

# The Analysis of the Adverse Effects of Medication -A New Approach in Cardiovascular Diseases

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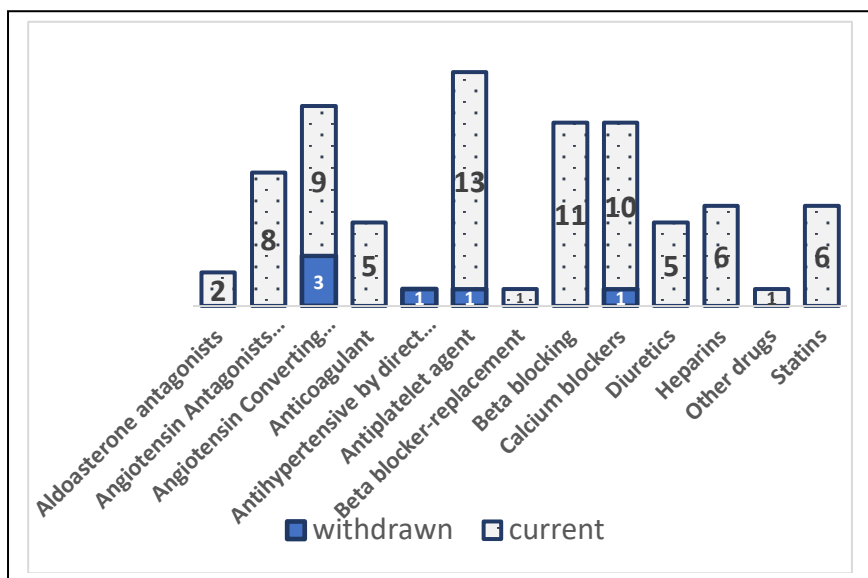
**ABSTRACT:** By centralizing the data from the presentation leaflets of a number of 83 drugs specific to the treatment of cardiovascular diseases, a database with side effects and frequency of occurrence was ensured. Their association with a number of 20 medical conditions / disorders and summary of medical tests affected by these adverse effects could have led to questions about the characteristics of these active substances individually as well as those of the group / class of drugs to which it belongs. At the end, it was possible to graphically determine the adverse effect according to the package leaflet published by the manufacturer, individually or by the group / classes of medication and with the possibility of combining them in case of using several drugs. Knowing these medication-related side effects may lead to a new approach to preventing and improving the symptoms of the disease as well as the side effects of medication from cardiovascular disease.

**KEYWORD:** cardiovascular diseases, the adverse effects, coronary heart disease

## Introduction

The adverse effect is defined as "a harmful and undesirable response, caused by a drug", ie the occurrence of an undesirable or unintended effect after the administration of a drug [www.anm.ro, ANMMDMR]. In an attempt to study this effect, we chose to detail and centralize the side effects in the package leaflets of some of the drugs used in cardiovascular disease. Centralization was performed for 81 active substances and 2 for combinations of two active substances each found in a single drug. When comparing the drugs in 2019 compared to MemoMed (Dobrescu and Negres 2021, 268-301), edition 27, year 2021, a number of 7 active substances were not found (Ghinghina 2019, 15), but we kept them in the statistics and highlighted them because we were interested in their side effects. For those found in the MemoMed 2021 records, the leaflets of the medicines found on the website www.anm.ro (66 pcs), www.ec.europa.eu (2 pcs, Cangrelor and Tenecteplaza), www.ema were used. I (2 pcs, Reteplaza and Nicardipine), https://base-donnees-publique.medicaments.gouv.fr/ (1 pcs, Acebutalol) but also due to the lack on the mentioned official sites were used those from other sites like this: www.pcfarm.ro (2 pcs, Eptibatide- injectable and Sreptokinase), www.medicamente.romedic.ro (3 pcs, Prasugrel, Ticagrelor and Tirofiban).

Fig.1 Numerical evidence of the active substances contained in the studied drugs.



The classification given by MemoMed edition 27, year 2021 was used, so the 81 active substances and 2 combinations used in the treatment of cardiovascular diseases are organized on 13 subgroups (classes) represented in Fig. 1: angiotensin antagonists (sartans) - 8 pcs, aldosterone antagonists - 2 pcs, antiplatelet agent - 13 pcs and 1 not included in MemoMed, anticoagulant - 5 pcs, antihypertensive by direct vasodilating action - 1 pcs not included in MemoMed, beta-blockers 1 not included in MemoMed, beta-blocker-replacement 1 piece, calcium blockers - 10 pcs and 1 not included in MemoMed, Diuretics - 5 pcs, Heparin - 6 pcs, Angiotensin converting enzyme inhibitors (ACE inhibitors) - 12 pcs and 3 not included in MemoMed, statine - 6 pcs (Dobrescu and Negres 2021, 302-398).

### Evaluation of adverse effects

From the contents of the package leaflet, only the data in the chapter "Possible side effects" were used. The initial phrase "like all medicines, this medicine can cause side effects, although not everybody gets them" indicates that the side effects are very much dependent on the patient. The use of data can only be made to the specific situation of each patient.

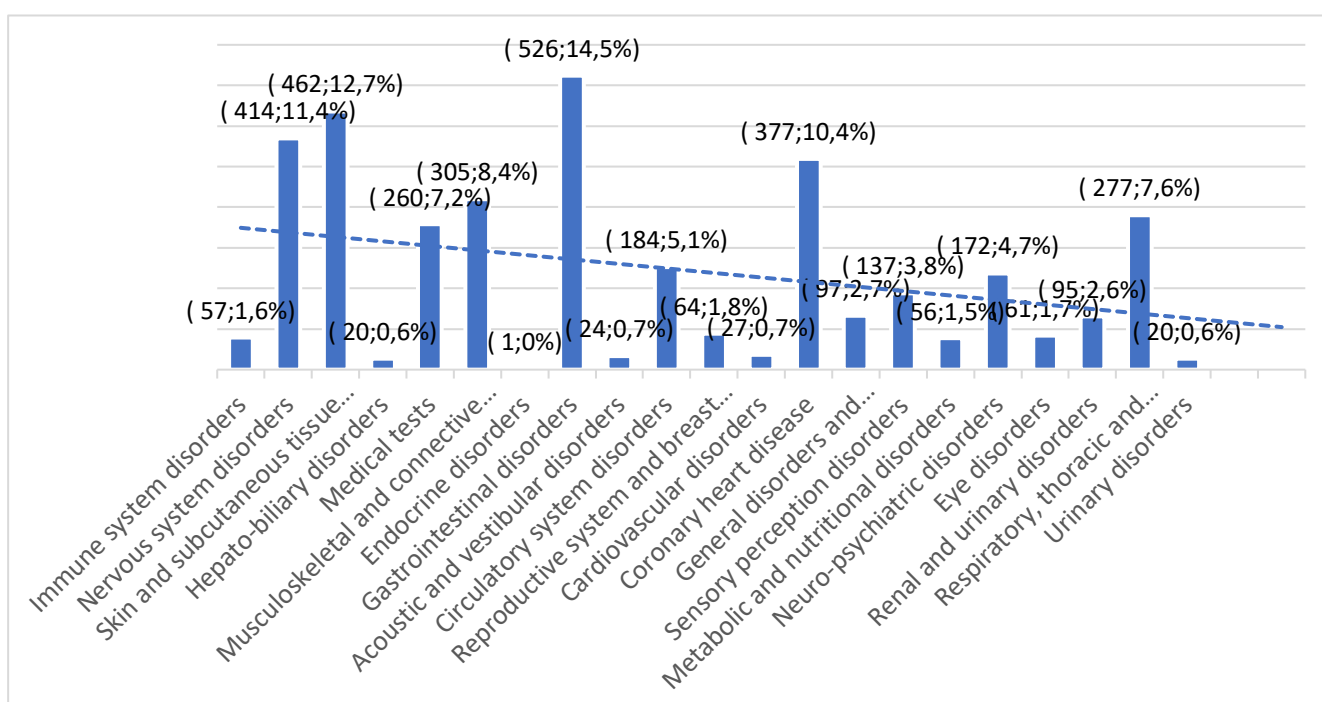
From the contents of the prospectuses, the data were selected according to the following criteria:

1. Processed side effects;
2. Frequency: Very common (FF), Frequent (F), Uncommon (PF), Rare (R), Very rare (FR), Unknown frequency (N);
3. Severity level (C - critical) associated with the frequency of occurrence: C + FF, C + F, C + PF, C + R, C + FR, C + N.

I associated each adverse effect with a medical condition / disorder (20 items plus a medical test item). The C-critical level refers to the mention that in the leaflets appears the obligation to urgently contact the attending physician or those in emergency medicine, most often being associated with the interruption of treatment. There were a number of 3636 records with a distribution by medical condition / disorder according to Fig. 2. It can be seen that the highest number of adverse effects is associated in descending order with the following medical conditions / disorders:

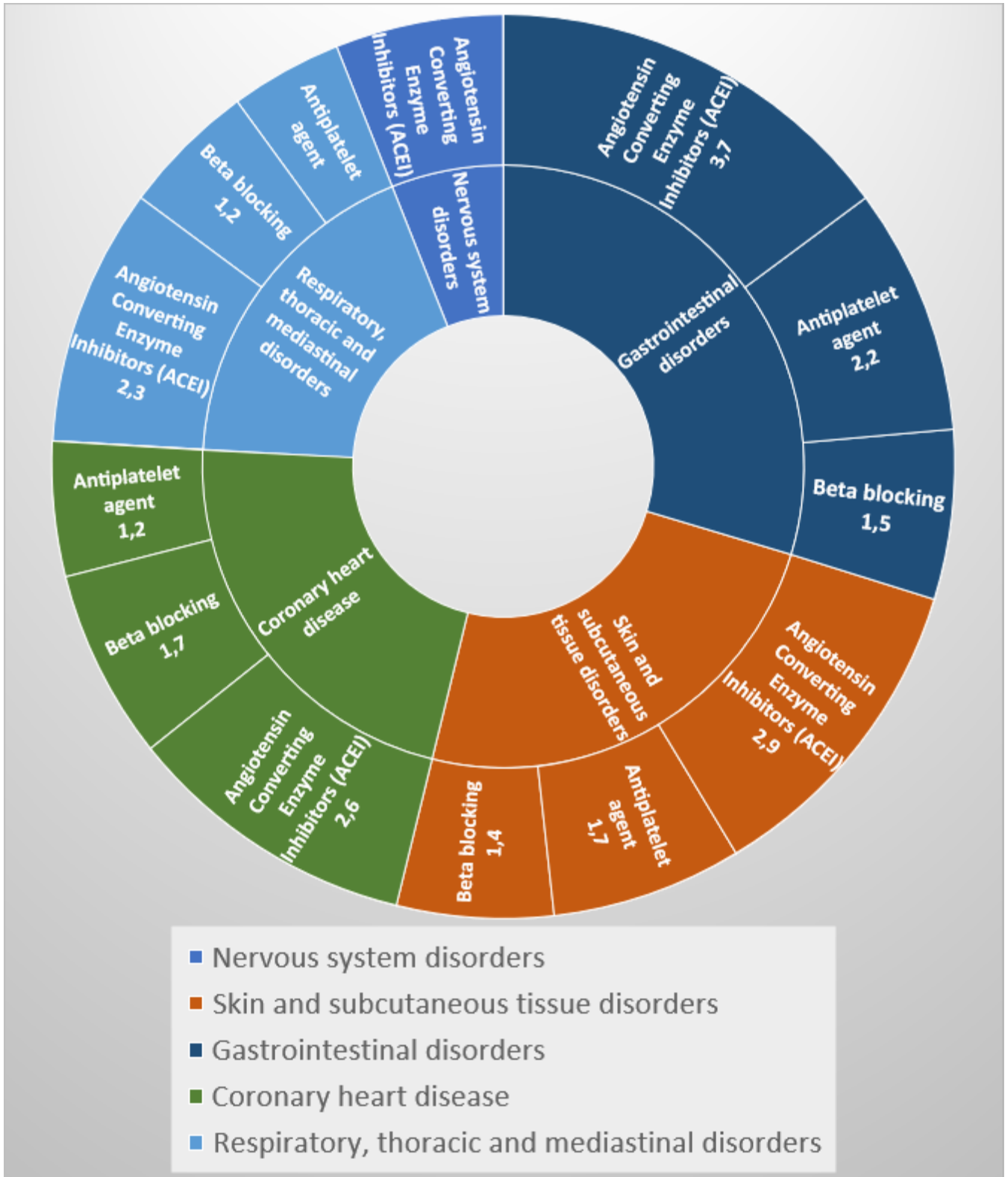
1. Gastrointestinal disorders - 526 references;
2. Skin conditions - 462 references;
3. Nervous system disorders - 414 references;
4. Coronary heart disease - 377 references;
5. Musculoskeletal system - 305 references.

Fig. 2 Frequency of side effects in the package leaflet of prescription drugs for cardiovascular diseases.



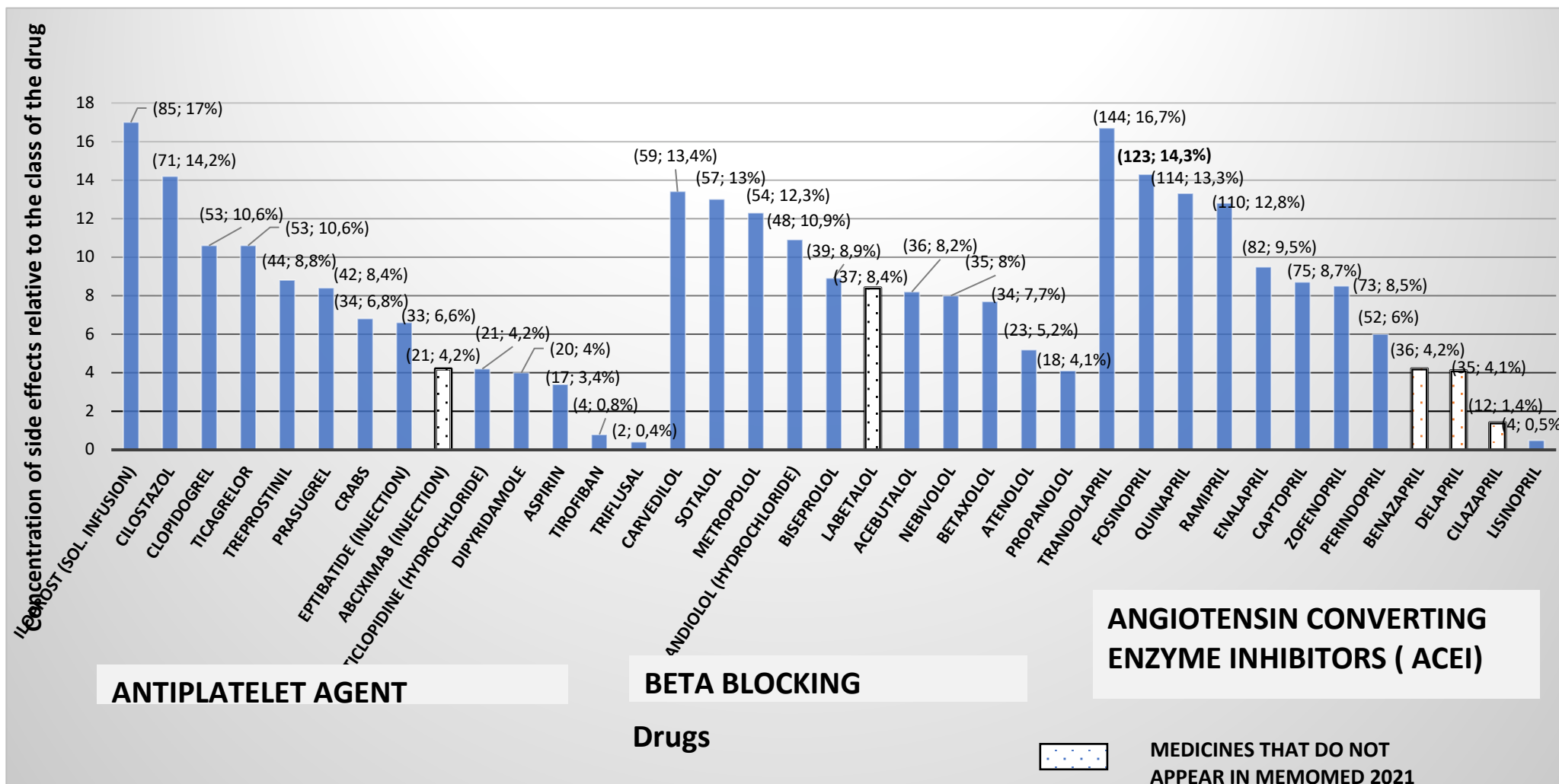
Because there are so many data, we will select the main 3 groups / classes that have a high weight in the 5 selected medical conditions / disorders (gastrointestinal disorders, skin and subcutaneous tissue disorders, coronary disorders, respiratory, thoracic and mediastinal disorders, nervous system disorders), with the mention that those that are specific to the patient can be chosen: 1) Angiotensin converting enzyme inhibitors; 2) Beta blocking; 3) Antiplatelet agent. Their distribution can be seen in Fig. 3.

Fig. 3 Distribution (%) of the main 5 Medical conditions / disorders by 3 subgroups / drug classes.

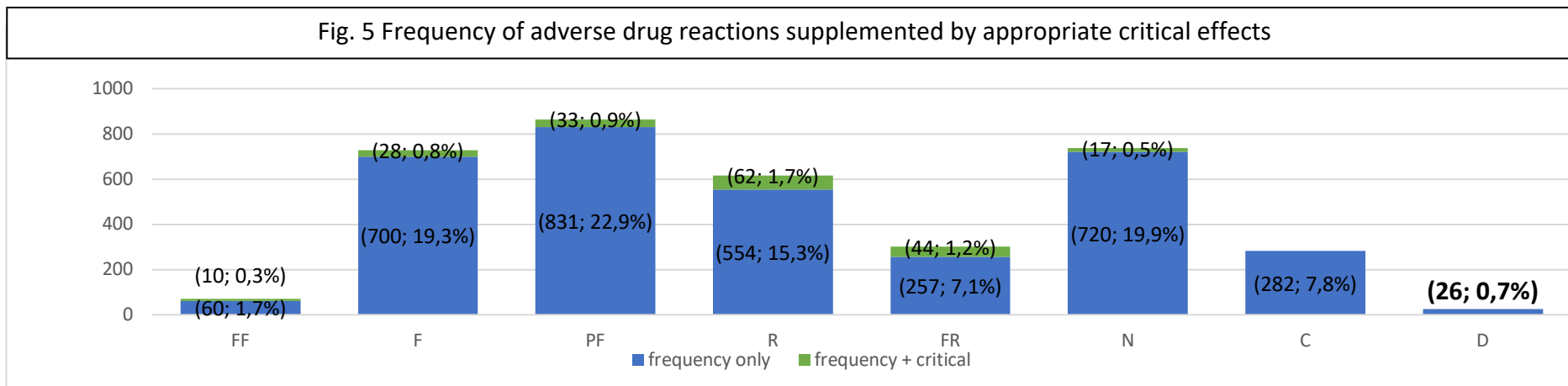


For these 3 groups / classes we analyze the share of negative effects of drugs (active substances) (Fig.4).

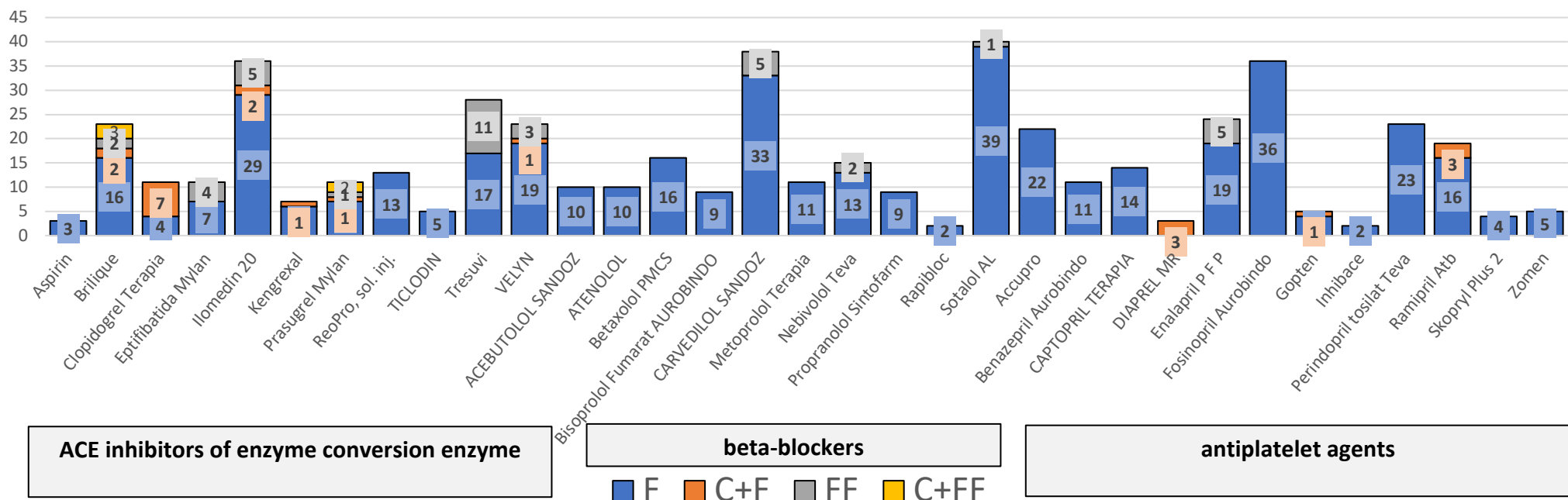
Fig. 4 FREQUENCY OF ADVERSE EFFECTS FOR FIRST CLASS 3 MEDICINES, the comparative situation



Taking into account the frequency of occurrence at the level of all analyzed prospectuses, we represented the comparative situation, as follows:



**Fig. 6 Comparative situation between 3 subgroups / classes of drugs (ACE inhibitors of enzyme conversion enzyme inhibitors, beta-blockers, antiplatelet agents) by active substance and a selection of frequency of adverse effects (very common FF, frequent F, critical C)**



We choose an active substance (medicine) from each class of medicine: Ticagrelor for Antiplatelet, Sotalol for Beta-Blocker and Fosinopril for Angiotensin Converting Enzyme Inhibitors (ACEI) so that we can compare them later.

Fig. 7 For Ticagrelor (Antiplatelet) Comparative Medical Disorders / Disorders for Ticagrelor by detailed frequency of adverse effects and / or critical C.

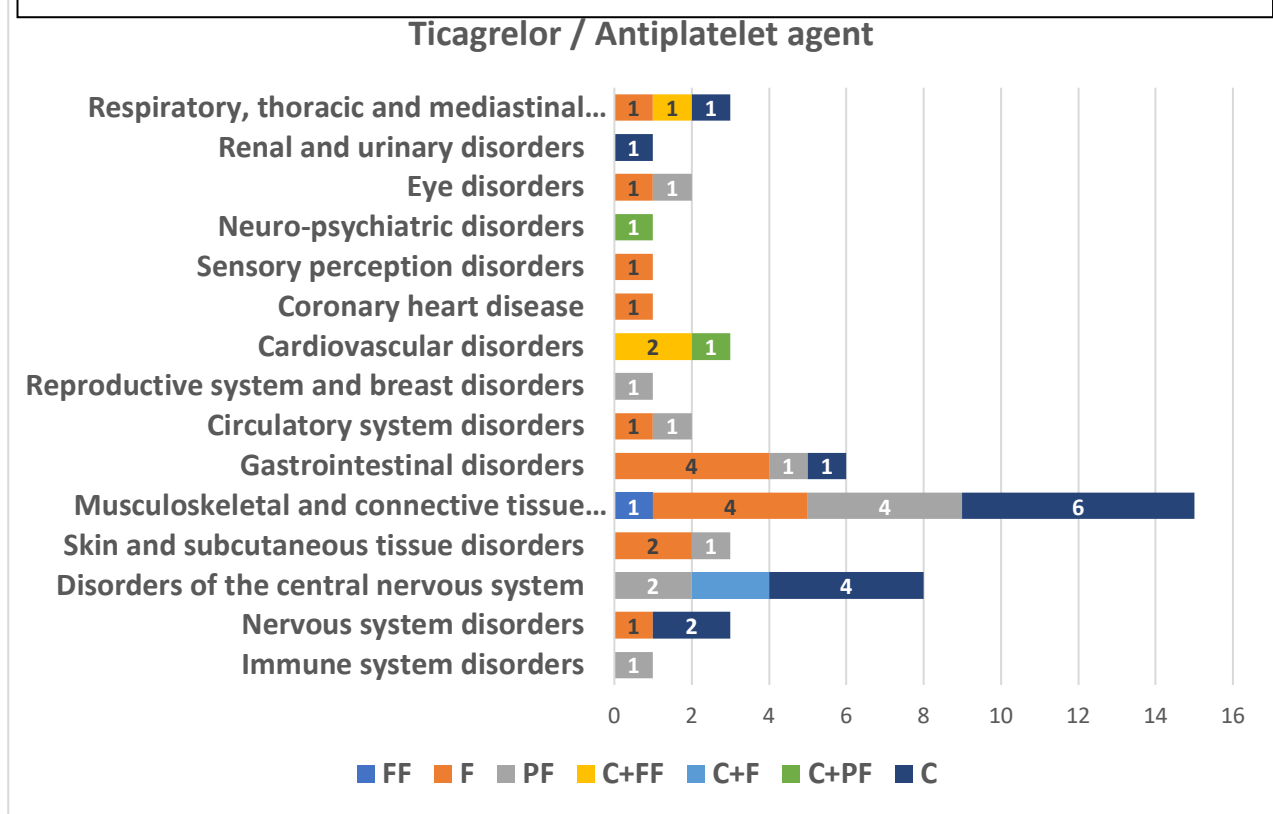
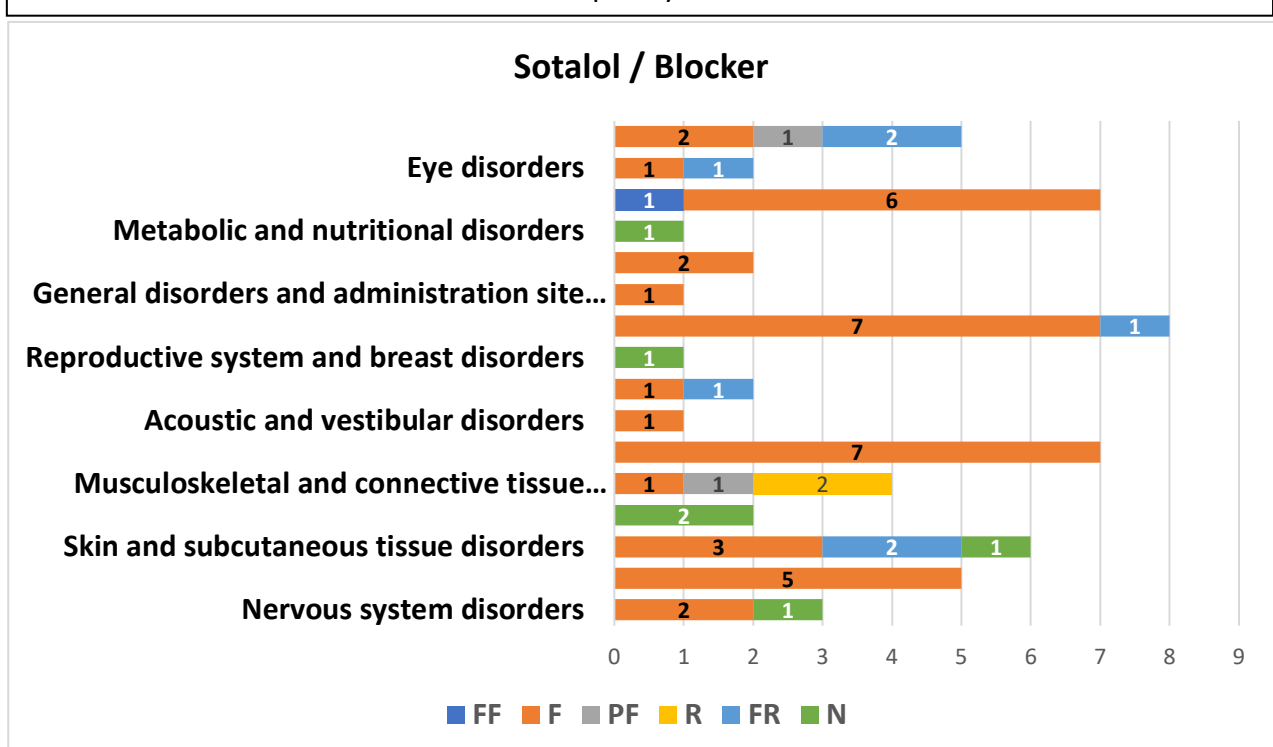
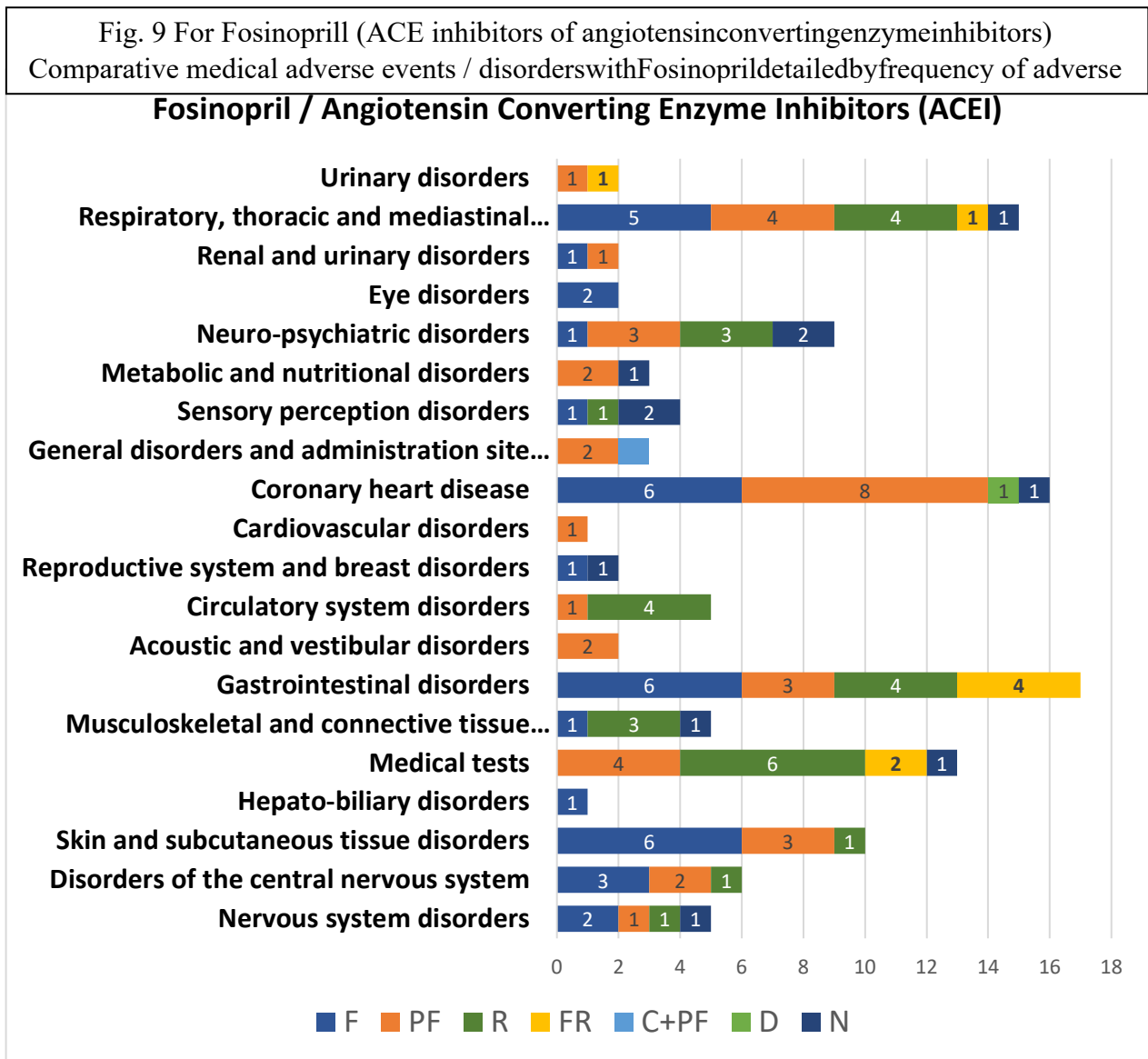


FIG. 8 For Sotalol (Betablocant) Comparative medical conditions for these side effects of Sotalol detailed frequency of adverse effects.





**Analysis of side effects:**

This study aims to capitalize on the adverse effects of medication in cardiovascular disease that are found in drug leaflets to address a diet aimed at counteracting these side effects. Understanding the complexity of the data can help you focus on the essentials and find a solution to these problems.

Nutrition is a method of preventing cardiovascular disease and its effect has proven results. Approaching this method in order to reduce the side effects of medication can be done in two ways:

1. Nutrition for the prevention of adverse effects aimed at a general approach to the effects of medication in cardiovascular disease and/or the specific combination of drugs
2. Individualized diet according to specific side effects

The following conclusions can be drawn from the analysis of graphical data:

The adverse effect on cardiovascular disease is most pronounced in the following medical conditions / disorders:

- ✓ Gastrointestinal disorders:
  - Digestive disorders, nausea, vomiting, diarrhea, constipation, flatulence, belching, burning sensation, etc.
- ✓ Skin conditions:

- Inflammation with erythema and flaking of the skin, allergies, blisters, hives, hair loss, eczema, reddening of the skin, yellowing of the skin, blemishes, itching, etc.
- ✓ Nervous system disorders:
  - Dizziness, numbness, hot flashes, convulsions, migraine, headache, tingling, dizziness, fainting, memory loss, drowsiness, tremor, etc.
- ✓ Coronary heart disease:
  - Stroke, arrhythmias, severe heart damage, irregular heartbeat, blockages, angina pectoris, fibrillation, heart attack, heart failure, ischemia, high blood pressure, etc.
- ✓ Musculoskeletal system:
  - Cramps, arthritis, arthralgia, back pain, myalgias, muscle rupture, rhabdomyolysis, bleeding, muscle weakness, swelling, etc.

However, the adverse effect of medical conditions/disorders is different from the group / class of medicines in which the studied active substance is included. We have selected 3 groups / classes that most influence the 5 selected medical conditions/disorders: Angiotensin converting enzyme inhibitors, Beta blocking and Antiplatelet agent.

In Fig. 5 it can be seen that within each drug group/class in the drug leaflets the number of mentioned side effects differs quite a lot. This is because some medicines have a more detailed leaflet and some do not. If we look at the active substances that were not included in MemoMed 2021 we notice the following:

- The number of side effects is certainly lower than other medicines and I can conclude that it is not a criterion for withdrawal from the market and therefore exclusion from MemoMed 2021;
- From the number of side effects it is observed that the documentation of the use of the drugs could not be completed and their evolution did not meet the expectations compared to the other drugs. For the particular case of antiplatelet agents, the 3 drugs that are no longer found had the worst documentation of side effects;
- Limiting the number of active substances within a drug group/class gives rise to new active substances. As can be seen, medicines with less than 1% of the total number of listed adverse effects of the drug group / class are stored, is very poorly documented.

For all 81 substances and 2 combinations of substances if we take stock of the frequency of side effects we can say that 1/3 of the total side effects (31%) is distributed as follows: 2% Very common (may affect more than 1 patient out of 10), 20% Common (may affect up to 1 in 10 patients), 8% Critical (requires referral to a specialist, discontinuation of medication) and 1% Risk of death.

We can say that 1 in 3 patients is frequently affected by one or more side effects due to the use of drugs in cardiovascular diseases.

It is observed in fig. 7 that there are some characteristics common to the drug group / class, as follows:

1. Angiotensin converting enzyme inhibitors:
  - a. Most have a high frequency of C (critical) side effects (between 25 and 260 items for each product). This is unusual compared to other medicines or classes of medicines and involves both careful monitoring of the patient and correct and complete information on how the patient reacts to an episode of adverse reaction C (critical).
  - b. Approximately 50% of the drugs have a fairly high number of FF (Very Common) items with values between 13 and 143.
  - c. For the particular case represented by Fosinopril (Fig. 10) we observe:
    - i. Comply with the rule on the high frequency of C (critical) side effects, stating that falls into group C + PF (critical + uncommon)
    - ii. There are no medical conditions / disorders with FF frequency (very common) but for F (common) there are 13 out of 19 items and the number of side effects for a large number of medical conditions / disorders can increase to 5 even 6.



iii. Among the most common ailments / disorders are musculoskeletal and conjunctival system, coronary heart disease, respiratory, thoracic and mediastal disorders, skin and subcutaneous tissue disorders and neuropsychiatric disorders.

Compared to those used for all drugs used in cardiovascular disease (point 2) even if the order is different, neuropsychiatric disorders (agitation, anxiety, depression, nightmares, insomnia, hallucinations, psychosis, confusion, balance disorders, sleep disorders, vision) and respiratory, thoracic and mediastinal disorders instead of nervous system disorders and gastrointestinal disorders.

2. Beta blocking:

a. Characterized by adverse effects F (Common)

b. For the particular case represented by Sotalol (Fig.9) we observe:

i. The rule on the existence of adverse events/disorders in all medical conditions/disorders is observed F (Common)

ii. No references to C (Critical)

iii. Compared to those established for all medicines used in cardiovascular diseases (point 2) even if the order is different, neuropsychiatric disorders and respiratory, thoracic and mediastinal disorders have appeared instead of musculoskeletal disorders.

3. Antiplatelet agent:

a. It is observed that the distribution is not homogeneous: there are 33% combinations of side effects with Critical and F frequency (Frequent), 33% drugs that are no longer found in MemoMed 2021, 22% combinations with side effects FF (very common) and F (common) and 11% only with F (common)

b. For the particular case represented by Ticagrelor (Fig.8) we observe:

i. Frequent reactions are only for disorders of the musculoskeletal system

ii. There are a large number of C (critical) reactions with frequencies FF (very common) 6%, F (frequent) 4%, PF (uncommon) 24% and separate Critical without specifying the frequency 30%, in total being a percentage of C (critical) effects of 74%. This percentage is unusually high.

iii. Compared to the established conditions/disorders for all drugs from cardiovascular diseases (point 2) we notice that the established criteria are maintained even if the weight is different. Musculoskeletal and conjunctival disorders are highlighted by 30% followed by Nervous system and central nervous system disorders by 22%, Gastrointestinal disorders 12%, the others having a lower share.

## Conclusions

The side effects of medicines as published in the package leaflets should be carefully considered before starting treatment. Each drug has a picture of medical conditions / disorders of specific side effects that can be interpreted both in the context of the drug group / class to which it belongs but especially in the context of side effects specific to each patient. The package leaflet details the frequency of side effects: Very common (FF), Common (F), Uncommon (PF), Rare (R), Very rare (FR), Unknown frequency (N) completed for each frequency with aspect C (Critical). Although the number of reactions is very different depending on the drug, the frequency is different or the share of those with unknown frequency is sometimes too high, I counted these reactions as number and frequency and tried to qualitatively highlight these side effects of cardiovascular disease medication. Approaching medication in cardiovascular disease as well as medication in associated diseases can complicate the understanding of the share of each active substance in the effect of adverse drug reactions. Furthermore, the combination of side effects may change the priority of general effects such as gastrointestinal disorders, skin conditions, disorders of the central nervous / nervous system, coronary disorders or musculoskeletal system. It can also amplify other symptoms, such as neuropsychiatric disorders.

Understanding these side effects can be used to address the beneficial diet for the prevention and amelioration of the symptoms of the disease but also the adverse effects of medication in cardiovascular diseases.

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