gene polymorphism.*

Резюме

ОСЛОЖНЕНИЯ ТРОМБООБРАЗОВАНИЯ И КРОВОТЕЧЕНИЯ ПОСЛЕ ИМПЛАНТАЦИИ УСТРОЙСТВ МЕХАНИЧЕСКОЙ ПОДДЕРЖКИ КРОВООБРАЩЕНИЯ: ПРИЧИНЫ И МЕХАНИЗМЫ РАЗВИТИЯ, ГЕНОМ – АССОЦИИРОВАННАЯ КОРРЕКЦИЯ. ОБЗОР ЛИТЕРАТУРЫ.

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Введение. Данный обзор посвящен о развитии осложнений тромбоза и кровотечения после имплантации вспомогательного устройства механической поддержки кровообращения (МПК) у пациентов с сердечной недостаточностью (СН), которые могут быть пролечены по результатам генотипирования.

Цель. Изучить литературу и клинические исследования о причинах развития осложнений и их возможные предотвращения при назначении корректной антитромботической терапии по результатам генотипирования на генетические полиморфизмы.

Стратегия исследования. Поиск научных публикаций выполнялся в поисковых системах, таких как Web of Science, ResearchGate, PubMed, Google Academy и e-Library.ru. Критериями включения публикаций в обзор литературы были публикации с полным текстом, на русском и английском языках, со статистически достоверными данными.

Результаты. Осложнения развиваются из-за наличия высокого нефизиологического напряжения сдвига в районе лопастей ротора МПК устройства. Напряжение сдвига становится причиной дисфункции тромбоцитов, что влияет на нормальную гемостатическую функцию. С другой стороны, развитие осложнений происходит из-за антитромботической терапии, которая может быть назначена в некорректной дозе пациентам с СН после имплантации устройства. На сегодняшний день, риски осложнений могут быть понижены с помощью геном - ассоциированной антитромботической терапии по результатам генотипирования генетических полиморфизмов генов *VKORC1, CYP2C9* и *UGT1A6*, обусловливающих вариабельность дозировки препаратов примерно на 50%.

Выводы. Определение генотипов полиморфизмов генов, кодирующие ферменты, влияющие на механизм и активацию антитромботических препаратов, необходимо провести у больных СН, что позволит подобрать рекомендуемую дозу препарата. Выявленная антитромботическая терапия, по геному пациента, позволит уменьшить и предсказать тромбозы/кровотечения до и после имплантации устройства МПК, что даст возможность пациентам выжить и прожить более долгую жизнь.

Ключевые слова: *сердечная недостаточность, антитромботическая терапия, варфарин, аспирин, полиморфизм генов.*

Түйіндеме

МЕХАНИКАЛЫҚ ҚАН АЙНАЛЫМЫН ҚОЛДАЙТЫН ҚҰРЫЛҒЫСЫННЫҢ ИМПЛАНТАЦИЯЛАУДАН КЕЙІНГІ ТРОМБТЫҢ ТҮЗІЛУ ЖӘНЕ ҚАН КЕТУДІҢ АСҚЫНУЛАРЫ: ДАМУ СЕБЕПТЕРІ МЕН МЕХАНИЗМДЕРІ, ГЕНОМ – НЕГІЗДЕЛГЕН ЕМ. ӘДЕБИЕТКЕ ШОЛУ.

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Кіріспе. Бұл мақала қан ағу және ұйығу жанама әсерлері көмекші механикалық құрылғысынның (КМҚ) жүрек жеткіліксіздігі (ЖЖ) бар науқастарда имплантацияланғаннан кейін дамуы және олардын генотиптеу нәтижелері бойынша емделуі туралы арналған.

Мақсаты. Асқынулардың себептерін және олардың генетикалық полиморфизмдерінің генотиптеу нәтижелері бойынша дұрыс антитромботикалық терапияны тағайындап асқынулардың азаю мүмкіндіктері туралы әдебиеттерді және клиникалық зерттеулерді зерттеу.

Іздену стратегиясы. Ғылыми басылымдар осындай жүйелерде жүргізілді: Web of Science, ResearchGate, PubMed, Google Academy және e-Library.ru. Басылымдарды әдебиетті шолуға қосу критерийлері статистикалық маңызды деректері бар орыс және ағылшын тілдеріндегі толық мәтіні бар мақалалар болды.

Нәтижелер. КМҚ құрылғының роторында жоғары физиологиялық емес ығысу кернеуінің болуына байланысты асқынулар дамиды. Ығысу кернеуі тромбоциттердің дисфункциясын тудырады, бұл қалыпты гемостатикалық функцияға әсер етеді. Екінші жағынан, құрылғыны имплантациялаудан кейін ЖЖ бар пациенттерге дұрыс емес антитромботикалық терапияның дозасы асқынулардың дамуын тудырады. Бүгінгі таңда асқынулардың қаупін геном - негізделген антитромботикалық терапия *VKORC1, CYP2C9* және *UGT1A6* гендерінің генетикалық полиморфизмдерін генотиптеу нәтижелері бойынша азайтуға болады, олар дәрілердің дозасының шамамен 50% өзгергіштігін анықтайды.

Қорытынды. Антитромботикалық препараттардың механизміне және белсендірілуіне әсер ететін ферменттерді кодтайтын гендік полиморфизмдердің генотиптерін анықтау жүрек жеткіліксіздігі бар науқастарда жүргізілуі керек өйткені бұл препараттың ұсынылған дозасын таңдауға мүмкіндік береді. Пациенттің геномына негізделген анықталған антитромботикалық терапия КМҚ құрылғысынның имплантациялау алдында және одан кейін тромбозды/қан кетуді азайтады және болжайды, бұл пациенттердің аман қалуына және ұзақ өмір сүруіне мүмкіндік береді.

Түйін сөздер: жүрек жеткіліксіздігі, антитромботикалық терапия, варфарин, аспирин, гендер полиморфизмі.

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Introduction

Heart failure (HF) is one the most significant problem of the healthcare in the worldwide as well as in the Republic of Kazakhstan [3]. There are about more than 30 million people have HF in the worldwide [15]. The incidence of the cardiovascular diseases is increasing in Kazakhstan too. In Kazakhstan about 2 million people have been registered with cardiovascular diseases [1].

However, about 0.5% - 5% of HF patients have progression of their disease to the end-stage [36]. The gold standard treatment of HF patients at their end-stage is heart transplantation (HT) [20]. However, not every patient at the end-stage could be treated with HT as only 5000 transplantations performed in the world which is not enough [3, 15]. Nowadays, implantation of the mechanical circulatory support (MCS) known as left ventricular assist device (LVAD) is an alternative method of the treatment instead of transplantation for the HF patients at their end-stage [3]. LVAD has a rotating pump with a constant blood flow which mechanically unloads the left ventricle of the patient's heart [3, 20]. The HF patient's survival rate with implanted LVAD performs about 80% in one year whereas survival rate with transplantation is 86% which proves an optimal outcome [20].

Despite to the improvements of the quality of life, LVAD is followed with complications in HF patients after implantation [24]. Thrombosis, pump thrombosis, bleeding, gastrointestinal bleeding, stroke or infection are an adverse event which causes discomfort and even mortality in HF patients [37]. One of the reason in the development of the complications is platelet dysfunction which is caused due to the presence of the high non-physiological shear stress at the blade region of the LVAD's rotary spin which leads to the formation of the platelet dysfunction [10, 11, 21]. On the other hand, complications development occurs due to the antithrombotic therapy which could be prescribed with incorrect dosage for HF patients after device implantation. Nowadays, complications could be reduced by genome-guided antithrombotic therapy according to the genotyping test results for genetic polymorphisms of genes which cause variability of drug dosage approximately for 50%. The genotype polymorphisms of genes encoding enzymes which influence to the mechanism and activation of the antithrombotic drugs are necessary to be determined in HF patients as it will help to identify appropriate dosage of the drugs. The identified genome-guided antithrombotic therapy will help to reduce and predict thrombosis/bleeding complications at pre and post-MCS device implantation period which will give opportunity for patients to survive and live longer life [9, 39].

Objective. To analyze literature and clinical investigations about cause of the complications and their prevention by genome-guided antithrombotic therapy according to the genotyping test results for genetic polymorphisms.

Research strategy. Search for scientific publications was carried out in search engines such as Web of Science, ResearchGate, PubMed, Google Academy and e-library.ru. These databases allowed us to identify the latest a large number of literature sources. Criteria for inclusion of publications in the literature review are defined as publications with the full text, in Russian and English, with statistically verified conclusions. Out of 78 literary sources, 45 publications were selected as analytical material for this article. The depth of the search was 20 years.

Results of the research and discussion

Heart failure (HF) is one the most significant problem of the healthcare in the worldwide as well as in the Republic of Kazakhstan [3]. There are about more than 30 million people have HF in the worldwide [15]. The incidence of the cardiovascular diseases is increasing in Kazakhstan too. In Kazakhstan about 2 million people have been registered with cardiovascular diseases [1].

Heart transplantation (HT) is one of the standard treatment of HF patients at their end-stage [20]. However, HT is not available for every HF patients due to the not

enough numbers of heart donors [3, 15]. Nowadays, implantation of the mechanical circulatory support (MCS) known as left ventricular assist device (LVAD) is an alternative method of the treatment instead of transplantation for the HF patients at their end-stage [3, 20]. The HF patient's survival rate with implanted LVAD performs about 80% in one year whereas survival rate with transplantation is 86% which proves an optimal outcome [20]. LVAD device could be implanted as a bridge-to-transplantation (BTT) for the short term of the period and as a destination therapy (DT) for the lifetime support. Decision of the LVAD implantation as a BTT or DT depends weather patient is a candidate for the heart donor or not listed due to the medical indications such as age, complications and medical conditions [43, 45].

LVAD implantation in Kazakhstan

The first surgery on heart was performed in Republic of Kazakhstan (RK) in 1958 [28]. The development of the cardiac surgery was going on slowly with approximately two hundred surgeries on the heart in a year. Further, the significant progress started from 1991. There were opened 26 cardiac surgery centers and departments in Kazakhstan which allowed to perform heart surgeries more widely [6].

However, there was no surgical treatments of end-stage HF patients with LVAD implantation apart from medical therapy in RK before 2011. For the first time, "National research cardiac surgery center" (NRCSC) (Astana, Kazakhstan) with support of international colleagues initiated a program for the surgical treatments of HF patients at their end-stage with implantation MCS in November 2011 [6]. There were implanted 232 MCS devices at the NRCSC from the beginning of the program to April 2017 [5]. NRCSC performs implantation of four type of MCS devices such as HeartMate II, CentriMag VAD, HeartMate 3 (St Jude Medical, Huntingdon, Cambridgeshire, UK) and HearWare HVAD (HeartWare International, Framingham MA, USA) [3, 6].

Furthermore, NRCSC initiated the program of heart transplantation for HF patients with end-stage in 2012. First whole heart transplantation from deceased donor was performed in August 8, 2012. Totally heart transplantations were performed for 51 HF patients between 2012 and 2017 [5]. Moreover, NRCSC became participant of the clinical trial in implantation HearMate 3 devices, in 2014. Therefore, Kazakhstan became the first country in the world to receive approval on the commercial use of HeartMate 3 according to the successful results of clinical trial [6]. Moreover, the newest total artificial heart (TAH) CARMAT was implanted in NRCSC on October 19, 2017. CARMAT is the newest TAH which gives a long-term support for HF patients at their end-stage [16, 25].

LVAD complications

Despite to the improvements of the quality of life, LVAD is beleaguered with complications in 70% of the HF patients after implantation [24]. Thrombosis, pump thrombosis, bleeding, gastrointestinal bleeding, stroke or infection are an adverse event which causes discomfort and even mortality in HF patients [37]. Thrombosis events causes embolic events, stroke, arterial thromboembolism and dysfunction of the LVAD devices. HF patients with pump thrombosis are required to do pump exchange or heart transplantation as with device malfunction their mortality rate is 50% which is dangerous for them. Device exchange in HF patients should be considered by the level of biochemical parameter of lactate dehydrogenase more than >1000 U/L [10, 11]. Bleeding complications are also adverse events with 10% of the mortality rate. It also causes rehospitalization of HF patient especially with thoracic bleeding after 30 days of LVAD implantation. Gastrointestinal bleeding is one of the adverse complications in 30% of HF patients with DT of LVAD implantation [24, 37]. Bleeding complications lead to reoperations in 69% of patients after LVAD implantation [10].

Platelet activation and dysfunction

Despite to the improvements of the LVAD device, thrombosis complications still happen due to the rough surface of the device where platelet adhesion occurs. Platelet adhesion starts as fibrinogen and von Willebrand factor (vWF) proteins absorb on the surface of the device. Therefore, stimulation of the platelet activation, layering of the fibrins, aggregation of the platelets, leukocytes and erythrocytes on the surface of the device occur [21].

One of the reason in the development of the thrombosis and bleeding complications is platelet dysfunction [21]. Presence of the high non-physiological shear stress at the blade region of the LVAD's rotary spin at 7000 – 12000 rotations per minute which leads to the formation of the platelet dysfunction [10, 11]. The shear stress causes damage and shedding of the receptors from the platelet membrane. Platelet activation, aggregation and adhesion are processed by the activation of the glycoprotein receptors such as GPIbα, GPVI, and GPIIb/IIIa which bind to vWF, collagen, and fibrinogen coagulation proteins to support hemostasis system [43, 17]. The process of the platelet adhesion between platelet receptors are disturbed due to the shedding of the platelet receptors from the surface. Presence of the high shear stress and contact of the blood cells to the rough surface leads to the development of the non-surgical bleeding events in HF patients with implanted LVAD devices. For instance, shedding of the glycoprotein receptors GPIbα leads to the development of the non-surgical bleeding events due to the shear stress. Investigations recommend that determination level of the glycoprotein receptors GPIbα in plasma might be good biomarker for the prediction of the bleeding events after LVAD implantation [3, 13, 17, 21].

Acquired Von Willebrand syndrome

Additionally, one of the reasons of the bleeding events is disruption of the Von Willebrand Factor (vWF) protein which is known as acquired von Willebrand syndrome (AVWS) in HF patients after LVAD implantation. vWF is multimeric glycoprotein with four types of domains which bind to coagulation factor VIII, glycoprotein receptors GPIbα and GPIIb/IIa. vWF binding performs adhesion and aggregation on the subendothelial matrix on the vascular damage site to achieve hemostasis or to form a platelet plug. Activity level of the vWF is decreased after LVAD implantation due to the high non physiological shear stress which causes development of the bleeding complications [24].

LVAD's shear stress unwinds the high molecular weight of the vWF multimers which are cleaved into short chains by protease A Disintegrin And Metalloprotease with

Thrombospondin type 1 repeats, number 13 (ADAMTS-13) [24]. Consequently, degraded vWF multimers becomes unable to support hemostasis activity with reduced potential for binding to collagen and platelets properly which causes HF patients with implanted LVAD devices to have higher prone to bleeding events [3, 15, 24]. The risks of the development of the bleeding events due to the acquired VWS could be treated by targeted pharmacotherapeutic treatment. For instance, Deconinck et al. (2022) [15] performed that inhibition the function of the ADAMTS-13 could prevent the loss of high molecular weight of the VWF multimers in *in vitro* LVAD device systems which might reduce the risks of the bleeding events. However, ADAMTS-13 inhibition was not performed in clinical trials [15].

Anticoagulant treatment of warfarin for HF patients

HF patients are usually prescribed with anticoagulant and antiplatelet therapy after LVAD implantation to prevent development of the thromboembolic events and pump thrombosis for the long term treatment. However, antithrombotic treatments might cause thrombosis and bleeding complications due to the incorrect dosage of the drug [36, 39].

Warfarin is frequently used an oral anticoagulant which acts through interference with vitamin K in the liver. The most of the HF patients are often prescribed with warfarin after LVAD implantation [9]. The dosing of the warfarin drug is processed individually by weakly measurement of the International Normalized Ratio of the patient (INR 2-3). To achieve stable INR 2-3 level warfarin dosage might vary from 1 - 20 mg per day. The average initial dosage might range from 3 – 5 mg, depending on population averages. The process of the identification individual appropriate warfarin dosage can take long time from weeks to months which increases risks to the development of the complications with over- and under-coagulation of the drug [19] Nowadays, post-LVAD complications can be reduced with identified individual warfarin dosage according to the genotyping test results for specific genes which are involved in the biotransformation of vitamin K, warfarin and vitamin K dependent coagulation factors [43, 41].

Genetic polymorphisms of *VKORC1* (vitamin K epoxide reductase complex 1) and *CYP2C9* (cytochrome P450 2C9) genes are the most important genetic factors which influence to the warfarin dosage variability approximately for 50% [39]. However, warfarin dosage might vary between different populations due to the allele frequency variations. For instance, genome - wide association studies (GWAS) and candidate gene studies showed that *VKORC1* and *CYP2C9* genotypes cause warfarin variability for up to 30% in European or Asian populations in non-LVAD patients [14, 27]. Scott et al [33] showed that mutant allele frequency of polymorphism rs9923231 (-1639G>A) in *VKORC1* gene is significantly higher in Asian population than wild type allele (0.667 vs. 0.333). On the other hand, allele frequencies of polymorphism of rs9923231 in *VKORC1* gene showed opposite results in African-American populations from Asian population with higher frequency of wild type allele (0.892 vs. 0.108, $p < 0.0001$) [33]. Kazakhstani population also performed higher frequency of mutant allele polymorphism of rs8050894 in *VKORC1* than wild type allele frequency like in Asian population (0.63 vs. 0.37) [18]. There were no many investigations of GWAS study of genotype polymorphisms in *VKORC1* and *CYP2C9* genes especially in HF patients with implanted LVAD [9, 39].

However, Topkara et al., [39] identified in HF patients with implanted LVAD that frequency of mutant allele of *CYP2C9* and *VKORC1* genes were significantly different between European-American (38.0% and 50%) and African-American (9.7% and 3.2%) populations ($p<0.05$). On the other hand, Zhang et al., [44] found allele frequency of polymorphisms in *VKORC1* and *CYP2C9* genes in Chinese patients with prescribed warfarin therapy after heart valve replacement. They found in their investigation higher distribution of AA mutant genotype (90.7%) and lower level of wild type GG genotype (1.2%) of *VKORC1* gene in Chinese population. Investigations show that warfarin is widely used anticoagulant drug in various cardiovascular diseases to prevent thromboembolism risks [34, 44]. Therefore, we could tell that genotype polymorphisms of *VKORC1* and *CYP2C9* genes could predict optimal warfarin dosage which will help to prevent over- and under-coagulation in HF patients with implanted LVAD [43].

VKORC1 is gene which is located on chromosome 16 and encodes enzyme vitamin K epoxide reductase complex subunit 1 which catalyzes vitamin K epoxide into active form of vitamin K, hydroquinone. Vitamin K hydroquinone is an important cofactor which activates coagulation factors such as FII, FVII, FIX and FX. Consequently, function of the warfarin is to inhibit enzyme coded by *VKORC1* gene for deactivation coagulation factors such as FII, FVII, FIX and FX [14, 19, 39]. Difference of warfarin metabolism and action depend on genotype polymorphisms of *VKORC1* gene. Thus, warfarin dose differs between genotype polymorphisms of *VKORC1* gene. For instance, patients with the wild type genotype polymorphism of *VKORC1* gene is recommended with higher warfarin dosage. On the contrary, lower warfarin dosage is recommended for patients with mutant genotype polymorphisms [19, 39, 43]. Topkara et al., investigated warfarin dose between three genotype polymorphisms of rs9923231 in *VKORC1* gene and found that patients with mutant genotype was prescribed with lower warfarin dose than with wild type genotype (3.7 ± 1.4 vs. 4.7 ± 1.7, $p = 0.012$) [39]. Investigation of Awad et al., also identified prescribed higher dosage of warfarin for patients in the presence of wild type genotype polymorphisms of *VKORC1* gene [9].

CYP2C9 is gene located on chromosome 10 which encodes enzyme of cytochrome P450. The R- and S – stereoisomers of warfarin are metabolized by cytochrome P450 [9]. Specific single nucleotide polymorphisms (SNP) of *CYP2C9* gene is associated with enzyme activity. Polymorphisms of rs1799853 in *CYP2C9*2* and rs1057910 in *CYP2C9*3* genes are associated with lower enzyme activity in European population [19]. Allele frequency of the *CYP2C9* and *VKORC1* genes are identified to be significantly different in between different racial groups such as Asian, European-American, Caucasian and African-American [33, 39, 43]. Nowadays, it is well known that *VKORC1* and *CYP2C9* are involved in the drug metabolism and action. In 2007, Food and Drug administration (FDA) mentioned on the warfarin label that genotypes of *VKORC1* and *CYP2C9* could be helpful in identification the initial

warfarin dose. And also, warfarin dose could be also identified by online algorithm which is available on http://www.warfarindosing.org [19].

Antiplatelet treatment of aspirin for HF patients

Acetylsalicylic acid (aspirin) is one of the most widely used treatment. In the USA, approximately 35.8 million people take aspirin for the initial prevention of the cardiovascular disease [29]. HF patients also prescribed with aspirin for prevention thrombosis complications after LVAD implantation. The dosage of the aspirin varies starting from 75 mg depending on the aim of the treatment and device type in HF patient. Aspirin therapy also causes complications like a warfarin treatment too [23, 30].

Platelet activation, coagulation and aggregation occur by thromboxane A2 which is activated by isoforms of cyclooxygenase-1 (COX-1)/cyclooxygenase-2 (COX-2) and arachidonic acid. Thromboxane A2 activity could lead to stroke events in patients with cardiovascular diseases [7, 38].

Normally, after absorption aspirin is deacetylated to salicylic acid. Therefore, salicylic acid inhibits platelet activation by acetylation of isoforms of COX-1 and COX-2 which therefore leads to deactivation of thromboxane A2 [7, 38].

The half-life of aspirin is about 20 minutes. During its half-life aspirin inactivates platelets which circulate at the present moment. In the beginning aspirin inhibits COX-1 and at the same time cytosolic mRNA produces new active COX-1 molecules which are active and resistant to acetylation. The new active COX-1 molecules are more resistant to aspirin than other mature platelets. Consequently, increased level of the new COX-1 molecules leads to activation and aggregations of the platelets which leads to the complications development in cardiovascular disease [26, 31].

Inactivation of the COX-1 and COX-2 isoforms occur on specific amount of aspirin dosage. Investigations show that lower dosage (75 – 150 mg) of the aspirin inhibits COX-1 isoforms whereas higher dosage of the aspirin (> 300 mg) inhibits both COX-1 and COX-2 isoforms [26, 42].

Metabolism of the aspirin carries on by genes which encodes three major enzymes such as cytochrome P450 (CYP2C9), uridine diphosphate (UDP)-glucuronosyl transferase (UGT) and acyl-coenzyme A synthetase (ACSM2B) (Figure 1). The figure illustrates the main metabolic pathways of aspirin. There are shown the major enzymes and the average percentage of the drug (shaded areas in circles) that is involved in each metabolic pathway [8, 12].

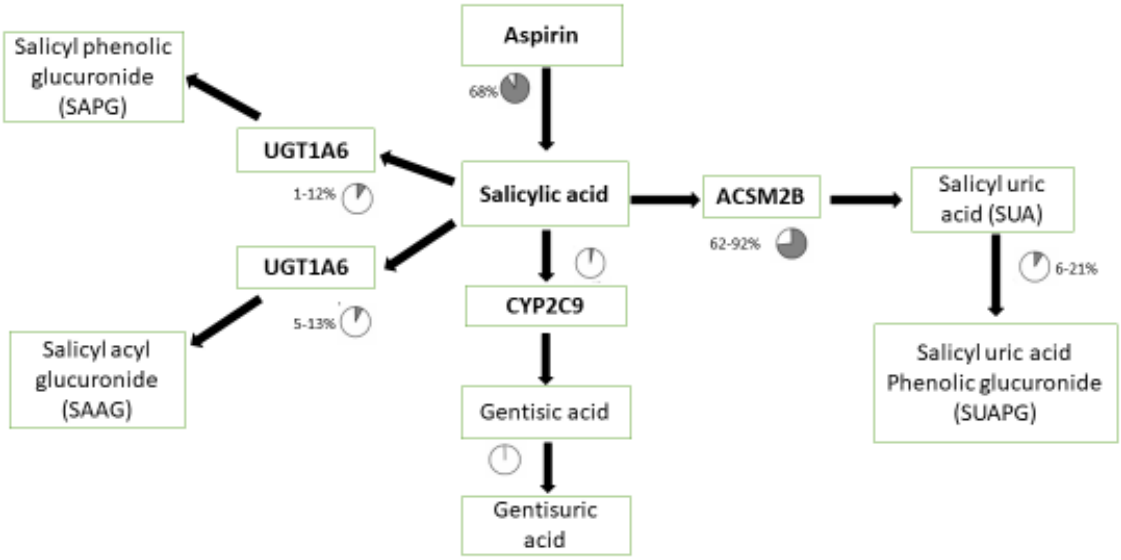

Figure 1. The scheme of aspirin metabolic pathways is modified from Chen Y., et al (2007) and Agundez J.A.G., et al (2009) [8, 12].

Aspirin metabolism occurs in two phases by listed enzymes: 1) phase I carries on by CYP2C9; 2) phase II carries on by UDP glucuronosyl transferase (UGT). These enzymes have important role in the biodistribution of the aspirin with different excretion speed of aspirin metabolites. There was no investigation on prescription of the aspirin dosage according to the genotype polymorphisms of *CYP2C9, UGT* and *ACSM2B* enzymes in patients with cardiovascular diseases [2, 12, 22].

On the other hand, one of the glucuronosyl transferase enzymes *UGT1A6* involved in the metabolism of aspirin, which is encoded by the *UGT1A6* gene. Polymorphism rs2070959 in *UGT1A6* gene was found to be associated with different level of the metabolism of the enzyme glucuronosyltransferase which is involved in the excretion of salicylic acid [8, 12]. The main function of the enzyme glucuronosyltransferase *UGT1A6* is to metabolize salicylic acid after deacetylation to salicyl acyl glucuronide (SAAG) and salicyl phenolic glucuronide (SAPG) (Figure 1). Chen et al. (2007) [12] identified that higher amount of aspirin metabolites of SAAG and SAPG were excreted due to the presence of the GG genotype of *UGT1A6* gene rather than with AA genotype in healthy participants. Polymorphism of rs2070959 in *UGT1A6* gene showed association with cancer such as colon and colorectal [32, 35]. On the other hand, van *Oijen et al.* [40] did not find association of polymorphism rs2070959 in *UGT1A6* gene in cardiovascular patients with gastrointestinal complications under aspirin therapy.

In our previous investigation (2022) [43], we also identified that aspirin metabolites excretes faster in HF patients with GG genotype of polymorphism rs2070959 in *UGT1A6* gene which concludes about faster metabolism. On the other hand, lower amount of aspirin metabolites

excretes slower with the presence of the AA genotype of polymorphism rs2070959 in *UGT1A6* gene in HF patients with implanted LVAD devices. Our research identified that HF patients with GG genotype of polymorphism rs2070959 should be prescribed with higher dosage of aspirin, whereas with AA genotype HF patients should be prescribed with lower amount of aspirin. According to this research results we received patent of Republic of Kazakhstan for invention on method of selection and correction of aspirin dose in patients with heart failure with implanted mechanical device of left ventricle [4, 43]. Thus, patients with cardiovascular diseases who are planned to be prescribed with antiplatelet drug of the aspirin should be treated with appropriate dosage to reduce and prevent complications because of overdosing by determination genotypes of *UGT1A6* gene [43].

Our investigation concludes, that genotype polymorphisms of genes encoding enzymes which influence to the antithrombotic treatments' dosage variability are necessary to be determined in HF patients with implanted LVAD. The implementation prescription of the antithrombotic drugs according to the genetic analysis will help to prevent and predict thrombosis/bleeding complications at pre and post-LVAD implantation period which will give opportunity for patients to survive and live longer life.

Conclusion

Chronic heart failure (HF) is one the most important problem of the healthcare system in the Republic of Kazakhstan which needs to be treated with heart transplantation. Implantation of the left ventricular assist device (LVAD) is one the alternative method for the treatment HF patients due to the lack of the heart donors. LVAD device improves HF patient's life and also it causes complications such as thrombosis and bleeding after implantation. These complications occur due to the device's non-physiological shear stress and incorrect dosage of the antithrombotic treatment which is prescribed after implantation.

After LVAD implantation the main aim of the cardiologist is reducing and prevention of these complications by administration appropriate dosage of the antithrombotic drugs or exchange of the LVAD device during pump thrombosis. Consequently, literature review and our investigation showed that genetic information of HF patients should be taken into consideration during treatment. The prescription of the antithrombotic drugs according the genotype polymorphisms could prevent and predict complications at the pre-/post-LVAD implantation periods which will reduce morbidity and mortality rate.

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