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Titel der Masterarbeit / Title of the Master's Thesis

„Analysis of the causality of protein – cardiac adverse drug reactions represented in the ADReCS data base"

verfasst von / submitted by

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Abstract

A lot of potential drugs fail in clinical trials due to serious adverse reactions (ADRs). These ADRs are in most cases caused by the interaction of pharmacologically active substances with target proteins in the human body. Therefore, predicting the toxic potential of drugs plays an important role at the stage of preclinical trials.

The aim of the thesis was to analyze the causality between proteins and adverse drug reactions collected in the ADReCS-Target database. Using the KNIME analytical platform a selected part of the ADReCS-Target database was supplemented with protein names. After such optimization a group of human proteins associated with cardiac disorders was isolated. For classification of ADRs standardized medical dictionaries MedDRA and MeSH were used.

The isolated group of ADR-protein associations was compared with the data from DisGeNet database as a well-known and verified data bank. Finally, the direct connection between protein function and potential cardiac adverse effects was evaluated by searching for information in scientific publications.

Zusammenfassung

Viele potenziellen Medikamente scheitern in klinischen Studien an schwerwiegenden unerwünschten Arzneimittelwirkungen (UAW). Diese UAWs werden in den meisten Fällen durch die Wechselwirkung von pharmakologisch aktiven Substanzen mit Zielproteinen im menschlichen Körper verursacht. Daher spielt die Vorhersage des toxischen Potenzials von Arzneimitteln im Stadium präklinischer Studien eine wichtige Rolle.

Ziel der Masterarbeit war es, die Kausalität zwischen Proteinen und unerwünschten Arzneimittelwirkungen, die in der ADReCS-Target-Datenbank gesammelt wurden, zu analysieren. Unter Verwendung der KNIME-Analyseplattform wurde ein ausgewählter Teil der ADReCS-Target-Datenbank durch Proteinnamen ergänzt. Nach solcher Optimierung wurde eine Gruppe von menschlichen Proteinen isoliert, die mit unerwünschten kardialen Wirkungen assoziiert sind. Zur Klassifizierung von UAWs wurden standardisierte medizinische Wörterbücher MedDRA und MeSH verwendet.

Die isolierte Gruppe von ADR-Protein-Beziehungen wurde mit den Daten aus der DisGeNet-Datenbank verglichen. DisGeNet wurde als bekannte und verifizierte Datenbank zum Datenvergleich ausgewählt. Schließlich wurde der direkte Zusammenhang zwischen der Proteinfunktion und möglichen kardialen unerwünschten Wirkungen durch die Suche nach Informationen in wissenschaftlichen Veröffentlichungen bewertet.

1. Introduction

1.1. Background

With the rapid development of the global economy, deteriorating environmental conditions and population growth, the need for new drugs and innovative medical technologies is also growing rapidly. Currently, one registered drug accounts for
- 5.000 - 10.000 potential pharmacologically active components;
- about 13 years of scientific research and experience;
- up to 2.2 billion euros development cost [1];
- human resources for the phase of clinical trials, laboratory animals for preclinical studies, expensive laboratory equipment and the work of many scientists.

Most potential drugs fail at various stages due to the undesirable effects and potential toxicity that arise. Therefore, a very important task of modern medicine is the earliest possible prediction of the toxicity of one or another chemical compound even at the stage of laboratory research using the latest computer technologies - in silico toxicity. This will speed up the drug development process and save human and financial resources.

1.2. In Silico Toxicology

The necessity of the determination of chemicals' toxicity in order to identify their harmful effects on the environment, plants, animals and, of course, people has long been known. Identification of the toxicity of a potential pharmacologically active substance is one of the main steps in drug development. Animal models have long been used for toxicity testing and are the main criterion for evaluating toxicity. However, in vivo animal testing is limited by cost, time consuming and ethical considerations. Therefore, in our time, computational methods for assessing the toxicity of chemicals are being actively developed. In silico toxicology is a form of possible toxicity assessment that uses computational methods to predict, model, visualize, and analyze the toxicity of chemicals. The goal of in silico toxicology is to complement existing toxicity tests to predict toxicity at the preclinical stage, determine the pharmacological action potential of chemicals, conduct toxicity tests, and minimize failures in the later stages of drug development.

It is obvious that in silico toxicology is a useful component in the process of determining the toxicity of potential drugs. Nowadays, as new data appear, in silico computational methods of toxicology are being developed, which are aimed at:

- expansion and inclusion of the model for specific and new types of endpoints of chemical toxicity;
- providing an understanding of toxicological pathways;
- combining and comparing the results of different models;
- customization and refinement of the model in accordance with the expectations of users [2].

1.3. Molecular Targets in Toxicity Research

After the discovery of the sequence of the human genome and the development of methods for modeling the molecular structures of the human body, drug development has reached a new level, based on target-oriented design. The main targets are species-specific genes, gene variations, RNA and DNA nucleic acids, as well as proteins (Figure 1). The interaction of a pharmacological substance with these targets can lead to both the desired therapeutic effect and undesirable effects. In this case, the number of undesirable effects is related to how specifically the drug binds to its target in the body.

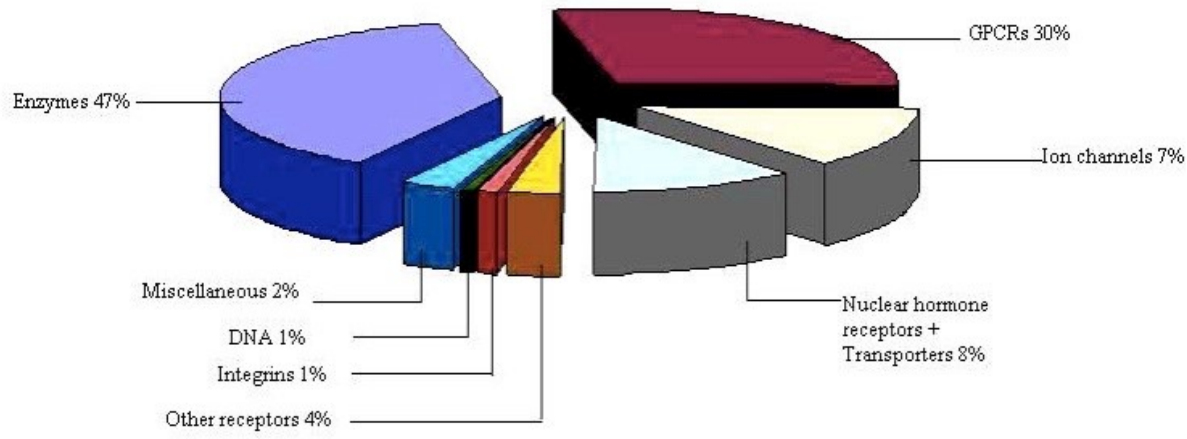

Figure 1: Molecular Targets in Drug Research (taken from [15])

As can be seen in the diagram, the overwhelming majority of drug targets are proteins. Proteins play a decisive role in the regulation of cell activity, namely intercellular interaction, cell growth and death. Therefore, proteins are the main subject of study of

pathological processes in the body. At the moment, about 300,000 different proteins are isolated, which can be targets for pharmacologically active molecules. In this case, one drug can bind to several proteins, causing, along with therapeutic, also undesirable effects. The main protein targets for pharmacologically active molecules are enzymes - macromolecules, the main function of which is to catalyze biochemical reactions in the human body. This physiological function makes enzymes an obvious target in drug development. Currently, there are many well-studied examples of therapeutic and side effects of drugs associated with modulation of enzymes, for example, inhibition of cyclooxygenase for anti-inflammatory and antipyretic effects.

Another very important group of targets of a proteinaceous nature are receptors, most of which are associated with the G-protein. It is a superfamily of seven transmembrane proteins that are found in almost all tissues of the body and can be activated by a large number of extracellular signals. Activation of receptors leads to the transmission of signals that regulate the most important physiological processes, for example, contraction of the muscles of the heart, signals of the sensory organs. That is why undesirable modulation of receptors by pharmacologically active substances leads to the most severe side effects [15].

One more important drug target family with which serious adverse effects can be associated are ion channels. Ionic channels play an important role in the regulation of physiological processes, however, the study of ion channels as a target for drugs remains problematic. The main problems are the complexity of modeling ion channels, with the need to use high-tech electrophysiological research methods and the validation of these methods [16].

1.4. Adverse Drug Reactions

Adverse drug reactions (ADRs) are an urgent problem of modern health care, especially taking into account the aging of the population, the growth of multimorbidity, as well as the increasing complexity of therapy. Adverse drug reactions (ADRs) - unintended harmful events associated with the use of drugs - occur as a cause and during a significant proportion of unplanned hospitalizations.

An adverse drug reaction (ADR) can also be defined as a perceptibly unpleasant or harmful reaction resulting from the use of a drug. Adverse effects usually indicate a potential hazard from future use and require prophylaxis, special treatment, dosage changes, or product withdrawal. Since 2012, the definition of ADR also includes

reactions resulting from erroneous use, misuse, or abuse of a drug, as well as suspected reactions to drugs that are not licensed or misused in addition to the authorized use of the drug at regular doses.

Current research demonstrates that adverse drug effects are common in clinical practice, with the frequency remaining relatively constant over time. In 5% - 10% of patients, unwanted effects are the cause of unplanned hospitalizations, and can also occur during hospitalization or appear after discharge, despite preventive measures. This frequency of potential harm must be carefully considered, as it is associated with morbidity and mortality rates, can be quite costly and adversely affect the doctor-patient relationship.

There are the following groups of drugs that have a particularly strong effect on hospitalization due to an adverse reaction: anticoagulants, antiplatelet agents, immunosuppressants, cytotoxic agents, diuretics, antibiotics and antidiabetic agents. The most severe adverse reactions, often fatal, are associated with bleeding. The most common perceived hazard is the concomitant use of antithrombotic / anticoagulants with non-steroidal anti-inflammatory drugs (NSAIDs).

Traditionally, there are two types of ADR:

Type A reactions - also called augmented reactions - are predictable adverse reactions, which depend on the dose and pharmacology of the drug.

Type B reactions - bizarre reactions – are extraordinary and impossible to predict.

This classification is basic, but it does not work for all adverse reactions, such as reactions with withdrawal reactions or chronic side effects associated with cumulative drug exposure. A more complete classification is "DoTS". It categorizes reactions according to drug dose, reaction time, and related susceptibility factors such as genetic, pathological, and other biological differences. DoTS helps to put the diagnosis and prevention of adverse reactions into practice.

Thus, individualized therapy is becoming more and more possible, since not only pharmacogenetics, but also other phenotypic information are taken into account when developing recommendations and prescribing pharmacotherapy for a patient. Current ADR research can help to achieve, at the national and international level, a positive balance of benefits and harms throughout the life cycle of a medicinal product. This remains a key goal for clinical pharmacologists because preventing or reducing the risk of adverse reactions continues to be a challenge in daily clinical practice [3].

1.5. MedDRA Hierarchy of Adverse Drug Reactions

MedDRA, or the Medical Dictionary for Regulatory Activities, is a data base, which includes standardized medical terms and is useful for many regulation procedures connected with drug approval. The main focus of the creation of MedDRA was to create the basis for internationally standardized communication between pharmaceutical companies and licensing authorities, as well as automated data transfer.

MedDRA suggests an identical classification of adverse events and side effects of drugs, including drugs in different stages of clinical trials and already registered drugs. In the EU and the US, adverse drug reactions are registered using the MedDRA terminology for electronic transfer to the responsible authorities. The MedDRA terminology is also very useful for the completion of the product characteristics summary [4].

MedDRA is structured very logically (figure 2). There are five levels in the MedDRA hierarchy, ranging from general to very specific. At the most specific level of “Lowest Level Conditions” (LLT), there are currently over 70,000 terms that correspond to the method of information transmission. This level supports the assignment of MedDRA terms in the user database and reflects how observation can be used in practice.

Members of the next level "Preferred Terms" (PT) are separate medical term descriptions for a symptom, sign, investigation, therapeutic indication, disease diagnosis, medical or surgical procedure, and characteristics of a medical, social, or family history. Each LLT can only be associated with one PT. Each PT has one or more LLTs, as well as synonyms and different lexical variations such as abbreviations, different word order, and others.

Linked PTs are in turn grouped into "high level terms" (HLT) based on physiology, anatomy, pathology, etiology, or function. HLTs that are related to each other in the above characteristics are called "high level group terms" (HLGT).

Finally, HLGTs are grouped into Systemic Organ Classes (SOC), which are grouped together:

- by etiology - infections and invasions;
- the place of manifestation - cardiovascular, gastrointestinal disorders;
- by purpose - surgical or medical procedures.

In addition, there is a SOC that contains questions related to products and one that contains social circumstances [5].

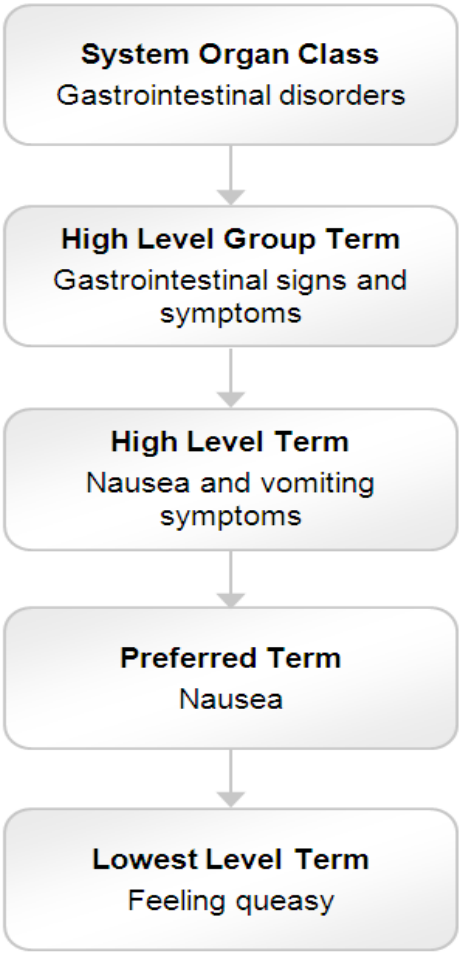

Figure 2: MedDRA Hierarchy (taken from [5])

1.6. The Medical Subject Headings Database

The Medical Subject Headings Database (MeSH) is a vocabulary of medical terminology, which is developed, organized and controlled by the National Library of Medicine. It includes the well-ordered terminology of adverse drug reactions and can be used to search or analyze different kinds of medical information. MeSH includes subject headings that appear in MEDLINE / PubMed, the NLM directory, ADReCS-Target, DisGeNet and other databases (figure 3) [6].

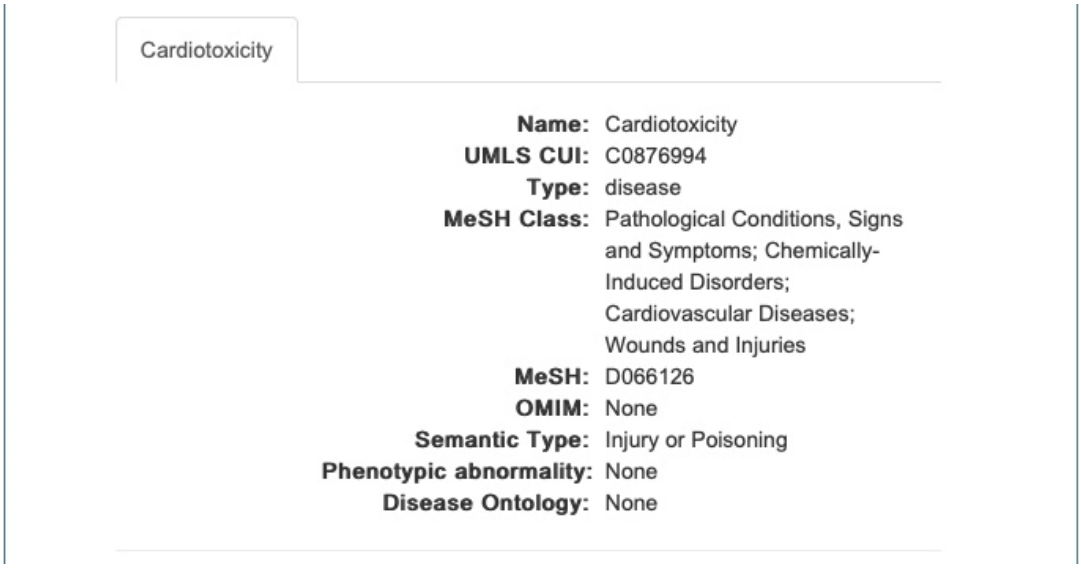

Figure 3: Screenshot from the DisGeNet Database

1.7. Terminology of Cardiac Disorders

All cardiac disorders taken into account in this work are standardized using MedDRA and MeSH terminology like in the following example. The full terminology of cardiac disorders is represented in Supplement 2.

MeSH: D002318

Cardiovascular disorders (Figure 4) is a common name for several cardiac disorders and functional abnormality of blood vessels. The main disorders and syndromes are:

- ischemic heart disease;
- cerebrovascular disease;
- disease of the peripheral arteries, which are responsible for the blood supply to the arms and legs;
- heart defects of various etiologies;
- various types of thrombosis of veins and arteries - blood clots that can move to the heart and lungs.

A group of acute conditions is especially distinguished, which can be caused mainly by blockage of blood vessels, which prevents blood flow to the heart and brain. These conditions include primarily heart attack and stroke.

Cardiovascular disease is still the main death reason in the world [7].

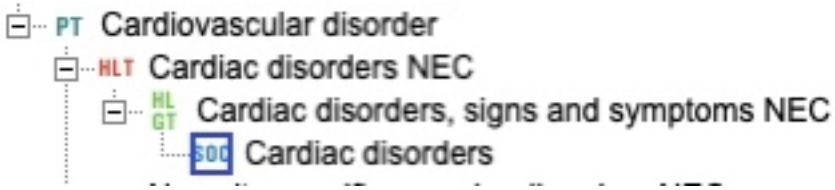

Figure 4: Cardiovascular disorder - Screenshot from MedDRA Browser

1.8. Aims of the Thesis

The occurrence of severe adverse reactions is a major cause of drug failure in clinical trials. Therefore, it is very important to assess their toxic potential at an earlier stage of drug development in order to save time, financial resources and the work of scientists. To achieve this goal, it is necessary to evaluate the interaction of a potential pharmacologically active compound with a target in the human body. Possible targets for the action of the drug can be proteins that play the role of receptors, enzymes, ion channels, carriers, and others, as well as genes responsible for the expression of these proteins. Also important are data on numerous gene variations that determine the individual response of the human body to a xenobiotic [27].

To effectively assess the safety and toxicity of a potential drug, various databases that analyze the association of a protein, gene, or gene variation with unwanted side effects are being actively developed. One such database is ADReCS-Target. In the course of this work, I had the following goals:

Supplementing the selected part of the ADReCS-Target database with the names of proteins using the Knime analytical platform.

Isolation of a group of human proteins associated with heart disease based on the data of the staged classification of the undesirable effects of MedDRA.

Search for protein groups associated with undesirable cardiac effects isolated from the ADReCS-Target database in the DisGeNET database using the MeSH ID of cardiac disorders.

Search for matches between protein data extracted from the ADReCS-Target and DisGeNET databases.

Evaluation of the direct relationship between protein function and potential cardiac adverse effects by searching for information in scientific publications.

2. Methods

2.1. ADReCS-Target Database

The main Data Base used in this work is The Target Profile of the Adverse Drug Reaction Classification System (ADReCS-Target). It is a new database that has been developed to assist in drug safety studies. This database provides comprehensive information on adverse drug reactions caused by drug interactions with proteins, genes and genetic variations. ADReCS-Target includes more than 65000 pairwise relationships, among which the main part is gene-ADR associations (63 298), about 2600 genetic variation-ADR associations, and 1700 protein-ADR associations. The ADReCS-Target can be a useful resource for the scientists engaged in biomedical research from web lab to high performance computing platform. The database can be useful for researchers in the fields of clinical pharmacology, precision medicine, and drug development. The main goal is to help identify the drug with the best adverse reaction profile and to provide safe and effective therapeutic treatment for patients.

The ADReCS-Target database mainly includes three types of associations: gene-ADR, protein-ADR and genetic variation-ADR. Protein-ADR associations were compiled from publicly available scientific literature. First of all using a self-coding program, the relevant fragments containing both keywords of the protein-ADR pair were collected from the local MEDLINE database. The protein name and synonyms were taken from the UniProt database. ADR terms and synonyms were taken from the ADReCS database. Protein-ADR relationships were formed by manually extracting information from abstracts or full articles. All information on protein-ADR relationships has been cross-checked.

MedDRA classification were used in the ADReCS-Target database for ADR standardization. The ADReCS-Target observes the same ADR hierarchy, that is, the four levels of the hierarchy are System Organ Class (SOC), High Level Group Term (HLGT), High Level Term (HLT), and Preferred Term (PT). Each ADR term in an ADReCS-Target is encrypted with a typical ADReCS identifier in the format xxx.xxx.xxx.xx.

In addition, the ADReCS-Target standardizes the protein name, gene name and genetic variation, referring to the UniProt database, NCBI Entrez database, and db-SNP database, respectively [27].

2.2. DisGeNet Database

Another Data Base used during this work is DisGeNet. DisGeNET is a database that contains one of the most universal compilation of genes and variants associated with human disease in the public domain. DisGeNET brings together data from expert repositories, academic literature, GWAS catalogs, and other data sources. DisGeNET data is standardized and controlled by community-driven vocabularies and ontologies. The DisGeNET database currently describes more than 1,000,000 gene-disease associations, between numerous genes, genes and various diseases, disorders, and abnormal human phenotypes. This database also describes more than 350,000 variant-disease associations, indicating the relationship between gene variants and diseases, traits and phenotypes.

DisGeNET is a versatile platform whose main applications are for a variety of research purposes. For example, analyzing the relationship between a gene and a disease, studying the foundations of human pathological conditions at the molecular level, as well as predicting the therapeutic effect of drugs, their possible side effects and computer analysis of the data obtained [28].

One of the most important indicators characterizing the connection between a gene and a disease is the GDAScore. This indicator is based on current research data and reflects how well a particular association is known and studied. GDAScore gives the highest value to associations which are reported by experts curated resources. These resources usually have a large number of supporting publications [28]. GDAScore takes a value from 0 to 1 and takes into account the number and type of information source, as well as the number of publications and databases in which information about a particular relationship between a gene and a disease can be found [29].

2.3. The Knime

The KNIME Analytics Platform is an open source data analysis software that helps to quickly and efficiently process, visualize, or analyze large amounts of data, predict new features, or implement new ideas. The analytical platform is open access, easy to use, and intuitive clear (Figure 5).

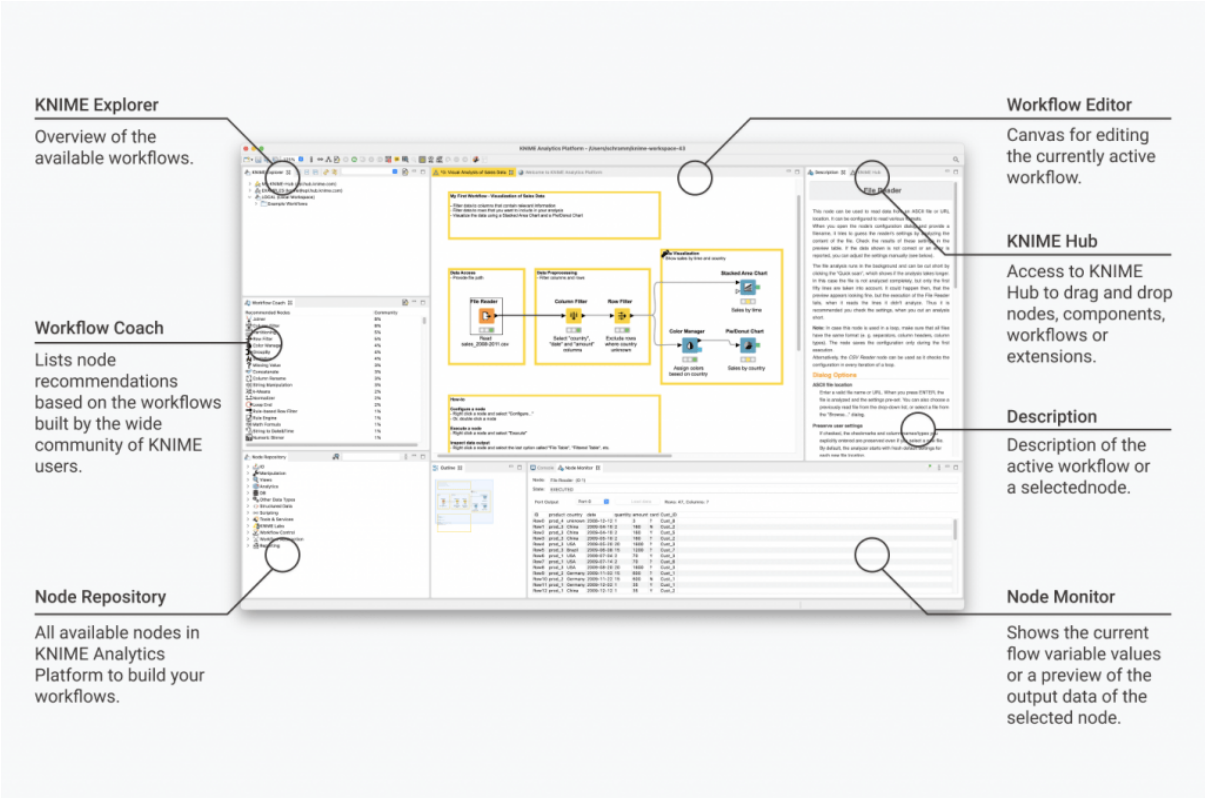

Figure 5: Starting Page of the Knime (taken from [30])

Data processing and analysis is performed in a process of creating a workflow. The single unit of the workflow is the node. A node is a block with different inputs and outputs, marked in different colors and having different shapes. A node can perform various tasks such as reading and writing, rendering, sorting, and transforming data. To accomplish these tasks each node has a settings window where it's possible to set the desired parameters. Nodes that have the same color and shape input and output ports can be interconnected to form a workflow. In this case, the data that is loaded into the node is called input data. Output data is the data obtained as a result of processing in this node [30].

2.4. Workflows

1. The task of the workflow is to enter the names of proteins and organisms from the uniprot site into the original table from the ADReCS-Target database, followed by filtering of human proteins (Figure 6).

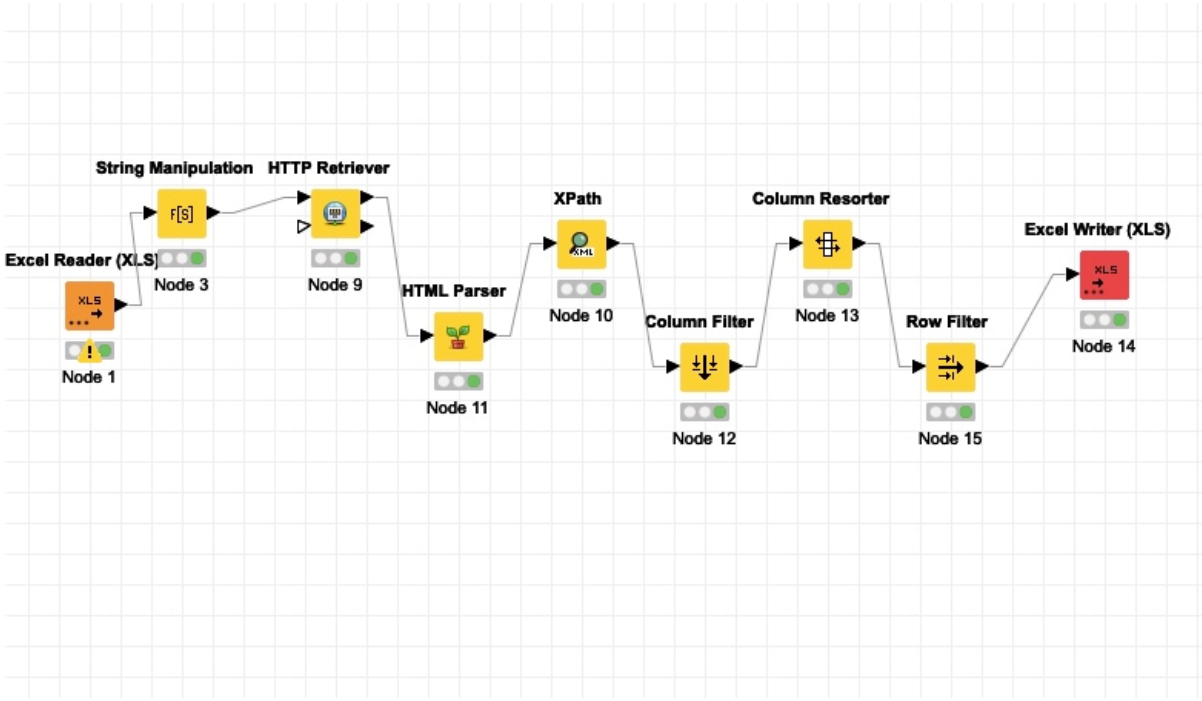

Figure 6: The Workflow for Extracting names of Proteins from UniProt Database

Node 1 – Excel Reader (XLS): loading data from the original Excel table. The extract from the original table is presented in the Table 1.

Table 1: an extract of the input data from the ADReCS-Target database

BADD_TID	ADR_ID	ADReCS ID	ADR Term	Uniprot AC	Drug_Name
R00019	BADD_A00503	01	Blood and lymphatic system disorders	P07204	Pentoxifylline
R00371	BADD_A00503	01	Blood and lymphatic system disorders	P07204	selenium
R01074	BADD_A00503	01	Blood and lymphatic system disorders	P07204	beta-carotene
R01458	BADD_A00503	01	Blood and lymphatic system disorders	P04275	selenium
R01492	BADD_A00503	01	Blood and lymphatic system disorders	P04275	beta-carotene
R01648	BADD_A00503	01	Blood and lymphatic system disorders	P05771	Glucose
R01648	BADD_A05675	14.11.02.002	Apoptosis	P05771	Glucose
R01378	BADD_A02515	01.10	Leukaemias	Q9UMN6	Etoposide
R01378	BADD_A02515	16.01	Leukaemias	Q9UMN6	Etoposide
R00364	BADD_A00770	02	Cardiac disorders	P04626	anthracyclines
R00607	BADD_A00770	02	Cardiac disorders	P00395	Zalcitabine
R01111	BADD_A00770	02	Cardiac disorders	Q9UHQ9	Zalcitabine
R00028	BADD_A00768	02.03	Cardiac arrhythmias	P35372	Morphine
R00509	BADD_A02934	02.04	Myocardial disorders	P08588	ANG II

Node 2 – String Manipulation: insertion a new column with a function to search for the corresponding protein name on the uniprot website:

join("https://www.uniprot.org/uniprot/",$Uniprot AC$) and getting an additional column with URL-Request.

Node 3 – HTTP Retriever: sending a request to the Uniprot database as binary data of each protein and getting HTTP Result column.

Node 4 – HTML Parser: parsing the HTTP Results and getting XML Documents column.

Node 5 - XPath: performing XPath queries on XML Documents column and getting two additional columns with Protein names and organism.

Node 6 – Column Filter: filtering out adjuvant columns which helped to transform the request to Uniprot.

Node 7 – Column Resorter: changing places of columns to get the protein name column just after the protein ID column.

Node 8 – Row Filter: filtering out all rows with not human proteins.

Node 9 – Excel Whiter (XLS): extracting the final table without a column with organism, because after previous steps the table has only human proteins. The final table has the following look (Table 2).

Table 2: an extract of the output Table

BADD_TID	ADR_ID	ADReCS ID	ADR Term	Uniprot AC	Protein Name	Drug_Name
R00019	BADD_A00503	01	Blood and lymphatic system disorders	P07204	Thrombomodulin	Pentoxifylline
R00371	BADD_A00503	01	Blood and lymphatic system disorders	P07204	Thrombomodulin	selenium
R01074	BADD_A00503	01	Blood and lymphatic system disorders	P07204	Thrombomodulin	beta-carotene
R01458	BADD_A00503	01	Blood and lymphatic system disorders	P04275	von Willebrand factor	selenium
R01492	BADD_A00503	01	Blood and lymphatic system disorders	P04275	von Willebrand factor	beta-carotene
R01648	BADD_A00503	01	Blood and lymphatic system disorders	P05771	Protein kinase C beta type	Glucose
R00697	BADD_A06135	01.01.03.003	Haemorrhagic diathesis	P04196	Histidine-rich glycoprotein	Asparaginase
R00659	BADD_A01943	01.01.03.004	Haemorrhagic disorder	P05164	Myeloperoxidase	aspirin
R00499	BADD_A02522	01.02.02	Leukopenias NEC	P05177	Cytochrome P450 1A2	Sulfasalazine
R01337	BADD_A02522	01.02.02	Leukopenias NEC	P05177	Cytochrome P450 1A2	Sulfasalazine
R00027	BADD_A02521	01.02.02.001	Leukopenia	P61626	Lysozyme C	Captopril
R00289	BADD_A02521	01.02.02.001	Leukopenia	P01100	Proto-oncogene c-Fos	arsenic trioxide
R00289	BADD_A02521	01.02.02.001	Leukopenia	P34932	Heat shock 70 kDa protein 4	arsenic trioxide
R00501	BADD_A02521	01.02.02.001	Leukopenia	P08236	Beta-glucuronidase	Captopril
R01304	BADD_A02521	01.02.02.001	Leukopenia	P01100	Proto-oncogene c-Fos	arsenic trioxide
R01306	BADD_A02521	01.02.02.001	Leukopenia	P34931	Heat shock 70 kDa protein 1-like	arsenic trioxide

The second small Workflow is designed to filter out similar proteins to estimate the total amount of proteins associated with cardiac adverse effects (Figure 7).

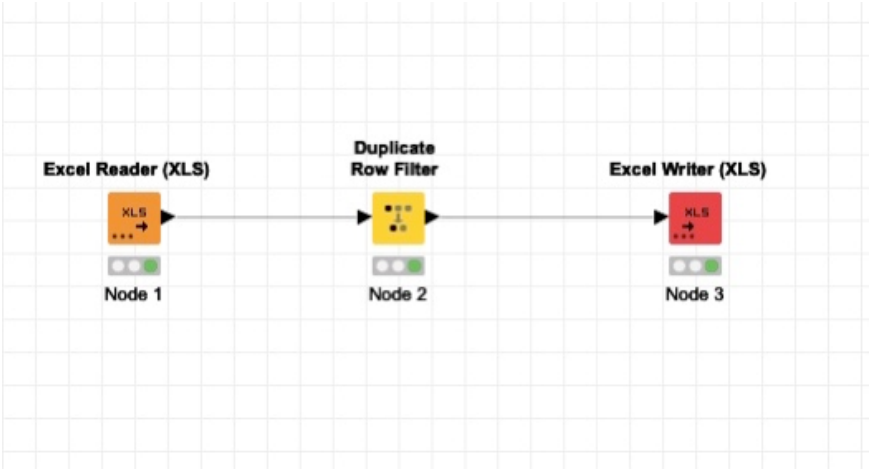

Figure 7: The Workflow for Filtrating Similarities

Node 1 – Excel Reader (XLS): loading data from the original Excel table with 02. Group "Cardiac Disorders"

Node 2 – Duplicate Row Filter: filtering out all rows, which have repeating proteins ID's

Node 3 – Excel Writer (XLS): extracting the final Excel table.

3. Results

As a result of supplementing the original table from the database ADReCS-Target with the names of proteins using the Knime Workflow, removing all non-human proteins and then isolating group 02 (SOC) cardiac disorders the table from supplement 1 was obtained.

The next step was to extract all proteins related to the same adverse reaction from the database DisGeNet using a MeSH ID to search.

Subsequently, all duplicate proteins were filtered out using the Knime workflow and the data represented in Table 3 was obtained. Black proteins were found in both databases, red were only in the ADReCS-Target database.

Table 3:The List of Proteins Related to Cardiac Disorders

Protein ID	*Protein name*	*gda Score*
P04626	Receptor tyrosine-protein kinase erbB-2	0,27
P00395	Cytochrome c oxidase subunit 1	0,1
Q9UHQ9	NADH-cytochrome b5 reductase 1	
P00568	Adenylate kinase isoenzyme 1	0,3
O43570	Carbonic anhydrase 12	
P02144	Myoglobin	0,21
P48788	Troponin I, fast skeletal muscle	
P60174	Triosephosphate isomerase	0,03
P17661	Desmin	0,16
P11021	Endoplasmic reticulum chaperone BiP	0,03
P09874	Poly [ADP-ribose] polymerase 1	0,22
O43301	Heat shock 70 kDa protein 12A	
P06276	Cholinesterase	0,3
P08684	Cytochrome P450 3A4	0,3
P07327	Alcohol dehydrogenase 1A	
P47895	Aldehyde dehydrogenase family 1 member A3	
P08254	Stromelysin-1	0,07
P02649	Apolipoprotein E	0,5
P35372	Mu-type opioid receptor	0,01
P10635	Cytochrome P450 2D6	0,3
P08172	Muscarinic acetylcholine receptor M2	0,3
P48549	G protein-activated inward rectifier potassium channel 1	
Q12809	Potassium voltage-gated channel subfamily H member 2	0,5
Q8N4C8	Misshapen-like kinase 1	
P51787	Potassium voltage-gated channel subfamily KQT member 1	0,2
P05164	Myeloperoxidase	0,4

P15382	Potassium voltage-gated channel subfamily E member 1	0,3
Q14524	Sodium channel protein type 5 subunit alpha	0,5
P08588	Beta-1 adrenergic receptor	0,6
P08183	ATP-dependent translocase ABCB1	0,03
P27487	Dipeptidyl peptidase 4	0,1

And finally, the causality between filtered proteins and cardiac disorders was manually searched in literature. For a better understanding of connections between proteins and cardiac disorders the following proteins were analyzed:

4 proteins found in both databases with the biggest GDAScore;

4 proteins found in both databases with the lowest GDAScore;

4 proteins found only in the ADReCS-Target database.

Results are represented in Table 4.

Table 4: Causality between Proteins and Adverse Cardiac Reactions

Protein ID	***Protein name***	***gda Score***	***Function***	***Causality of Adverse Cardiac Reactions***
Q9UHQ9	NADH-cytochrome b5 reductase 1		Enzyme	no direct causality found
O43570	Carbonic anhydrase 12		Enzyme	no causality found
P48788	Troponin I, fast skeletal muscle		Strukture protein	hypothetical causality of little value
P60174	Triosephosphate isomerase	0,03	Enzyme	no causality found
P11021	Endoplasmic reticulum chaperone BiP	0,03	Transporter	hypothetical causality of little value
P07327	Alcohol dehydrogenase 1A		Enzyme	no direct causality found
P02649	Apolipoprotein E	0,5	Transporter	strong causality
P35372	Mu-type opioid receptor	0,01	Receptor	not severe causality because of strong compensatory mechanisms
Q12809	Potassium voltage-gated channel subfamily H member 2	0,5	Ion channel	strong causality
Q14524	Sodium channel protein type 5 subunit alpha	0,5	Ion channel	strong causality
P08588	Beta-1 adrenergic receptor	0,6	Receprot	strong causality
P08183	ATP-dependent translocase ABCB1	0,03	Transporter	no direct causality found

4. Discussion

The following proteins were analyzed:

4.1. Apolipoprotein E

Apolipoprotein E is a multifunctional protein involved in lipid metabolism in the human body. Macrophages and hepatocytes are the main producers of ApoE in peripheral organs and tissues of the human body. The main functions of ApoE are hepatic absorption of lipoproteins, control of phlogistic and immune reactions and induction of efflux of cholesterol from macrophages in atherosclerotic plaques. This implies the obvious role of apolipoprotein in the potential for the development of cardiovascular undesirable effects [31].

The ApoE is a glycoprotein, it has a molecular weight of ~ 34 kDa and consist of 299 amino acids. It includes two domains connected by a loop region. Three existing isoforms of Apolipoprotein are known: apoE2, apoE3 and apoE4. They have different amino acids at two positions: 112 and 158. ApoE2 contains Cys in both positions, ApoE3 has Cys at the position 112 and Arg at the position 158 and is considered as the “wild” type. ApoE4 has Arg in both positions [32].

Such variations in the amino acid sequence change chemical interactions of isoforms and lead to a difference in the stability of proteins and their interactions. ApoE4 is the least stable isoform and the least friendly for cardiovascular health followed by ApoE3, and ApoE2 is the most stable one. The Cys112 is replaced by Arg112 in ApoE4, so the protein loses its ionic bond between Glu109 and Arg61. The released Arg61 interacts with Glu255 to form an additional bond between the domains. As a result, ApoE4 connects preferably to triglyceride-rich very-low-density lipoproteins, that is leading to inhibition of LDL receptors and as a result to increasing atherogenic LDL level in blood. In the ApoE3 and ApoE4 isoforms, a salt bridge is formed between Arg158 and Asp154, which is lost in ApoE2, with Cys at position 158. In ApoE2, a salt bridge is formed between Asp154 and Arg150, moving Arg150 away from the LDL receptor-binding region. This affects its binding capacity, it binds poorly to LDL receptor, that can lead to hyperproteinemia. However, this disorder occurs only in the presence of concomitant diseases such as diabetes, obesity, hypothyroidism. These conditions lead to impaired metabolism of VLDL or fewer LDL receptors, inhibiting the limited ability of apoE2 to regulate triglyceride and cholesterol-rich β-VLDL.

The understanding of the structural differences between the apoE isoforms opens up new possibilities for creating potential chemical compounds that reduce the level of the apoE4 isoform and thereby reduce the risk of cardiovascular diseases. And it also leads to an understanding of the mechanism of the undesirable effect of some existing and avoiding undesirable cardiotoxicity of potential medicines [33].

4.2. Potassium Voltage-gated Channel Subfamily H Member 2

hERG (the human *Ether-à-go-go*-Related Gene it is a gene that encodes a protein called Kv11.1, which is the alpha subunit of the potassium ion channel. This ion channel, designated hERG, plays an important role in the electronic activity of the heart. hERG modulates the bulk of one of the ion channel proteins, which removes potassium ions from cardiomyocytes. The potassium ion current plays a decisive role for the correct timing of cell membrane repolarization during cardiac action. If the ability of this channel to conduct electrical current through the cell membrane is suppressed or impaired as a result of mutations or the use of drugs, then this leads to a serious dysfunction of the heart - long QT syndrome. With an increase in current through the hERG ion channels, short QT syndrome may occur.

A surprisingly diverse group of drugs, such as class 1A and III antiarrhythmics, antipsychotics, some antibiotics, and others, can cause arrhythmias due to blockade of hERG channels. This unwanted effect is a common cause of failure of a potential drug in preclinical safety studies [34].

This is why testing of new compounds for proarrhythmic potential is concentrated nowadays on preventing activity on the hERG K + channel. The most common hERG analytical test involve ligand binding and electrophysiology. These assays can also be accompanied by measurements of activity on other ion channels that play a role in the functioning of the heart, and detailed measurements of the action potential and repolarization of cardiac tissue. Ultimately, a comprehensive assessment of the risk of proarrhythmic potential takes place based on the totality of the activity of a potential drug on ion channels. This estimate is the best predictor of the risk of developing adverse effects on the heart in vivo [35].

4.3. Sodium Channel Protein Type 5 Subunit Alpha

The subunit alpha of the sodium channel protein type 5 - it is a large transmembrane protein of the voltage-gated sodium channel. In the human body the protein is coded by the gen SCN5A, which is situated primarily in the heart muscle. This protein affords a quick inflow of Na+ ions through the cell membrane. This leads to a phase of rapid depolarization of the heart action potential. Thus, NaV1.5 plays an essential role in the impulse's conduction through the heart muscle. The conformational structure of the channel depends on time and voltage and predetermines the opened or closed state of the channel. The channel pore consists of the four domains. Sodium ions flow through the part formed by the S5 and S6 segments, the remaining segments are responsible for the voltage change. The segment S4 plays a determinative role, it moves outward and opens NaV1.5 channel after the cell-membrane depolarization under the influence of a stimulation pulse conducted by a neighboring cell. This leads to the action potential generation. Under physiological conditions, the channel remains closed until the cell membrane repolarizes [36].

The cardiac sodium channel NaV1.5 is a target in the pharmacological therapy of arrhythmias. A large group of antiarrhythmic drugs are classic sodium channel blockers. There are also other drugs such as propofol, dexmedetomidine, 5-HT3 receptor antagonists, and local anesthetics, which modify the sodium channel and can cause prolongation of the QRS interval and arrhythmia as a side effect [37,38]. Thus, preclinical studies of the effects of potential drugs on the sodium channel can provide insight into possible dangerous adverse effects on the heart.

4.4. Beta-adrenergic Receptor

Beta-adrenergic receptors of the heart refer to the family of G-protein-coupled receptors and are important in the regulation of cardiac functions such as heart rate, strength, and cardiac conduction. There are three subtypes of beta-adrenergic receptors: beta1, beta2, and beta3. The receptor consists of one extracellular N-terminal domain and one intracellular C-terminal tail, three loops inside and three loops outside the cell and seven transmembrane domains. The main physiological stimulants of beta-adrenergic receptors are catecholamines. The receptor is activated through the accumulation of the second messenger cAMP and the activation of protein kinase A

(PKA). Protein kinase A phosphorylates the beta-adrenergic receptor and thereby causes uncoupling and desensitization of the receptor [39].

Uncoupling of the receptor causes internalization of the receptor, that is, the receptor moves from the membrane to the cytosol of the cell. With chronic stimulation, receptor suppression occurs, but the expression of the receptor decreases as a compensatory mechanism. In addition to a decrease in the expression of beta-adrenergic receptors in such patients, the expression of the inhibitory G-protein is increased. These changes can be caused by an increased content of catecholamines in the blood, as well as long-term treatment with beta-adrenergic agonists. Due to severe side effects such as vascular collapse, arrhythmia, hyperglycemia, excitation of the central nervous system, tremors, the latter are mainly used by inhalation [39]. Thus, testing the interaction of potential pharmacologically active substances with beta-adrenergic receptors in preclinical trials can help to avoid cardiotoxicity and other serious undesirable effects.

4.5. Triosephosphate Isomerase

Triose phosphate isomerase is an enzyme that forces the isomerization of glyceraldehyde 3-phostphate and dihydroxyacetone phosphate. This chemical reaction take part in glycolysis, gluconeogenesis and biosynthesis of fat acids. TPI catalyzes an intramolecular redox reaction, namely the isomerization of ketose to aldose via the cis-endiol intermediate [40].

The enzyme consists of two identical proteins and is coded by the TPI1 gene. A mutation in this gene is associated with a severe autosomal recessive hereditary disease - triose phosphate isomerase deficiency. This disease is characterized by anemia, neurodegeneration, impaired musculoskeletal function, increased susceptibility to infections and muscle weakness, which negatively affects the functioning of the heart and respiration [41].

TPI is the target of some research to develop cell-oriented pharmacotherapeutic schemas for treating various diseases such as cancer and probably COVID-19 [42]. In addition, there is evidence of a decrease in the level of triose phosphate isomerase in skeletal muscle as a result of treatment with zalcitabine – a nucleoside analog reverse-transcriptase inhibitor (NRTI). Zalcitabine causes short-term cardiac side effects such as prolonged RR, PR and QT intervals and impaired energy metabolism in the heart [43]. However, there is no evidence of a direct link between reduced enzyme levels and impaired heart function.

4.6. Endoplasmatic Reticulum Chaperone BIP

Binding immunoglobulin protein (BiP) named also (GRP-78) or heat shock 70 kDa protein 5 (HSPA5) is a molecular chaperone situated in the endoplasmic reticulum of human cells. This protein is coded by the *HSPA5* gene. The protein binds the newly synthesized proteins in the EP and keeps them in a form, which passes for subsequent folding. BiP is also an important component of the transport mechanism and plays a role in the clearance of EP proteins across the membrane that are intended to be degraded by proteasomes. BiP is a widely distributed protein in all growing tissues [44].

Currently there is some research on the role of BiP in the development of cardiac dysfunction and atherosclerosis. As a result of these studies, it was found that overexpression of BiP reduces damage and death of cardiomyocytes, and also suppresses the development or progression of atherosclerosis by alleviating EP stress, preventing apoptosis of vascular endothelial cells, inhibiting the activation of genes responsible for cholesterol / triglyceride biosynthesis, and suppressing the procoagulant potential of cells [45]. There is also some data of the hypothesized role of a decreased amount of BiP in skeletal muscle in the development of the short-term cardiotoxicity, the most common side effect of zalcitabine [43].

4.7. Mu-type Opioid Receptor

The mu opioid receptor refers to the G protein coupled receptors family (GPCR). MOR signaling includes the modification of inhibitory G-proteins and as a result result the dissociation of the heterotrimeric G-protein complex. The release of the Gα subunit inhibits adenyl cyclase (AC), and the release of the Gβγ subunits activates K+ channels and inhibits voltage-gated Ca2+ channels (VGCC), thereby reducing the level of cAMP [46].

Opioid receptors play an important role in the regulation of the cardiovascular system, they are involved in modulation of electrophysiological function, heart rate, myocardial inotropy, cell resistance to stress and vascular function. The opioid system is also involved in the development of the cardiovascular system, adaptation to trauma and the consequences of old age [23].

Modulation of opioid receptor induces cytoprotective conditions in the myocardium and makes these receptors an attractive target for pharmacological research to protect the

heart from serious heart diseases. Opioid system takes part in various cardiovascular diseases such as hypertension, hyperlipidemia, myocardial ischemia, coronary artery disease and congestive heart failure, despite the mechanism of this role of receptors is still not fully understood. Biochemical, physiological, pharmacological and behavioral studies were carried out in in vitro and in vivo systems, experimental models of hypertension and in people with hypertension. While biochemical and pharmacological studies in animals show the presence of opioid receptors at strategic sites of cardiovascular control and a strong cardiovascular response to modulating agents, no sequential blockade or serious complications of hypertension have been identified in experimental animals or humans. One possible explanation for this phenomenon may be the enormous redundancy of the systems that regulate blood pressure, since a blockage of one system still leaves many other systems fully capable of quickly compensating for the eliminated system [24]. Hence, it can be concluded that modulation of the opioid receptor by a potential drug substance can lead to undesirable reactions in the heart, but due to the activation of compensatory mechanisms, these reactions will not be severe.

4.8. ATP-dependent Translocase ABCB1

Multidrug resistance protein (MDR1) is a protein in the cell membrane of animal, fungal and bacterial cells. It is also called PGP pump, where PGP stands for P-glycoprotein. It is an active carrier that pumps toxic substances out of the cell when ATP is consumed. MDR1 is a member of the class B family of multidrug-resistant ABC transporter proteins. In humans, protein is expressed in the brain, liver, kidneys, and small intestine. [25]

The MDR1 pump can perform the following functions:

- removal of cytostatics from tumor cells;
- removal of the antibiotic from bacterial cells;
- removal of neurotoxins from brain cells through the blood-brain barrier into the bloodstream for subsequent metabolism and others [26].

Thus, MDR1 can have a significant effect on the bioavailability of oral drugs and, as a result, cause unwanted side effects, including cardiotoxicity. However, no direct link has been found between protein expression and adverse cardiac effects. This outlines that interaction with P-GP per se does not cause cardiotoxicity, but that PGP is involved in drug-drug interactions, which might lead to toxic effects.

4.9. NADH-cytochrome b5 reductase 1

Cytochrome b5 reductase is an enzyme that belongs to the flavoprotein family and is represented in the human body by two isoforms found in different tissues and cells. The amphipathic microsomal isoform is produced in all types of cells with the exception of erythrocytes and consists of two domains: the hydrophobic domain attached to the membrane and the catalytic hydrophilic domain. Accordingly, the second soluble isoform of the enzyme is produced in erythrocytes and consists only of the catalytic domain.

The main function of cytochrome b5 reductase is to transfer reducing equivalents from NADH (biological electron donor) to cytochrome b5 molecules via FAD. A special function of the soluble isoform in erythrocytes is the reduction of methemoglobin to hemoglobin. Deficiency of the autosomal cytochrome b5 reductase gene causes congenital methemoglobinemia associated with the accumulation of Fe^{3+} ions in the body [8].

This enzyme is of scientific interest, as it takes part in the metabolism of xenobiotics. Pharmacogenetic variability of the enzyme can affect the concentration and half-life of drugs and their metabolites, which may be the reason for the insufficient therapeutic effect of the drug or the occurrence of undesirable effects. Hence, it can be concluded that as a result of insufficient or overexpression of cytochrome b5 reductase in the human body, undesirable effects on the heart may occur as a result of drug metabolism, but not due to a direct relationship between the expression of the enzyme in tissues with the function of the heart muscle [9].

4.10. Carbonic Anhydrase XII

Carbonic anhydrases (CA) are enzymes that catalyze the hydration and dehydration of carbon dioxide. Depending on their location in the cell, CAs are subdivided into four different groups: membrane-associated, mitochondrial, cytosolic, and secretory. All isoforms of the enzyme differ in activity and, from a pharmacological point of view, in the degree of inhibition by CA inhibitors.

CAXII is a membrane associated isoform and is a glycoprotein. The presence of histidine residues and disulfide bridges play an important role in the functioning of the enzyme. Olisaccharide protein residues do not affect enzymatic function.

CAXII is a tumor marker for human cancer. Expression of this isoform can be caused by hypoxia in breast tumors, which is an indicator of a low degree of disease and helps to make a positive prognosis of the course of the disease. CAXII is also seen in kidney and brain tumors. Scientific research is currently underway to investigate the structure and function of CAXII and to use this knowledge in effective anticancer therapy [10].

4.11. Troponin I, fast skeletal muscle

Troponin I (TnI) is an inhibitory subunit of the troponin complex, which also includes cTnT, a tropomyosin binding subunit, and calcium ions. The troponin complex performs a function in the calcium-dependent regulation of muscle relaxation and contraction and is located in the thin filaments of the sarcomere of striated muscles. In the human body, 3 isoforms of TnI are isolated: the first is found in slow skeletal muscles, the second in fast skeletal muscles, and the third in the heart muscle.

TnI of skeletal and cardiac muscles are markers of muscle tissue damage and are widely used in laboratory diagnostics. In particular, the determination of cardiac TnI plays a huge role in the diagnosis of myocardial infarction [11].

In studies of the cardiotoxicity of the anthracycline antibiotic doxorubicin was found a decrease in the expression of genes specific for the heart muscle, including troponin I. These changes in gene expression entail myopathy typical for doxorubicin, which limits its use in cancer therapy. Hence, it’s possible to conclude that it makes sense to test the effect of potential drugs on the expression of troponin I and other genes of the heart muscle in preclinical trials in order to avoid the occurrence of serious adverse effects on the heart [12].

4.12. Alcohol dehydrogenase 1A

Alcohol dehydrogenase is an well known enzyme in the human body whose main function is to oxidize ethanol. Many isoforms of ADH are known, which are located in different tissues and organs and exhibit genetic polymorphism. As a result, people of different ethnic groups react differently to alcohol and have a different predisposition to alcoholism and the development of alcohol-related diseases [13].

Diseases include, among others, complex dysfunctions of the cardiovascular system, such as arterial hypertension, atherosclerosis, cardiomyomathy, coronary heart disease up to stroke.

Although the dose and frequency of alcohol consumption play a major role in the development of cardiovascular and other diseases, the patient's genetic and physiological characteristics should also be taken into account [14]. The study of the effect of potential drugs on alcohol dehydrogenase in preclinical trials would help to avoid serious undesirable effects, especially in patients with alcohol dependence.

5. Conclusion

Modern medicine uses a large number of different computer technologies to develop new drugs. At the stage of preclinical testing of a potential pharmacologically active substance, its toxicity and safety are assessed, among other things, by analyzing various databases containing information on the connection between biological target molecules and physiological processes in the human body. The creation of such databases is accompanied by great difficulties, among which the main ones are a huge number of potential targets for the action of pharmacologically active substances, insufficient knowledge about some targets and their functions in the human body, as well as the problematic validation of toxicity study methods when using several databases.

Due to the large number of databases and the lack of validated criteria for including certain molecular targets in the databases, information on the causal relationship between target molecules and adverse drug reactions in the human body should be critically assessed and analyzed. To solve this problem, analytic platforms such as KNIME are used to sort, organize and analyze large amounts of data by creating workflows. Ultimately, the more the safety and toxicological profile of a new drug is studied at the preclinical stage, the more likely is that at the stage of clinical trials there will be no serious adverse effects due to which the drug cannot be registered, which will help reduce costs on the development of new drugs and save time.

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Bibliography

[1] „Pharmig | Arzneimittelforschung & Entwicklung" Access via https://www.pharmig.at/arzneimittel/forschung-entwicklung/ on 30.03.2021

[2] Arwa B. Raies, Vladimir B. Bajic "In silico toxicology: computational methods for the prediction of chemical toxicity", Wiley Interdiscip Rev Comput Mol Sci, 2016 Mar;6(2):147-172, doi: 10.1002/wcms.1240. Epub 2016 Jan 6.

[3] Jamie J Coleman, Sarah K Pontefract "Adverse drug reactions", Clin Med (Lond). 2016 Oct; 16(5): 481-485, doi: 10.7861/clinmedicine.16-5-481

[4] "ICH | MedDRA Medical Dictionary for Regulatory Activities", Access via https://www.ich.org/page/meddra on 27.03.2021

[5] MedDRA Browser "MedDRA Hierarchy", Access via https://www.meddra.org/how-to-use/basics/hierarchy on 27.03.2021

[6] "U.S. National Library of Medicine", Access via https://meshb.nlm.nih.gov/ on 28.03.2021

[7] "World Health Organisation | Cardiovascular diseases (CVDs)", Access via https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds) on 28.03.2021

[8] Fatemeh Elahian, Zargham Sepehrizadeh, Bahareh Moghimi, Seyed Abbas Mirzaei "Human cytochrome b5 reductase: structure, function, and potential applications", Crit Rev Biotechnol. 2014 Jun; 34(2):134-43.
doi: 10.3109/07388551.2012.732031.Epub 2012 Nov 1

[9] Joseph R Kurian, Sunil U Bajad, Jackie L Miller, Nathaniel A Chin, Lauren A Trepanier "NADH cytochrome b5 reductase and cytochrome b5 catalyze the microsomal reduction of xenobiotic hydroxylamines and amidoximes in humans", J Pharmacol Exp Ther. 2004 Dec;311(3):1171-8.
doi: 10.1124/jpet.104.072389. Epub 2004 Aug 9.

[10] Abdul Waheed, William S. Sly and Edward A. Doisy "Carbonic Anhydrase XII Functions in Health and Disease", Gene. 2017 Aug 5; 623: 33–40. Published online 2017 Apr 19. doi: 10.1016/j.gene.2017.04.027

[11] Yuanhua Cheng and Michael Regnier "Cardiac Troponin Structure-Function and the Influence of Hypertrophic Cardiomyopathy Associated Mutations on Modulation of Contractility", Arch Biochem Biophys. 2016 Jul 1; 601: 11–21.
Published online 2016 Feb 4. doi: 10.1016/j.abb.2016.02.004

[12] H Ito, S C Miller, M E Billingham, H Akimoto, S V Torti, R Wade, R Gahlmann, G Lyons, L Kedes, F M Torti "Doxorubicin selectively inhibits muscle gene expression in cardiac muscle cells in vivo and in vitro", Proc Natl Acad Sci U S A. 1990 Jun;87(11):4275-9. doi: 10.1073/pnas.87.11.4275.

[13] S J Yin "Alcohol dehydrogenase: enzymology and metabolism", Alcohol Alcohol Suppl. 1994;2:113-9.

[14] Mariann R. Piano "Alcohol's Effects on the Cardiovascular System", Alcohol Res. 2017; 38(2): 219–241.

[15] Shailiza Singh, Balwant Kumar Malik, Durlabh Kumar Sharma "Molecular drug targets and structure based drug design: A holistic approach", Bioinformation. 2006; 1(8): 314–320. Published online 2006 Dec 23. doi: 10.6026/97320630001314

[16] Gregory J. Kaczorowski, Owen B. McManus, Birgit T. Priest, and Maria L. Garcia "Ion Channels as Drug Targets: The Next GPCRs", J Gen Physiol. 2008 May; 131(5): 399–405. doi: 10.1085/jgp.200709946

[17] "U.S. National Library of Medicine", Access via https://medlineplus.gov on 28.03.2021

[18] “DocCheck Flexikon”, Access via https://flexikon.doccheck.com/de on 28.03.2021

[19] “National Heart, Lung, and Blood Institute”, Access via https://www.nhlbi.nih.gov on 28.03.2021

[20] Filippo Crea, Gaetano Antonio Lanza“Myocardial ischaemia: definition and causes”, Access via https://oxfordmedicine.com/view/10.1093/med/9780198784906.001.0001/med-9780198784906-chapter-327 on 28.03.2021

[21] D Evéquoz**,** M Zuber**,** P Erne „Sudden cardiac death: definition, mechanisms and risk factors”, Praxis (Bern 1994). 1996 Feb 13;85(7):188-96, PMID: 8701183

[22] Johnny Chahine; Heidi Alvey “Left Ventricular Failure”, Access via https://www.ncbi.nlm.nih.gov/books/NBK537098/ on 28.03.2021

[23] John P Headrick, Salvatore Pepe, Jason N Peart “Non-analgesic effects of opioids: cardiovascular effects of opioids and their receptor systems”, Curr Pharm Des. 2012;18(37):6090-100. doi: 10.2174/138161212803582360.

[24] G Feuerstein, A L Siren „The opioid peptides. A role in hypertension?”, Hypertension. 1987 Jun;9(6):561-5. doi: 10.1161/01.hyp.9.6.561.

[25] “UniProtKB P08183 (MDR1_HUMAN) | UniProt”, Access via https://www.uniprot.org/uniprot/P08183 on 16.03.2021

[26] “Wenn Arzneistoffe Transportproteine beeinflussen | Pharmazeutische Zeitung“, Access via https://www.pharmazeutische-zeitung.de/ausgabe-502006/abda-datenbank-wenn-arzneistoffe-transportproteine-beeinflussen/ on 18.02.2021

[27] Li-Hong Huang, Qiu-Shun He, Ke Liu, Jiao Cheng, Min-Dong Zhong, Lin-Shan Chen, Li-Xia Yao and Zhi-Liang Ji “ ADReCS-Target: target profiles for aiding drug safety research and application”, Nucleic Acids Research, 2018, Vol. 46, Database issue D911–D917, doi: 10.1093/nar/gkx899

[28] Janet Pin˜ ero, Juan Manuel Ram´ırez-Anguita, Josep Sau¨ch-Pitarch, Francesco Ronzano, Emilio Centeno, Ferran Sanz and Laura I. Furlong “The DisGeNET knowledge platform for disease genomics: 2019 update”, Nucleic Acids Research, 2020, Vol. 48, Database issue D845–D855, doi: 10.1093/nar/gkz1021

[29] “DisGeNet Browser – About”, Access via https://www.disgenet.org/dbinfo on 25.03.2021

[30] “The Knime | Getting Started Guide”, Access via https://www.knime.com/getting-started-guide on 24.03.2021

[31] Kirsty Greenow, Nigel J Pearce, Dipak P Ramji “The key role of apolipoprotein E in atherosclerosis”, J Mol Med (Berl). 2005 May;83(5):329-42.
doi: 10.1007/s00109-004-0631-3.Epub 2005 Apr 13.

[32] A David Marais “Apolipoprotein E in lipoprotein metabolism, health and cardiovascular disease”, Pathology. 2019 Feb;51(2):165-176.
doi: 10.1016/j.pathol.2018.11.002.Epub 2018 Dec 28.

[33] Robert W Mahley “Apolipoprotein E: from cardiovascular disease to neurodegenerative disorders”, J Mol Med (Berl). 2016 Jul;94(7):739-46.
doi: 10.1007/s00109-016-1427-y.Epub 2016 Jun 9.

[34] Sanguinetti MC, Tristani-Firouzi M (March 2006). "hERG potassium channels and cardiac arrhythmia". Nature. 440 (7083): 463 9. doi:10.1038/nature04710. PMID 16554806. S2CID 929837

[35] Mark R Bowlby, Ravi Peri, Howard Zhang, John Dunlop “hERG (KCNH2 or Kv11.1) K+ channels: screening for cardiac arrhythmia risk”, Curr Drug Metab. 2008 Nov;9(9):965-70. doi: 10.2174/138920008786485083.

[36] Chen-Izu Y, Shaw RM, Pitt GS, Yarov-Yarovoy V, Sack JT, Abriel H, Aldrich RW, Belardinelli L, Cannell MB, Catterall WA, Chazin WJ, Chiamvimonvat N, Deschenes I, Grandi E, Hund TJ, Izu LT,

Maier LS, Maltsev VA, Marionneau C, Mohler PJ, Rajamani S, Rasmusson RL, Sobie EA, Clancy CE, Bers DM (March 2015). "Na+ channel function, regulation, structure, trafficking and sequestration", J Physiol. 2015 Mar 15;593(6):1347-60. doi: 10.1113/jphysiol.2014.281428.

[37] Carsten Stoetzer, Svenja Reuter, Thorben Doll, Nilufar Foadi, Florian Wegner, Andreas Leffler "Inhibition of the cardiac Na^+ channel α-subunit Nav1.5 by propofol and dexmedetomidine", Naunyn Schmiedebergs Arch Pharmacol. 2016 Mar;389(3):315-25. doi: 10.1007/s00210-015-1195-1. Epub 2015 Dec 15.

[38] Mariet P Van't Klooster, Nilufar Foadi, Axel Hage, Carsten Stoetzer, Florian Wegner, Mirjam Eberhardt, Andreas Leffler "Local-anesthetic like inhibition of the cardiac sodium channel Nav1.5 α-subunit by 5-HT3 receptor antagonists", Eur J Pharmacol. 2016 Oct 15;789:119-126. doi: 10.1016/j.ejphar.2016.07.020

[39] Gerd Wallukat "The beta-adrenergic receptors", Herz. 2002 Nov;27(7):683-90. doi: 10.1007/s00059-002-2434-z.

[40] "TPI1 triosephosphate isomerase 1 [Homo sapiens (human)]", Gene ID: 7167, updated on 7-Mar-2021, Access via https://www.ncbi.nlm.nih.gov/gene?Db=gene&Cmd=ShowDetailView&TermToSearch=7167 on 12.02.2021

[41] "Triose phosphate-isomerase deficiency | Orphanet", Access via https://www.orpha.net/consor/cgi-bin/OC_Exp.php?Lng=GB&Expert=868 on 12.02.2021

[42] Sergio Enríquez-Flores, Luis Antonio Flores-López, Itzhel García-Torres, Ignacio de la Mora-de la Mora, Nallely Cabrera, Pedro Gutiérrez-Castrellón, Yoalli Martínez-Pérez, Gabriel López-Velázquez "Deamidated Human Triosephosphate Isomerase is a Promising Druggable Target", Biomolecules. 2020 Jul 15;10(7):1050. doi: 10.3390/biom10071050.

[43] G Skuta, G M Fischer, T Janaky, Z Kele, P Szabo, J Tozser, B Sumegi „Molecular mechanism of the short-term cardiotoxicity caused by 2',3'-dideoxycytidine (ddC): modulation of reactive oxygen species levels and ADP-ribosylation reactions", Biochem Pharmacol. 1999 Dec 15;58(12):1915-25.cdoi: 10.1016/s0006-2952(99)00282-8.

[44] M. P. Mayer and B. Bukau "Hsp70 chaperones: Cellular functions and molecular mechanism", Cell Mol Life Sci. 2005 Mar; 62(6): 670–684. doi: 10.1007/s00018-004-4464-6

[45] Min Ni, Amy S Lee "ER chaperones in mammalian development and human diseases", FEBS Lett. 2007 Jul 31;581(19):3641-51. doi: 10.1016/j.febslet.2007.04.045. Epub 2007 Apr 25.

[46] Adrian W. R. Serohijos, Shuangye Yin, Feng Ding, Josee Gauthier, Dustin G. Gibson, William Maixner, Nikolay V. Dokholyan and Luda Diatchenko "Structural basis for mu-opioid receptor binding and activation", Structure. 2011 Nov 9; 19(11): 1683–1690. doi: 10.1016/j.str.2011.08.003

Supplement 1: *Filtered Cardiac Disorders from ADReCs-Target Database*

ADReCS ID	*ADR name*	*Protein ID*	*Protein name*	*Drug name*
02	Cardiac disorders	P04626	Receptor tyrosine-protein kinase erbB-2	anthracyclines
02	Cardiac disorders	P00395	Cytochrome c oxidase subunit 1	Zalcitabine
02	Cardiac disorders	Q9UHQ9	NADH-cytochrome b5 reductase 1	Zalcitabine
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	Formestane
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	Exemestane
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	fadrozole hydrochloride
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	atamestane
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	Aminoglutethimide
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	Anastrozole
02.01.01.001	Cardiovascular disorder	O43570	Carbonic anhydrase 12	Acetazolamide
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	vorozole
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	Letrozole
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	liarozole hydrochloride
02.01.01.001	Cardiovascular disorder	P00568	Adenylate kinase isoenzyme 1	rogletimide
02.01.01.002	Cardiotoxicity	P02144	Myoglobin	Zalcitabine
02.01.01.002	Cardiotoxicity	P48788	Troponin I, fast skeletal muscle	Doxorubicin
02.01.01.002	Cardiotoxicity	P60174	Triosephosphate isomerase	Zalcitabine
02.01.01.002	Cardiotoxicity	P17661	Desmin	Zalcitabine
02.01.01.002	Cardiotoxicity	P48788	Troponin I, fast skeletal muscle	Cyclophosphamide
02.01.01.002	Cardiotoxicity	P11021	Endoplasmic reticulum chaperone BiP	Zalcitabine
02.01.01.002	Cardiotoxicity	P09874	Poly [ADP-ribose] polymerase 1	Zalcitabine
02.01.01.002	Cardiotoxicity	O43301	Heat shock 70 kDa protein 12A	Zalcitabine
02.01.02.004	Dizziness	P06276	Cholinesterase	eptastigmine
02.01.02.004	Dizziness	P06276	Cholinesterase	rivastigmine
02.01.02.004	Dizziness	P06276	Cholinesterase	physostigmine
02.01.02.004	Dizziness	P06276	Cholinesterase	donepezil
02.01.02.004	Dizziness	P06276	Cholinesterase	metrifonate
02.01.02.004	Dizziness	P06276	Cholinesterase	galantamine
02.01.02.004	Dizziness	P06276	Cholinesterase	tacrine
02.01.02.008	Syncope	P08684	Cytochrome P450 3A4	Ritonavir
02.01.03	Dyspnoeas	P07327	Alcohol dehydrogenase 1A	pyrazole
02.01.03	Dyspnoeas	P47895	Aldehyde dehydrogenase family 1 member A3	Disulfiram

02.02.02.001	Acute myocardial infarction	P08254	Stromelysin-1	Simvastatin
02.02.02.001	Acute myocardial infarction	P08254	Stromelysin-1	Pravastatin
02.02.02.001	Acute myocardial infarction	P08254	Stromelysin-1	Atorvastatin
02.02.02.001	Acute myocardial infarction	P08254	Stromelysin-1	Fluvastatin
02.02.02.002	Angina pectoris	P08254	Stromelysin-1	Simvastatin
02.02.02.002	Angina pectoris	P08254	Stromelysin-1	Pravastatin
02.02.02.002	Angina pectoris	P08254	Stromelysin-1	Atorvastatin
02.02.02.002	Angina pectoris	P08254	Stromelysin-1	Fluvastatin
02.02.02.008	Myocardial ischaemia	P02649	Apolipoprotein E	Pravastatin
02.02.02.008	Myocardial ischaemia	P02649	Apolipoprotein E	Atorvastatin
02.02.02.008	Myocardial ischaemia	P02649	Apolipoprotein E	Fluvastatin
02.02.02.008	Myocardial ischaemia	P02649	Apolipoprotein E	Simvastatin
02.03	Cardiac arrhythmias	P35372	Mu-type opioid receptor	Morphine
02.03.01.002	Atrioventricular block	P08684	Cytochrome P450 3A4	Amitriptyline
02.03.01.002	Atrioventricular block	P08684	Cytochrome P450 3A4	Amitriptyline
02.03.01.004	Atrioventricular block first degree	P10635	Cytochrome P450 2D6	Carvedilol
02.03.02.001	Arrhythmia	P10635	Cytochrome P450 2D6	Amitriptyline
02.03.02.002	Bradycardia	P08172	Muscarinic acetylcholine receptor M2	xanomeline
02.03.02.002	Bradycardia	P08172	Muscarinic acetylcholine receptor M2	Carbamylcholine
02.03.02.002	Bradycardia	P08684	Cytochrome P450 3A4	Propranolol
02.03.02.002	Bradycardia	P08684	Cytochrome P450 3A4	Propranolol
02.03.02.002	Bradycardia	P08172	Muscarinic acetylcholine receptor M2	sabcomeline
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Pimozide
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Clonidine
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Clonidine
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Thioridazine
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Pimozide
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Haloperidol
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Haloperidol
02.03.03.010	Sinus tachycardia	P48549	G protein-activated inward rectifier potassium channel 1	Thioridazine
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Cisapride
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Quinidine
02.03.04.005	Torsade de pointes	Q8N4C8	Misshapen-like kinase 1	Cisapride
02.03.04.005	Torsade de pointes	Q8N4C8	Misshapen-like kinase 1	Quinidine
02.03.04.005	Torsade de pointes	P51787	Potassium voltage-gated channel subfamily KQT member 1	Terfenadine

02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Terfenadine
02.03.04.005	Torsade de pointes	Q8N4C8	Misshapen-like kinase 1	Erythromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Cisapride
02.03.04.005	Torsade de pointes	P51787	Potassium voltage-gated channel subfamily KQT member 1	Cisapride
02.03.04.005	Torsade de pointes	P51787	Potassium voltage-gated channel subfamily KQT member 1	Erythromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Erythromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Erythromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Clarithromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Clarithromycin
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Terfenadine
02.03.04.005	Torsade de pointes	Q12809	Potassium voltage-gated channel subfamily H member 2	Quinidine
02.03.04.005	Torsade de pointes	P51787	Potassium voltage-gated channel subfamily KQT member 1	Clarithromycin
02.03.04.005	Torsade de pointes	Q8N4C8	Misshapen-like kinase 1	Clarithromycin
02.03.04.005	Torsade de pointes	P51787	Potassium voltage-gated channel subfamily KQT member 1	Quinidine
02.03.04.005	Torsade de pointes	Q8N4C8	Misshapen-like kinase 1	Terfenadine
02.03.04.008	Ventricular fibrillation	P05164	Myeloperoxidase	Ibuprofen
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Tikosyn
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Propranolol
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Quinidine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Tikosyn
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Verapamil
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Diltiazem
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Diltiazem
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Tambocor
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Covera
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Quinidine
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Ethmozine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Toprol XL

02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Pronestyl
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Diltiazem
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Tambocor
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Procanbid
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Sotalol
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Quinidine
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Amiodarone
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Quinidine
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Propafenone
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Propafenone
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Ethmozine
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Covera
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Mexitil
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Covera
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Propafenone
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Terfenadine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Sotalol
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Tenormin
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Ethmozine
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Sotalol
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Verapamil
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Pacerone
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Amiodarone
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Tikosyn
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Propranolol
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Toprol XL
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Norpace
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Tenormin

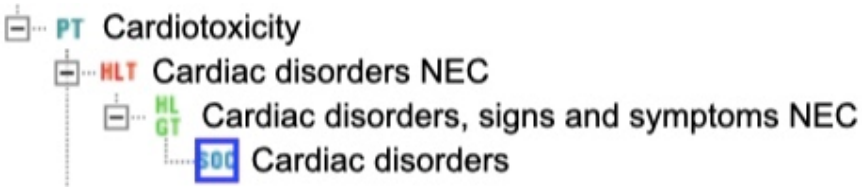
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Disopyramide
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Quinidine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Terfenadine
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Propranolol
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Hydrochlorothiazide
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Terfenadine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Covera
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Tambocor
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Tikosyn
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Terfenadine
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Procanbid
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Tenormin
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Pronestyl
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Mexitil
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Amiodarone
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Pronestyl
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Disopyramide
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Tocainide
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Diltiazem
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Diltiazem
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Sotalol
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Propranolol
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Pacerone
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Toprol XL
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Tocainide
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Verapamil
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Hydrochlorothiazide

02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Mexitil
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Tocainide
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Diltiazem
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Diltiazem
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Lopressor
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Verapamil
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Amiodarone
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Diltiazem
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Procanbid
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Ethmozine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Tambocor
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Hydrochlorothiazide
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Tenormin
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Procanbid
02.03.04.016	Sudden cardiac death	P15382	Potassium voltage-gated channel subfamily E member 1	Pacerone
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Quinidine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Quinidine
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Pronestyl
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Pacerone
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Disopyramide
02.03.04.016	Sudden cardiac death	Q12809	Potassium voltage-gated channel subfamily H member 2	Toprol XL
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Quinidine
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Mexitil
02.03.04.016	Sudden cardiac death	P51787	Potassium voltage-gated channel subfamily KQT member 1	Tocainide
02.03.04.016	Sudden cardiac death	Q14524	Sodium channel protein type 5 subunit alpha	Propafenone
02.04	Myocardial disorders	P08588	Beta-1 adrenergic receptor	ANG II
02.04.02.011	Left ventricular dysfunction	P08183	ATP-dependent translocase ABCB1	Carvedilol
02.05.01.001	Cardiac failure	P27487	Dipeptidyl peptidase 4	saxagliptin

Supplement 2: *Terminology of Cardiac Disorders (all figures are taken from 5)*

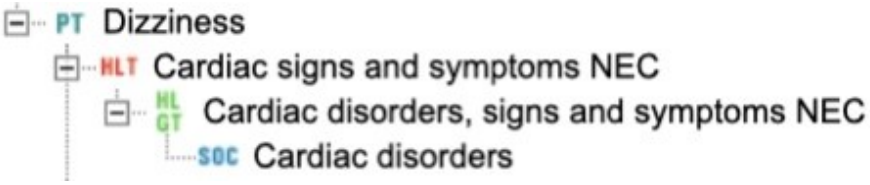
MeSH: D066126

Cardiotoxicity – it's damage of the heart muscle or its function resulting from chemical poisoning, radiation or the use of drugs such as chemotherapy, immunotherapy, cytostatics and others [6].



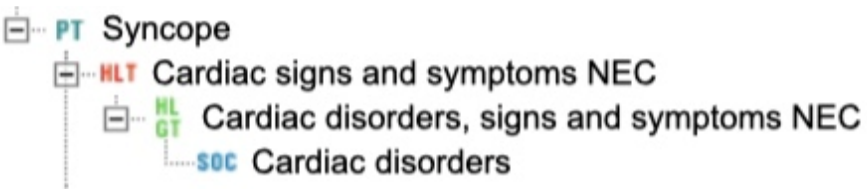
MeSH: D004244

Dizziness - is a condition or group of symptoms characterized by dizziness, nausea, spatial disorientation, sensation of movement in the environment. This condition is usually associated with a drop in blood pressure, dehydration, diseases of the inner ear and others [17].



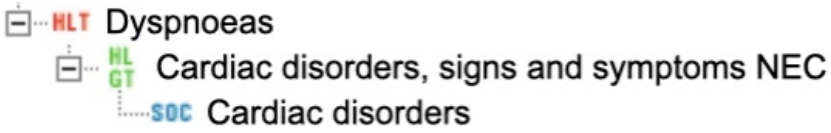
MeSH: D013575

Syncope - is a accidental loss of consciousness. It usually occurs as a result of a blood pressure decrease and, as a result, a decrease of the blood flow to the brain. Lightheadedness is characterized by dizziness, nausea, increased sweating, pallor of the skin, darkening of the eyes, and loss of muscle control and as a result falling down. The most common causes can be rapid changes in body position from horizontal to vertical, low blood sugar level, high ambient temperatures and dehydration, stress and medication [17].



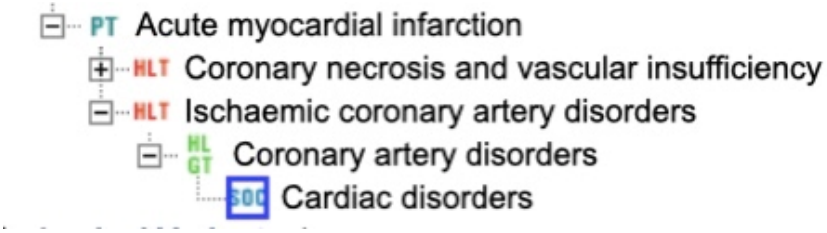
MeSH: D004417

Dyspnea - is subjectively felt shortness of breath or breathing difficulty. The patient feels deficiency of air. Outward signs of shortness of breath can be expressed by shallow and rapid or pronounced deep breathing [18].



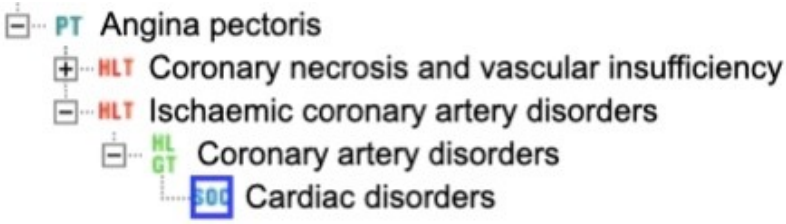
MeSH: None

Acute myocardial infarction or heart attack - it is a necrosis of a part of the myocardium that occurs as a result of a sudden blockage of the flow of oxygen-rich blood. As a result, the affected area of the heart does not receive oxygen and begins to die off. This condition is acute. It is very important to provide an immediate medical intervention [19].



MeSH: D000787

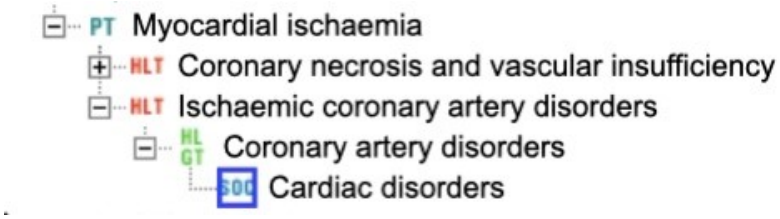
Angina pectoris ("chest tightness") - is a condition characterized by paroxysmal pain in the chest or chest region, which is caused by ischemia of the heart and is the main symptom of coronary artery disease (CHD) [18].



MeSH: D017202

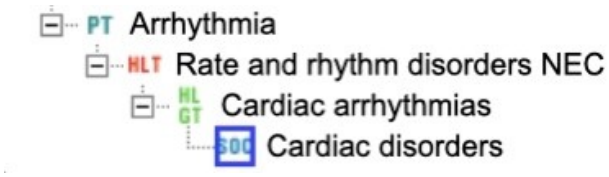
Myocardial ischemia - is a heart disease caused by insufficient blood flow to the heart muscle and, accordingly, a lack of oxygen. the main causes can be thrombosis,

atherosclerosis, microcirculation disorder, spasms of the coronary arteries and others. Prolonged impaired circulation leads to the development of chronic heart disease [20].



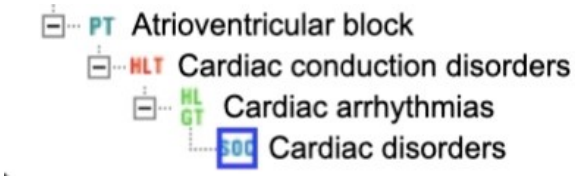
MeSH: D001145

Arrhythmia - is a disorder characterized by anomaly of the heart rate and rhythm. The heart rhythm becomes irregular, may be slower or faster than usual. The main reason is a distress of the heart conduction. The most common diagnostic method is the electrocardiogram [19].



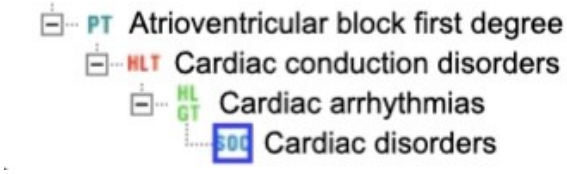
MeSH: D054537

Atrioventricular block - violation of the rhythm of the heart caused by a slow conduction of an impulse from the atria to the ventricles or its complete absence [18].



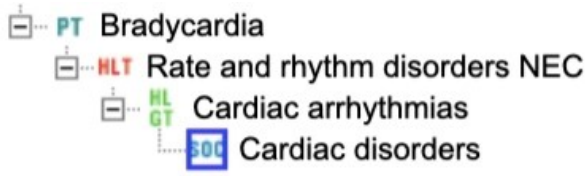
MeSH: None

First-degree AV block is a kind of AV block, which occurs because of the postponement of conduction between the atria and ventricles. At the same time, there are no serious violations of the heart rhythm, therefore, this pathology is not of big clinical significance [18].



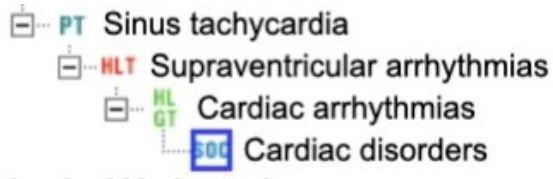
MeSH: D001919

Bradycardia - is a lowering of heart rate below physiological. The benchmark is considered to be the frequency of 60 beats per minute, but this indicator can vary depending on age, physical fitness and other individual characteristics of a person [18].



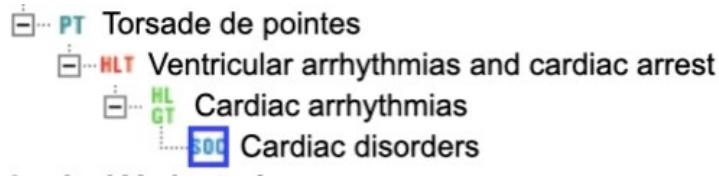
MeSH: D013616

Sinus tachycardia - is a heart rhythm disorder in which the heart rate increases by more than 100 beats per minute. This pathology begins in the sinus node, where the name comes from, and passes through the conducting system of the heart [18].



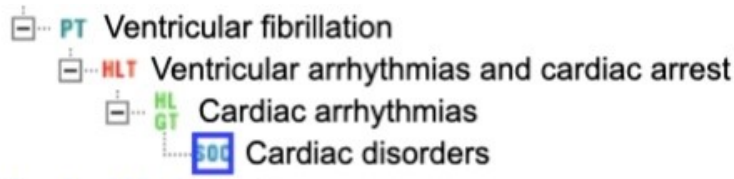
MeSH: D016171

Torsade de Pointe tachycardia is a type of ventricular tachycardia with characteristic ECG changes that have a fusiform shape [18].



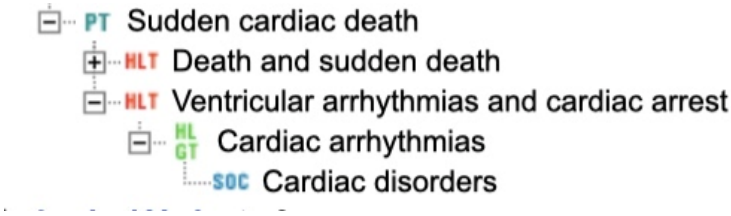
MeSH: D014693

Ventricular fibrillation - is a life-threatening violation of the rhythm of the ventricles of the heart, in which the ventricles generate heart impulses very quickly and uncoordinatedly. As a result of this asynchronous tremor, the ventricles cannot perform their direct function of ejection of blood, which can lead to loss of consciousness and death [6, 19].



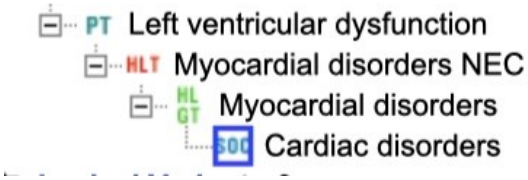
MeSH: D016757

Sudden cardiac death - is the death of a person due to heart disorder, which is characterized by a sudden loss of consciousness within one hour after the onset of acute symptoms. The causes leading to sudden cardiac death are various types of arrhythmias (ventricular tachycardia, ventricular fibrillation, torsade de pointe), as well as bradycardia and subsequent asystole. Any functional disorder or chronic heart disease can be a prerequisite [21].



MeSH: D018487

Left ventricular dysfunction - is a dysfunction of the left ventricle function, in which the amount of ejected blood decreases and, as a result, the blood does not sufficiently flow to the vital organs. The severity of dysfunction is assessed after establishing the ejection fraction and the level of motility of the muscle wall of the ventricle [6, 22].



MeSH: D006333

Cardiac failure - is a heart disease characterised by disability of the heart to pump over sufficient quantity of blood for all body requirements. The most common causes of this disorder are structural defects of the heart itself or overload, due to which the heart cannot fully perform its function [6].