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Source / Izvornik: **Diabetology, 2024, 5, 406 - 429**

Journal article, Published version
Rad u časopisu, Objavljena verzija rada (izdavačev PDF)

https://doi.org/10.3390/diabetology5040031

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:491768

diabetology

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Review

Metabolic Syndrome Drug Therapy: The Potential Interplay of Pharmacogenetics and Pharmacokinetic Interactions in Clinical Practice: A Narrative Review

Sandra Knežević [1,†], Francesca Filippi-Arriaga [2,3,†], Andrej Belančić [1,4,*], Tamara Božina [5], Jasenka Mršić-Pelčić [1] and Dinko Vitezić [1,4]

1 Department of Basic and Clinical Pharmacology with Toxicology, Faculty of Medicine, University of Rijeka, 51000 Rijeka, Croatia; sandra.knezevic@uniri.hr (S.K.); jasenka.mrsic.pelcic@uniri.hr (J.M.-P.); dinko.vitezic@uniri.hr (D.V.)
2 Centre Investigació Medicaments (CIM), Institut de Recerca Sant Pau (IR-Sant Pau), 08041 Barcelona, Spain; mfilippi@santpau.cat
3 Diabetes and Metabolism Research Unit, Vall d'Hebron Institut de Recerca (VHIR), 08035 Barcelona, Spain
4 Department of Clinical Pharmacology, Clinical Hospital Centre Rijeka, 51000 Rijeka, Croatia
5 Department of Medical Chemistry, Biochemistry and Clinical Chemistry, University of Zagreb School of Medicine, 10000 Zagreb, Croatia; tamara.bozina@mef.hr
* Correspondence: a.belancic93@gmail.com
† These authors contributed equally to this work.

Abstract: Metabolic syndrome (MetS) presents a significant global health challenge, characterized by a cluster of metabolic alterations including obesity, hypertension, insulin resistance/dysglycemia, and atherogenic dyslipidemia. Advances in understanding and pharmacotherapy have added complexity to MetS management, particularly concerning drug interactions and pharmacogenetic variations. Limited literature exists on drug–drug–gene interactions (DDGIs) and drug–drug–transporter gene interactions (DDTGIs), which can significantly impact pharmacokinetics and pharmacodynamics, affecting treatment outcomes. This narrative review aims to address the following three key objectives: firstly, shedding a light on the PK metabolism, transport, and the pharmacogenetics (PGx) of medicines most commonly used in the MetS setting (relevant lipid-lowering drugs, antihypertensives and antihyperglycemics agents); secondly, exemplifying potential clinically relevant pharmacokinetic drug interactions, including drug–drug interactions, DDGIs, and DDTGIs; and, thirdly, describing and discussing their potential roles in clinical practice. This narrative review includes relevant information found with the use of interaction checkers, pharmacogenetic databases, clinical pharmacogenetic practice guidelines, and literature sources, guided by evidence-based medicine principles.

Keywords: metabolic syndrome; pharmacogenetics; pharmacokinetics; drug–drug–transporter gene interactions; drug–drug-gene interactions; lipid-lowering agents; antihypertensives; antihyperglycemics; clinical decision making

Citation: Knežević, S.; Filippi-Arriaga, F.; Belančić, A.; Božina, T.; Mršić-Pelčić, J.; Vitezić, D. Metabolic Syndrome Drug Therapy: The Potential Interplay of Pharmacogenetics and Pharmacokinetic Interactions in Clinical Practice: A Narrative Review. *Diabetology* **2024**, *5*, 406–429. https://doi.org/10.3390/diabetology5040031

Academic Editor: Giancarlo Tonolo

Received: 16 May 2024
Revised: 20 August 2024
Accepted: 27 August 2024
Published: 3 September 2024

1. Introduction

Metabolic syndrome (MetS) is an escalating global public-health problem most commonly defined as the cluster of several metabolic alterations, including visceral obesity, elevation of arterial blood pressure, insulin resistance/dysglycemia, and atherogenic dyslipidemia [1].

Due to substantial progress in the understanding of the latter metabolic entities and pharmacotherapy armamentarium, the management of MetS has become even more complex. Besides bearing in mind the anorexigenic potential of medicines and the impact on major adverse cardiac events (MACEs), in the current era of polytherapy it is increasingly important to consider potential drug–drug interactions (DDIs). The management of MetS is becoming even more demanding in cases of pharmacogenetic variations leading to substantial drug–drug–gene interactions which are influencing pharmacokinetics (PK) and/or pharmacodynamics (PD) [2].

In general, the body of literature on DDGIs as well as drug–drug–transporter genes interactions (DDTGIs) is quite scarce. Inhibitory and induction interactions may substantially affect PK conditions and thus increase or decrease drug concentrations, respectively. Since MetS is a complex phenomenon, both clinically and pharmacologically speaking, it is important to decrease the rate of adverse drug reactions (ADRs) and improve treatment outcomes in the setting of increasing multi-morbidity and polytherapy [3].

The aim of the present narrative review is to (i) shed the light on the PK metabolism, transport, and pharmacogenetics (PGx) of medicines most commonly used in the MetS setting (relevant lipid-lowering drugs, antihypertensive, and antihyperglycemic agents), (ii) to exemplify potential clinically relevant pharmacokinetic DD, DDG, and DDTG interactions that may arise, and (iii) to describe and discuss their potential role in clinical practice.

2. Methodology

To conduct this narrative review, current clinical practice guidelines were consulted to identify relevant lipid-lowering drugs as well as antihypertensive and hypoglycemic drug therapies. Drug labels were reviewed to compile the most relevant pharmacokinetic and pharmacogenetic information for each identified drug group. The Lexicomp Drug Interactions tool [4] was used to identify potential drug–drug interactions, and the PharmGKB [5] database and DrugBank [6] database were utilized to further explore relevant pharmacogenetic data and to identify relevant drug transporters or enzymes. Finally, we examined existing recommendations within pharmacogenetic guidelines, including those from the Clinical Pharmacogenetics Implementation Consortium (CPIC) [7] and the Dutch Pharmacogenetics Working Group (DPWG) [8].

3. Pharmacogenetics of Lipid-Lowering Drug Drugs

Dyslipidemias are disorders of lipoprotein metabolism (cholesterol, low-density lipoprotein cholesterol (LDL-C), triglycerides, and high-density lipoprotein cholesterol (HDL-C)) and represent an important risk factor for atherosclerotic cardiovascular disease (ASCVD) [9,10]. Different drugs are used for its treatment [11]. Recent data on the PGx and PK of statins, fibrates, and ezetimibe will be presented.

3.1. 3-Hydroxy-3-Methylglutaryl-Coenzyme A Reductase (HMG-CoA Reductase) Inhibitors

Statins are HMG-CoA reductase inhibitors and belong to the most prescribed drugs in the world, being used to reduce cholesterol and prevent cardiovascular diseases. Although they are considered safe drugs, 5–10% of the patients develop statin intolerance, most often due to statin-associated musculoskeletal symptoms (SAMSs) that affect adherence and, ultimately, treatment outcomes. PGx studies have identified several biomarkers that impact statin PK, modulating drug exposure and ADRs. These biomarkers are often called ADME genes because they have an impact on absorption, distribution, metabolism, and excretion. Some of them have been included in the guidelines for personalized treatment [12] while, for others, it is still necessary to collect additional evidence on their relevance for clinical practice.

According to their PK, statins are administered orally and absorbed into systemic circulation via intestinal cells through both passive diffusion and active transport facilitated by ABC and SLC gene family transporters. The liver and, to a lesser extent, the kidney are the primary sites of metabolism and elimination. Metabolism is catalyzed by CYP and UGT gene family enzymes, and the predominant elimination pathway is biliary excretion mediated by ABC transporters [5].

Organic anion-transporting polypeptide 1B1 (OATP1B1), coded by the *SLCO1B1* gene, has a vital role in transporting statins into the liver for hepatic clearance. ABCG2 (BCRP) is an efflux transporter involved in absorption and disposition and CYP2C9 is involved in the metabolism of some statins (fluvastatin, rosuvastatin). All of these biomarkers are polymorphic, and gene variants can modulate the PK of statins (i.e., simvastatin,

atorvastatin, rosuvastatin, fluvastatin, pravastatin, pitavastatin, lovastatin), representing a genetic predisposition to an increased risk of SAMSs.

Due to genetic variability or drug inhibition, decreased functioning of OATP1B1/*SLCO1B1* can result in significantly increased systemic exposure to statins, resulting in higher risk for SAMSs [13]. The most studied variant, *SLCO1B1* c.521T>C (rs4149056, p.V174A), contained within *SLCO1B1**5 and *15 haplotypes, causes nearly total loss of OATP1B1 function and raises systemic exposure to statins and ADRs risk [14–16].

From the data obtained in vitro, decreased transport function has been associated with the minor C allele at c.521T>C, while increased systemic exposure to several drugs has been observed in vivo. A recent study reported that a *SLCO1B1* variant with increased activity (c.388A>G, rs2306283) has a significant impact on atorvastatin PK, also finding that the area under the curve (AUC) (0–∞) was 41% smaller compared to individuals with a normal function genotype [17].

Differences in allele frequencies have been observed across populations and races. The variant allele *SLCO1B1* 521C is more common in European (15%) populations than in Asian (14%) and African (1%) populations [18].

Besides statins, OATP1B1 is responsible for the uptake of mainly weakly acidic drugs like valsartan, bosentan, enalapril, methotrexate, rifampicin, SN-38 (the active metabolite of irinotecan), and HIV protease inhibitors, as well as some endogenous compounds (bilirubin, bile acids (taurocholic acid), conjugated steroids, and leukotriene C4, into the liver [19–21].

ABCG2 gene encodes the membrane transporter adenosine triphosphate (ATP)–binding cassette G2 (also known as breast cancer resistance protein, BCRP). It is expressed in many tissues, including the intestine, liver, blood–brain barrier, and kidney [5,22].

As an efflux transporter on the cell membrane, it limits the entry of drugs and other xenobiotics into the cell. Its primary role is in the enterocyte membrane, where it limits the entry of xenobiotics from the gastrointestinal system into circulation. It acts as a canalicular efflux pump on the hepatocyte membrane, transporting substrates from hepatocytes into the bile, while, in the brain, microvascular endothelial cells limit the entry of substrates into the CNS. Acting in renal proximal tubular cells additionally contributes to the modulation of drug exposure. Therefore, genetically determined variable ABCG2 activity may have an impact on absorption, distribution, and elimination of drugs, as well as on tissue protection against xenobiotic exposure [23].

In addition to xenobiotics, ABCG2 also has endogenous substrates. Its important role is in renal and extrarenal urate secretion, and reduced function ABCG2 variants are linked to the risk for developing hyperuricemia and gout [5,24].

Clinically relevant drug substrates of ABCG2 other than lipid-lowering drugs (rosuvastatin, atorvastatin, fluvastatin, ezetimibe, fibrates) are cytostatics, such as camptothecin analogs (diflomotecan, irinotecan, topotecan), mitoxantrone, methotrexate, tyrosine kinase inhibitors (TKIs, e.g., erlotinib, gefitinib, imatinib, nilotinib), proton pump inhibitors (PPIs, e.g., pantoprazole), cimetidine, anticoagulants (apixaban, rivaroxaban), cyclosporine, prazosin, sulfasalazine, etc. [22,25–30].

ABCG2 is considered an important factor in drug interactions because it can be inhibited by drugs and other xenobiotics [29,31,32]. A number of ABCG2 inhibitors have been identified [22] and many convincing data point to ABCG2 as an important mediator of DDGIs in humans [21,33,34].

The common, most extensively studied *ABCG2* variant is c.421C>A (rs2231142 p.Q141K). The minor A allele is associated with 30–40% reduced protein expression compared with the C allele and increased plasma levels of drug substrates have been observed. Many studies have highlighted the *ABCG2* c.421C>A variant as a determinant of the PK variability, efficacy, and toxicity of different drugs [28,32,35,36].

In populations of European descent, the frequency of the *ABCG2* variant allele is estimated at around 10–15% [37]. The highest frequency was recorded in the Asian population (30%) and the lowest was recorded in the African population (2%) [32,35,37]. Although a CPIC guideline has only been issued for rosuvastatin, some study results found an ABCG2

variant associated with the PK and PD of other statins. The AUC of inactive simvastatin lactone was 111% higher, and, for fluvastatin, 97% higher in subjects with *ABCG2* 421 A/A genotype compared to concentrations in the carriers of 421 C/C genotype. This increase is likely due to decreased efflux transporter function [38]. The Keskitalo group reported that *ABCG2* 421 A/A genotype carriers had a 72% greater atorvastatin AUC and a 144% greater rosuvastatin AUC compared to the *ABCG2* 421 C/C genotype [35]. Similar results were obtained for atorvastatin in the Japanese population [39].

The prolonged bioavailability of statins in carriers of variant *ABCG2* allele represents a risk for the development of ADRs, as was confirmed in a case–control study for rosuvastatin, atorvastatin, and fluvastatin [40–42].

ABCG2 transporter has been recognized as one of the key drug transporters involved in clinically relevant drug disposition [36,43,44]. A study in hypertensive breastfeeding women found that concentrations of nifedipine in breast milk in *ABCG2* c.421 C/A genotype carriers were approximately three times greater than in the 421 C/C genotype [45].

The CYP2C9 enzyme participates in the metabolism of many clinically important drugs such as coumarin anticoagulants, antidiabetics, sartans, fluvastatin, antiepileptics, and nonsteroidal anti-inflammatory drugs, most of which have a narrow therapeutic range [46]. People with poor or no activity of the CYP2C9 enzyme may experience toxic side effects (phenytoin, diclofenac) or life-threatening bleeding (warfarin). The *CYP2C9* gene belongs to the *CYP2C* gene cluster (2C8-2C9-2C19-2C18) located on chromosome 10q24. More than 70 different alleles of the CYP2C9 enzyme are known, and the most important are alleles *2 (rs1799853, p.R144C) and *3 (rs1057910, p.I359L) due to their association with a reduced drug-substrate metabolism of ~30–40% and 80%, respectively, resulting in increased systemic drug exposure. The frequency of allele *2 in the Caucasian population is ~12% and allele *3~8%.

Among the first pieces of evidence of the association of the CYP2C9 polymorphism with the side effects of statins was a case–control study in renal transplant patients taking fluvastatin [42]. Results showed that *CYP2C9* homozygous and heterozygous variant allele (*2 or *3) carriers had 2.5 times greater odds of developing adverse effects (p = 0.037). Besides patients who were carriers of at least one variant *CYP2C9* allele (*2 or *3) and who were receiving CYP2C9 inhibitors, had more than six times greater odds of having adverse effects than those without the inhibitor (p = 0.027). Besides that, patients with *ABCG2* 421CA or AA (taken together) had almost four times greater odds of developing adverse effects than those with the *ABCG2* 421CC genotype (p = 0.013; OR: 3.81; 95% CI: 1.27–11.45).

Given that patients with MetS are most often on polytherapy with drugs that may be substrates of CYP2C9 and/or ABCG2, they may have an increased risk of ADRs due to DDIs and/or genetic variability.

The most recent CPIC guidelines for statins [12], published in January 2022, replace the original 2012 guidelines and the updates from 2014 [47,48]. In addition to previous gene-based guidelines prescribing simvastatin based on *SLCO1B1* genotype, recommendations based on the *SLCO1B1* (simvastatin, rosuvastatin, atorvastatin, pravastatin, pitavastatin, fluvastatin, and lovastatin), *CYP2C9* (fluvastatin), and *ABCG2* (rosuvastatin) genotypes were added. The guidelines are specifically used in cases when the results of PGx tests are available to achieve the best possible clinical results with the most suitable statin in its optimal dose [12].

There are other relevant genetic polymorphisms for hypolopidemic theraphy that are not yet in the guidelines. The published literature includes studies that have investigated other enzymes involved in statin metabolism, such as CYP3A4/5 [49–51]. Because of insufficient evidence to support clinical implementation, there are still no recommendations for their application in practice.

Although not covered by the guidelines for statins, *CYP3A4/5* gene polymorphisms could be relevant, especially in concomitant therapy with drugs that are CYP3A substrates. Given that nearly 50% of drugs are metabolized by CYP3A enzymes which show significant interindividual variability in activity, DDGIs in the treatment of MetS may be relevant.

The *CYP3A* gene cluster is located on chromosome 7q22. Important substrates of the CYP3A besides statins are antibiotics, antivirals, antiepileptics, antidepressants, anticoagulants, antipsychotics, immunosuppressants, tyrosine kinase inhibitors, etc. CYP3A4/5 enzymes are expressed in the liver and intestines, whereby CYP3A5 predominates in extrahepatic tissues. Both enzymes mostly share substrates and show very high variability in activity [52]. In the Caucasian population, only 3–15% of people have an active enzyme CYP3A5 (carriers of the allele *1, (expressers), while the most common variant *CYP3A5*3*, substitution 6986A>G in the intron 3 (nonexpressers) results in the synthesis of an inactive enzyme [46]. The *CYP3A5* expression may overcome/prevent drug interactions at the CYP3A4 level.

Several polymorphisms affect CYP3A4 expression and function [53]. The polymorphism *CYP3A4*22* (rs35599367, c.522-191C>T), an intronic variant with a frequency of 5–7% in the Caucasian population, determines a significantly reduced activity of the enzyme. *CYP3A4*22* can change hepatic CYP3A4 enzyme expression by 2–6 times. The *CYP3A4*20* in/del variant results in a complete loss of function [54]. However, according to the Genome Aggregation Database, the frequency in the European population is only 0.04%. The *CYP3A4*6* variant also results in very low enzyme activity and a low frequency in the Caucasian population. According to the Ensembl genome database, a variant with enhanced CYP3A4 function, *CYP3A4*18*, has been described in Asians but has not been detected in the European population. Studies indicate a possible role of *CYP3A* polymorphisms in PK modulation and dosing of some drug-substrates such as statins, tacrolimus, cyclosporin, and DOACs [55]. The *CYP3A4*22* variant may increase the cholesterol-lowering efficacy of atorvastatin [56].

In a study of a Finish group [49] of individuals with the intermediate metabolizer *CYP3A4* genotype (*CYP3A4*2* or *CYP3A4*22* heterozygotes), 33% (p = 0.022) had larger atorvastatin AUC0–∞ compared to those with a normal metabolizer genotype. The same authors reported the results of a genome-wide association study (GWAS) of atorvastatin PK. Besides the relevance of the well-known variant *SLCO1B1* c.521T>C (rs4149056) for the increased AUC0–∞ of atorvastatin (140%), an intronic LPP variant, rs1975991 was found to be associated with reduced atorvastatin lactone; three *UGT1A* variants linked with *UGT1A3*2* were associated with increased 2-hydroxy atorvastatin lactone, and increased function *SLCO1B1* variants were associated with 41% smaller AUC0–∞. These data suggest that genetic variations in *SLCO1B1*, *UGT1A3*, *LPP*, and *CYP3A4* affect atorvastatin PK. The relevance of these newly discovered correlations for efficacy and side effects remains to be examined.

In addition to genetic predisposition, *CYP3A* variability is strongly influenced by environmental factors such as food, smoking, and other concurrently administered drugs, such as some azole compounds, antibiotics, antiepileptics. Citrus fruits, especially grapefruit juice, have considerable inhibitory effects on CYP3A4 already at the intestinal level, but they also have effects on the drug transporter, P-glycoprotein, which can result in increased bioavailability of drug-substrates [57].

Of phase II polymorphic enzymes, *UGT1A3*2* is relevant for statin therapy, which increases UGT1A3 enzyme expression and the lactonization of atorvastatin [58].

As for the transporters, polymorphisms of P-gp/ABCB1 and ABCG2 has been found to modulate PK of some statins [38,59,60].

3.2. Fibrates

In addition to statins, fibrates (gemfibrozil, fenofibric acid) and ezetimibe are often prescribed for MetS. Risk of myopathy increases if fibrates are given with statins [61].

Although the results of PGx research on these drugs are insufficient and there are no relevant guidelines, it is important to consider the pathways of metabolism and transport and the potential interactions in MetS polytherapy (Table 1). Drug interactions can additionally be complex and significant for the development of side effects in patients carrying inactivating ADME gene variants involved in the PK of drugs in use (drug–drug–gene interactions).

Table 1. Enzymes and transporters of metabolic syndrome drugs.

Group	Drug	ABCB1	ABCG2	CYP2C8	CYP2C9	CYP2C19	CYP2D6	CYP3A4/5	UGT1A	UGT1A9	UGT2B4	UGT2B7	SLC2A2	SLC22A/OCT	SLC47A1	SLC47A2	SLC5A2	SLCO1B1/OATP1B1	SLC29A4/PMAT	SLC47A1/MATE1	SLC47A2/MATE2	SP1
HMG-CoA Reductase Inhibitors	Simvastatin	+	+				+	+	+	+		+						+				
	Atorvastatin	+	+	+				+	+	+		+						+				
	Lovastatin	+				+		+	+	+		+						+				
	Pitavastatin	+	+	+	+			+	+			+						+				
	Fluvastatin	+	+	+	+													+				
	Rosuvastatin		+		+	+												+				
	Pravastatin	+	+															+				
Fibrates	Fenofibrate									+												
	Gemfibrozil	+																+				
SCAI	Ezetimibe	+	+															+				
BB	Atenolol						+											+				
	Bisoprolol	+					+	+														
	Carvedilol	+			+	+	+	+	+			+										
	Metoprolol						+	+						+								
	Nebivolol					+	+	+														
	Propranolol	+			+	+	+	+														
ARBs	Losartan	+			+	+		+	+			+										
CCBs	Amlodipine	+	+					+														
	Lacidipine		+					+														
	Lercanidipine		+					+														
	Diltiazem	+				+	+	+														
	Verapamil	+		+	+	+		+														
Biguanides	Metformin												+	+	+	+			+	+	+	+
Glitazones	Pioglitazone	+		+	+			+										+				
Sulphonylureas	Gliclazide				+	+																
	Glimepiride				+																	
	Glibenclamide		+		+	+		+														
SGLT2i	Empagliflozin	+	+						+	+		+					+	+				
	Ertugliflozin	+	+						+	+		+										
	Dapagliflozin	+			+		+	+		+	+	+										
	Canagliflozin	+			+			+		+	+											
GLP1-RA	Exenatide																					+
DPP4-inhibitors	Sitagliptin							+														
	Saxagliptin							+														

CCBs: calcium channel blockers, ARBs: angiotensin receptor blockers, BB: beta-blockers, GLP1-RA: glucagon-like peptide-1 receptor agonists, HMG-CoA reductase inhibitors: 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, SCAI: selective cholesterol absorption inhibitors, SGLT2i: sodium glucose co-transporter-2 inhibitors, DPP4-inhibitors: dipeptidyl peptidase-4 inhibitors.

Gemfibrozil undergoes hydroxylation and O-glucuronidation to form gemfibrozil 1-beta glucuronide, an inhibitor of CYP2C8 [62]. Glucuronidation is primarily mediated by UGT2B7 and several UGT1A enzymes. The metabolism of fenofibric acid is also mediated primarily by glucuronidation and excretion in urine.

As fibrates can inhibit some CYPs and UGTs [62] this can have important implications for the mechanism of the clinical interaction observed between gemfibrozil and CYP2C8 substrates such as cerivastatin (withdrawn from market), repaglinide, rosiglitazone, and pioglitazone.

Physiologically based PK models for prediction of complex CYP2C8 and OATP1B1 (*SLCO1B1*) drug–drug–gene interactions have been proposed for several drugs, including gemfibrozil, repaglinide and pioglitazone [63].

3.3. Selective Cholesterol Absorption Inhibitors

Ezetimibe, a selective cholesterol absorption inhibitor, is primarily metabolized in the liver and small intestine by glucuronide conjugation (UGT1A) with subsequent renal and biliary excretion [64]. It is also the substrate of several transporters (*ABCB1*, *ABCC2*, *ABCG2*, *SLCO1B1*) [65,66]. Various genetic polymorphisms seem to influence the PK of ezetimibe with different effects [67]. Ezetimibe also has the potential to interact (by inhibition) at the level of drug metabolism and transport. These interactions can be clinically significant, especially in patients with a PGx predisposition, i.e., with a low metabolic and/or transport capacity [68]. Relevant genetic polymorphisms for lipid-lowering drug therapy are not yet contemplated in guidelines.

3.4. Novel Lipid-Lowering Drugs

3.4.1. Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9) Inhibitors

PCSK9 inhibitors, alirocumab, and evolocumab are fully humanized monoclonal antibodies that target PCSK9, a serine protease primarily produced in the liver. PCSK9 binds to LDL receptors (LDL-Rs) on hepatocytes, leading to the degradation of LDL-Rs and elevated plasma LDL-C levels. By inhibiting this binding, these antibodies increase the expression of LDL-Rs on the hepatocyte surface and reduce plasma LDL-C levels [69]. They are given as subcutaneous injections, administered every 2 to 4 weeks, with flexibility to adjust the interval based on clinical judgment and patient outcomes. Evolocumab and alirocumab are composed solely of amino acids and carbohydrates, functioning as natural immunoglobulins. Consequently, they are unlikely to be metabolized via hepatic pathways. Instead, their metabolism and clearance are anticipated to follow the typical routes for immunoglobulins, leading to their degradation into smaller peptides and individual amino acids. Genetic variations in PCSK9 and LDLR genes may affect drug response, but significant pharmacogenetic insights are still lacking. Despite their efficacy, the pharmacogenetic landscape of PCSK9 inhibitors is still under development [69,70].

3.4.2. Inclisiran

Inclisiran, a small interfering RNA that inhibits PCSK9 synthesis, provides an even more efficient mechanism of action compared to monoclonal antibodies. It offers the advantage of less frequent dosing (as the initial dose is followed by a second dose after 3 months and the dosing regimen subsides to a 6-month interval), making it an efficient option for long-term management of hypercholesterolemia in metabolic syndrome [71].

Inclisiran is not a substrate for common drug transporters and, although in vitro studies have not been performed, it is not expected to be a cytochrome P450 substrate; therefore, it is not expected to have clinically significant interactions with other drugs. Although inclisiran's clinical efficacy and safety profile have been demonstrated, its pharmacogenetic implications need further investigation [70,71].

4. Pharmacogenetics of Antihypertensive Drugs

Arterial hypertension is a widespread global health issue affecting millions of people worldwide. Its prevalence varies across different populations and is influenced by factors such as age, gender, ethnicity, lifestyle, and genetics [72–74]. Clinicians frequently rely on a "trial-and-error" approach or a combination approach to identify the most suitable drug treatment for patients. However, hypertension PGx aims to discover genetic markers that predict individual drug responses. As new data emerge and evidence accumulates, there is potential for this field to reach a point where the evidence supports its clinical implementation [75,76].

Recent data on PGx and PK of beta-blockers (BBs), calcium channel blockers (CCBs), angiotensin receptor blockers (ARBs), and hydralazine and angiotensin converting enzyme inhibitors (ACEIs) will be presented.

Various antihypertensive medications, including BBs, CCBs, and ARBs, undergo hepatic metabolism primarily through CYP enzymes. This metabolism process contributes to

significant interindividual variability in drug response due to differences in enzyme expression and activity levels [74]. Polymorphisms, age, hepatic dysfunction, and conditions affecting hepatic blood supply contribute to changes in biotransformation, affecting drug exposure during antihypertensive therapy and cardiovascular response [77].

The labels of hydralazine, losartan, and metoprolol mention metabolic enzymes, implying that, if these enzymes are affected, the drug concentrations may be altered [78–80]. For some antihypertensive drugs, major society guidelines are available, as DPWG published guidelines for metoprolol and carvedilol that will be mentioned in the following section [80–82].

4.1. Beta-Blockers (BB)

Beta-adrenergic receptor antagonists, commonly known as BBs, are prescribed for various cardiovascular conditions, including heart failure, hypertension, and the secondary prevention of myocardial infarction. While some beta-blockers, like atenolol and nadolol, are eliminated unchanged in urine, most undergo hepatic metabolism. Carvedilol, metoprolol, nebivolol and propranolol, as a majority of BBs, are primarily metabolized by the highly polymorphic CYP2D6 enzyme. Factors affecting CYP2D6 activity, such as age, race, smoking, and concomitant medications, influence beta-blocker PK, leading to variability in drug response [83]. Common genetic variants in CYP2D6 can result in a range of enzyme phenotypes, from increased function due to gene duplication to complete loss of function due to gene deletion or splicing defects [84,85].

Metoprolol undergoes primary metabolism via the CYP2D6 enzyme. Approximately 8% of Caucasians and 2% of other populations lack CYP2D6 activity and are categorized as "CYP2D6 poor metabolizers" [86]. A retrospective cohort study by Collet et al. that aimed to evaluate adverse effects such as bradycardia, hypotension, and syncope in patients who were expected to have absent CYP2D6 enzyme activity due to DDIs or DGIs found statistically significant differences in the incidence of bradycardia amongst poor metabolizers and phenoconverters [87]. Phenoconversion occurs due to strong inhibition, in this case, of CYP2D6, causing patients who display normal or intermediate metabolism to mimic a poor metabolizer. Certain drugs that cause strong CYP2D6 inhibition and are frequently prescribed include antidepressant drugs (fluoxetine, paroxetine, bupropion), antifungic terbinafine, and antiarrhythmic propafenone [88]. Metoprolol and propafenone are common cardiological drug entities used in the treatment of atrial fibrillation, so the DDI of these drugs is important and should be noted [89]. CYP2D6 was investigated to have potential as a predictive biomarker of beta-blocker maintenance dose in heart failure patients. Consistent with the role of CYP2D6 in the metabolism of metoprolol, the tolerated maintenance dose of metoprolol was lower in *CYP2D6*4* carriers compared to non-carriers. Conversely, with the dosage of carvedilol, the finding was also consistent, as it was higher in *CYP2D6*4* carriers compared to non-carriers [90].

As aforementioned, the DPWG published guidelines for metoprolol that offer clinical genotype-guided dosing recommendations based on CYP2D6 metabolizer status. When prescribing metoprolol to CYP2D6 poor and intermediate metabolizers, if gradual heart rate reduction is desired or symptomatic bradycardia occurs, the guideline recommends using smaller titration steps and/or prescribing no more than 25% (poor metabolizers) or 50% (intermediate metabolizers) of the standard dose. Conversely, for CYP2D6 ultra-rapid metabolizers, the guideline suggests starting with the maximum dose for the relevant indication and, if needed, increasing it up to 2.5 times the standard dose or considering an alternative drug if efficacy remains insufficient [80,81].

Reguarding carvedilol, DPWG assessed the impact of the CYP2D6 genotype on carvedilol dosing and concluded that no dose adjustments are necessary based on this gene–drug interaction. Although variations in CYP2D6 metabolism may lead to differences in carvedilol plasma concentrations, these differences have not been shown to significantly affect the drug's efficacy or side effects [8,82].

Nebivolol, on the other hand, even though it is metabolized by CYP2D6 phenotypes, does not present a significant difference between poor metabolizer and extensive metabolizer patients and does not significantly affect clinical outcomes [91].

Although some evidence supports the influence of *CYP2D6* genetic polymorphisms on the PK of beta-blockers, the overall evidence on the use of genetic information in prescribing beta-blockers is weak [7,92].

As for other BBs, atenolol is a hydrophilic molecule that primarily goes through renal elimination, where only about 5% is metabolized by the liver [93]. Key factors influencing atenolol PK include transporter genes and their variants, and potential DDI in vitro studies suggest that the organic anions transporting polypeptides—OATP1A2 and OATP2B1 coded by *SLCO1A2* and *SLCO2B1*—are responsible for atenolol intestinal uptake [91]. These transporters are located on the luminal side of small intestine enterocytes. Uptake is inhibited by orange (*SLCO1A2*) and apple juice (SLCO2B) [94,95]. Apple juice ingestion reduced the systemic exposure to atenolol in healthy Korean population; nevertheless, genetic variations in *SLCO2B1* were unlikely to contribute to PK variability of atenolol [95].

4.2. Calcium Channel Blockers (CCBs)

CCBs are classified into two major categories, either non-dihydropyridines or dihydropyridines. CCBs are found to be a first agent of choice in hypertension but are also indicated for various cardiovascular diseases such as coronary spasm, angina pectoris, supraventricular dysrhythmias, hypertrophic cardiomyopathy, and pulmonary hypertension [96]. CCBs are largely metabolized through CYP3A5, with considerable interindividual variability due to differences in enzyme expression and activity.

In Chinese population *CYP3A5*3* allele was associated with better antihypertensive responses to amlodipine therapy [97,98]. Nevertheless, connections were not found between CYP3A5 variants in Korean and African American population [99,100]. The observed discrepancies in responses to amlodipine may be attributed to various factors, including ethnicity, environmental influences and others.

Regarding treatment induced ADRs, Liang et al. showed that allele frequencies of *CYP3A5*1D* (rs15524), *CYP3A5*1E* (rs4646453) and *CYP3A5*3* (rs776746) were significantly different between cases and controls ($p < 0.05$), associated with amlodipine-induced peripheral edema in Han Chinese patients with hypertension [101].

While some beta-blockers and ARBs have few significant PK interactions, interactions with CCBs are more prevalent due to their metabolism primarily through CYP3A isoenzymes. Non-dihydropyridine CCBs, verapamil and diltiazem, are strong inhibitors of CYP3A4, so further inhibition of hepatic activity could increase the risk of hypotension and bradycardia. Such inhibition might increase statin blood concentration, owing to DDIs. There is a possible risk of adverse reactions such as acute kidney injury following the co-prescription of CYP3A4 metabolized statins and CCBs that inhibit CYP3A4 [102].

Clinically important mechanism based CYP3A4 inhibitors include antibacterials (e.g., clarithromycin, erythromycin and isoniazid), anticancer agents (e.g., tamoxifen and irinotecan), anti-HIV agents (e.g., ritonavir and delavirdine), antihypertensives (e.g., hydralazine, verapamil and diltiazem), sex steroids and their receptor modulators (e.g., gestodene and raloxifene), and several herbal constituents (e.g., bergamottin and glabridin). Grapefruit juice, a known CYP3A4 inhibitor, can significantly alter the bioavailability of certain CCBs, impacting treatment efficacy and safety [53]. However, predicting DDIs involving CYP3A4 inactivation is difficult since the clinical outcomes depend on a number of factors that are associated with drugs and patients and the clinical relevance of the interaction is unclear [53,83].

4.3. Angiotensin Receptor Blockers (ARBs)

ARBs offer significant benefits in various conditions, including diabetic nephropathy, chronic heart failure, heart failure following myocardial infarction, hypertension with left ventricular hypertrophy, and in patients with a high cardiovascular risk due to previous

events or complicated diabetes. In the treatment of hypertension, ARBs can be chosen as first-line therapy or added during later stages of treatment titration [103].

Losartan is majorly metabolized by the CYP3A4, CYP2C9 and CYP2C10 isoenzymes [104]. Losartan is a prodrug, metabolized to its active carboxylic acid metabolite form E-3147 by CYP2C9, which is featured as its most important pathway [105]. The single *CYP2C9*3* variant significantly decreases losartan metabolism to its active form and its hypotensive effect [106,107]. Therefore, several studies have been conducted on the effect of CYP isoenzyme inhibitors/inducers on the concentration of losartan and E-3147. Fluconazole inhibits the metabolism of losartan to its E-3147 responsible for most of the angiotensin Il-receptor antagonism of losartan [108]; however, the percentage that would result in a relevant effect on blood pressure is unclear at this point [104].

The CKD-PGX study assessed uncontrolled hypertension (uHTN) in patients with chronic kidney conditions and concluded that variants in CYP2C9 had reduced efficacy (OR: 5.2; 95% and CI: 1.9 to 14.7). Conversely, individuals classified as intermediate metabolizers or poor metabolizers of the CYP2D6 enzyme, resulting in higher circulating concentrations of metoprolol or carvedilol, were less likely to have uHTN compared to normal metabolizers taking either agent (OR of 0.55; 95% CI of 0.3 to 0.95) [76].

4.4. Angiotensin Converting Enzyme Inhibitors (ACEIs)

ACEIs are common first choice antihypertensive drugs. These are prodrugs that undergo biotransformation upon administration. They release the active component through hydrolysis by esterases, primarily in the liver, plasma, and intestinal wall. The active metabolites of ACEIs are mainly eliminated through the kidneys, and conditions like renal failure or heart failure can prolong drug excretion. Unlike other drugs, ACEIs are not metabolized by CYP enzymes, thus reducing the variability in drug responses.

4.5. Vasodilators

Hydralazine is a direct vasodilator used as an oral agent in essential hypertension refractory to other therapeutic agents. Hydralazine undergoes phase-2 metabolism via acetylation, predominantly facilitated by N-acetyltransferase type 2 (NAT2) in the liver. Individuals classified as fast or intermediate acetylators may experience lower concentrations and reduced efficacy of hydralazine at a given dose [109].

The *NAT2*4* allele signifies the common rapid acetylator phenotype while alleles such as *NAT2*5*, **6*, and *7 indicate slow acetylators. Individuals with a combination of alleles, like *4/*5, are classified as intermediate acetylators [110]. Studies have demonstrated that rapid acetylators exhibit reduced hydralazine exposure compared to slow acetylators, potentially affecting the drug's efficacy. Notably, slow acetylators may experience greater blood pressure reduction.

However, the acetylator status has the potential to affect the risk of adverse effects. Although oral hydralazine use is sporadically associated with lupus-like symptoms, the relationship remains uncertain [111]. Indirect evidence suggests that slow acetylators may face a heightened risk of these adverse effects upon hydralazine exposure, but definitive conclusions are lacking [111,112]. Consequently, further research is necessary to establish the utility of NAT2 genotyping in predicting both the safety and effectiveness of hydralazine treatment.

5. Pharmacogenetics of Antihyperglycemic Drugs

Type 2 diabetes (T2D) is a chronic complex disease characterized by hyperglycemia due to a non-autoimmune progressive loss of adequate β-cell insulin secretion, frequently an underlying element of insulin resistance and metabolic syndrome [113]. Pharmacological therapy has changed in recent years due to new treatment strategies that, beyond improving glycemic control, take comorbidities, cardiovascular benefit, cardiorenal risk, chronic weight management, and risk of adverse events into consideration [114–116]. PGx is a promising concept for pharmacological treatment, as the response, effectiveness and safety

of drug classes for T2D could depend on genetic variability [117,118]. However, data regarding PGs and potential DDIs or DDGIs in recent drug classes for T2D remain scarce. Below is described the most relevant PGx and PKs findings of main antihyperglycemics drugs according to current clinical guidelines [114–118].

5.1. Biguanides

Metformin is a biguanide hypoglycemic agent that lowers basal and postprandial plasma glucose, suppresses hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Metformin is not metabolized and is excreted unchanged in the urine and distributed in the liver and kidney via various organic cation transporters [119–122].

PGx related to metformin has been studied with heterogeneous results for genes that encode organic cation transporters (OCTs), multidrug and toxin extrusion transporters (MATEs), plasma membrane monoamine transporters (PMATs), or others [123–125]. Up to the present date, for metformin, no data have been so far identified in the CPIC guidelines, PharmGKB, and in the prescribing information or Drug Label Annotation [45]. However, there are recently published studies in the literature, meta-analyses, GWAS, and clinical notes on the PGx of metformin.

According to its PK, after metformin oral consumption, it is first absorbed into intestinal epithelial cells by PMAT/*SLC29A4* and OCT3/*SLC22A3* and then transported into the blood by OCT1/*SLC22A1*. Subsequently, metformin binds to corresponding receptors and exerts its effects on various target cells through blood circulation. It is transported to the liver by OCT1/*SLC22A1* and OCT3/*SLC22A3* and then transferred into bile by the MATE1 protein. Alternatively, metformin is eliminated through the urine pathway, in which metformin is absorbed by OCT2 in the kidney and transported into the urine by MATE1 and MATE2 [123,125–128].

A review and meta-analysis evaluated the associations between OCT genetic polymorphisms and metformin response in individuals with T2D. A total of 30 related eligible studies about OCT genes (*SLC22A1*, *SLC22A1*, and *SLC22A3*) and metformin PGx were identified, and 14, three, and six single nucleotide polymorphisms (SNPs) in *SLC22A1*, *SLC22A1*, and *SLC22A3*, respectively, were investigated. The meta-analysis showed that *SLC22A1* rs622342 was associated with a reduction in HbA1c levels ($p = 0.001$). The GG genotype of *SLC22A1* rs628031 was associated with a reduction in fast plasma glucose levels (GG vs. AA: $p = 0.007$; GG vs. AG: $p < 0.001$) [125].

A GWAS studied the association between metformin response and variants on gene *SLC22A1*, the variants R61C and 420del were genotyped in a total of 3450 patients who were incident users of metformin with T2D. In 1531 patients that were identified as metformin responders, the R61C and 420del variants did not affected the initial HbA1c reduction ($p = 0.47$ and $p = 0.92$, respectively), the chance of achieving a treatment target ($p = 0.83$ and $p = 0.36$), the average HbA1c on monotherapy up to 42 months ($p = 0.44$ and $p = 0.75$), or the hazard of monotherapy failure ($p = 0.85$ and $p = 0.56$). The researchers concluded that the *SLC22A1* loss-of-function variants, R61C and 420del, did not attenuate the HbA1c reduction achieved by metformin in patients with T2D [126].

For gene SP1 variant rs2683511, allele C was associated with decreased HbA1c levels and secretory clearance when treated with metformin in people with T2D as compared to allele T [124]. With the variant rs784888, allele G was associated with decreased severity of hyperglycemia when treated with metformin in people T2D as compared to allele C. Allele C was not associated with exposure to metformin as compared to allele G [127,128].

It is important to mention that metformin only passes through the liver by its transporters, OCTs and MATEs, which is why they are of clinical relevance regarding DDIs [129]. Recent studies have highlighted various medications that can interfere with metformin uptake and elimination pathways, although a majority of them are on in vitro models. Proton-pump inhibitors, such as omeprazole, have been found to inhibit metformin transporters OCT1, OCT2, and OCT3 in vitro [130]. Regarding literature findings, transporter-mediated

interactions between metformin and certain tyrosine kinase inhibitors, such as imatinib, nilotinib, gefitinib, and erlotinib, which could impact metformin's efficacy, toxicity leading to potential state of lactic acidosis [131,132].

5.2. Thiazolidinedinones (TZDs)

Pioglitazone, a member of TZDs, belongs to a class of peripheral insulin sensitizer drug family. It is a specific activator of the peroxisome proliferator-activated receptor gamma (PPARG) and is extensively metabolized in the liver by hydroxylation and oxidation [133]. Four primary (M-I, M-II, M-IV and M-V) and two secondary metabolites (M-III and M-VI) have been described. The M-III and M-IV are the principal metabolites found in human serum after multiple dosings. The major contributors to pioglitazone metabolism are CYP2C8 and CYP3A4 [134–136]. Regarding pioglitazone transporters, *SLCO1B1* gene encodes the hepatic drug transporter OATP1B1, which may participate in transporting TZDs from the blood into the liver [118].

A study of pioglitazone PK in healthy African American volunteers found that the metabolites M-III AUC0-48 ratio was significantly lower in *CYP2C8*2* carriers than *CYP2C8*1* homozygote ($p = 0.006$). Similarly, *CYP2C8*2* carriers had a significantly lower M-III:M-IV AUC0-48 ratio than participants with the *CYP2C8 *1/*1* genotype ($p = 0.006$) [137]. In Chinese individuals, a study with 244 subjects suggested that the *CYP2C8*, *CYP3A5*, and *ABCB1* genes play no significant role in the interindividual variation of pioglitazone PK, whereas *CYP2C9 *1/*3* was significantly associated with increased metabolism of pioglitazone as compared to *CYP2C9 *1* [138].

Anther study that enrolled 30 healthy Caucasian subjects found that *CYP2C8*3* was associated with decreased pioglitazone plasma exposure AUC0, ∞ [139]. Also, after studied the effects of the co-administration of the CYP2C8 inhibitor trimethoprim and pioglitazone in 16 healthy subjects, a rise in the pioglitazone AUC 0, ∞ of 42% ($p < 0.001$) and a decreased formation rate of pioglitazone metabolites M-IV and M-III ($p < 0.001$) were observed. In the same study, during the placebo phase the *CYP2C8*3* variant was associated with a pioglitazone reduced AUC (0, ∞). Authors concluded that drug interactions and PGx affecting the CYP2C8 enzyme may change the safety of pioglitazone [140].

A study carried out in 80 T2D subjects concluded that gene ADIPOQ polymorphism rs2241766 T/G was significantly associated with pioglitazone efficacy. Patients with TG and TT genotypes had a better response to treatment measured by HbA1c decrease [141]. Also, there was an association between the CYP2C8*3 variant with less weight gain compared to the wildtype [142].

5.3. Sulphonylureas (SU)

Despite the advent of newer classes of antidiabetic medications, SU remain widely prescribed due to their efficacy and affordability. However, their use is not without controversy, particularly regarding the risk of hypoglycemia. The antihyperglycemic drug gliclazide is a first-generation SU. It binds to the β-cell sulfonylurea receptor, blocking ATP-sensitive potassium channels, enhancing insulin secretion from pancreatic beta cells. Accordingly, the PK is rapidly absorbed with peak plasma concentrations at 4–6 h after oral administration and is extensively metabolized in the liver by CYP2C9 and CYP2C19 [6,143,144]. In everyday clinical practice, the *CYP2C9* genotype may impact the likelihood of hypoglycemia events among elderly patients, but it does not seem to have the same effect across the broader population of individuals with type 2 diabetes [145].

Finding from the Go-DARTS study, involving 1073 patients treated with SU (with 80% receiving gliclazide), revealed that patients carrying two copies of the inactivating allele *CYP2C9*(*2, *3) were found to be 3.4 times more likely to achieve a treatment HbA1c level of less than 7% compared to the wild type, which resulted in a 0.5% greater reduction in HbA1c levels [146].

Pharmacokinetic studies found that CYP2C9*3/*3 carriers had only 20% clearance of glibenclamide and glimepiride compared to wild-type carriers [147]. Additionally, non-

diabetic *CYP2C9*2/*3* carriers showed a significantly reduced clearance of these drugs [148]. The DPWG evaluated therapeutic dose recommendations for glimepiride based on the *CYP2C9* genotype; after the evaluation, they concluded that no clinical practice action is needed for this gene–drug interaction [79].

Glucose-6-phosphate dehydrogenase (G6PD) mediates the production of NADPH and Ribose-5-phosphate and is one of the first genes found to be associated with variable drug response. Individuals with G6PD deficiency may have increased risks of adverse reactions. However, according CPIC guidelines, there are currently no clinical recommendations for dosing of gliclazide, glimepiride, or glipizide based on the G6PD genotype [7].

5.4. Sodium Glucose Co-Transporter-2 Inhibitors (SGLT2i)

Recent clinical practice guidelines of T2D give great value to SGLT2i (ertugliflozin, dapagliflozin, canagliflozin, and empagliflozin). These reduce the renal tubular glucose reabsorption that subsequently results in reduction in plasma glucose concentrations in blood [149].

SGLT2i rely primarily on glucuronidation for their metabolism. Ertugliflozin (via UGT1A9 and UGT2B7), dapagliflozin (via UGT1A9), canagliflozin (via UGT1A9 and UGT2B4), and empagliflozin (via UGT2B7, UGT1A3, UGT1A8, and UGT1A9) are transformed into inactive glucuronide conjugates. Oxidative metabolism via the CYP450 system is a minor pathway for these drugs. For dapagliflozin or canagliflozin, CYP3A4 may play a very minor role in the metabolism. Importantly, none of the drugs demonstrate clinically significant inhibition or induction of common CYP450 enzymes.

The UGT1A9 gene encodes UDP-glucuronosyltransferase, an enzyme that transforms drugs into soluble and excretable metabolites. SGLT2i are glucuronidased by UGT enzymes, thereby polymorphisms of their genes may potentially influence their treatment response [120]. A study with 134 participants indicated that alleles *UGT1A9*3* and *UGT2B4*2* increased canagliflozin plasma exposure [150]. Another study that had the aim to understand canagliflozin PK also indicates that carriers of the *UGT1A9*3* allele had greater exposure to canagliflozin [151].

Ertugliflozin is primarily metabolized via glucuronidation by enzyme UGT1A9. A study that included data from 25 phase 1 clinical trials evaluated the effect on 3 UGT1A9 polymorphisms (*UGT1A9-2152*, *UGT1A9*3*, *UGT1A9*1b*) on ertugliflozin exposure. Overall, the mean effects of the selected UGT1A9 variants on ertugliflozin AUC were within ±10%. These findings were considered not clinically meaningful in healthy subjects, and researchers concluded that no dose adjustments were required with the UGT1A9 variants assessed [152].

5.5. Glucagon-like Peptide-1 Receptor Agonists (GLP1-RA)

GLP1-RA bind and activate the GLP-1 receptor, the endogenous incretin hormone that potentiates glucose-dependent insulin secretion from the pancreatic beta cells. The synthetic GLP1-RA receptor agonists (exenatide, liraglutide, dulaglutide, semaglutide, lixisenatide) are variably resistant to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4) and therefore have a longer half-life.

Semaglutide is extensively metabolized through proteolytic cleavage of the peptide backbone and sequential beta-oxidation of the fatty acid side chain. The enzyme neutral endopeptidase (NEP) is expected to be involved in semaglutide metabolism. Liraglutide is primarily excreted intact, while exenatide is eliminated independently of the dose by glomerular filtration [153–155].

The last approved antihyperglycemic drug, tirzepatide, is a dual GIP and GLP-1 receptor agonist. According to PK, 99% is bound to plasma albumin and is metabolized by proteolytic cleavage of the peptide backbone, beta oxidation of the C20 fatty diacid moiety, and amide hydrolysis [156]. To the best of our knowledge, through searching the literature, no relevant PGx evidence for tirzepatide was currently identified.

Although novelty drugs GLP1-RA and tirzepatide revolutionized the treatment of obesity, and therefore MetS, most of the PGx studies are based on PD rather than PK aspects.

5.6. Dipeptidyl Peptidase-4 (DPP-4) Inhibitors

DPP-4 inhibitors are a class of oral glucose-lowering agents which accomplish their glucose lowering effect by inhibiting the DPP-4 enzyme, which is responsible for the rapid degradation of incretin hormones such as GLP-1 and GIP. By inhibiting DPP-4, these drugs prolong the activity of incretin hormones, thereby enhancing glucose-dependent insulin secretion and suppressing glucagon release, which contributes to better glycemic control [114,115,157,158].

DPP-4 inhibitors generally exhibit no significant interactions with other drugs, and gliptins do not markedly alter the pharmacokinetics or exposure of co-administered medications. As a result, dosage adjustments are typically unnecessary when gliptins are used in combination with other pharmacological agents. However, important exceptions exist with sitagliptin and saxagliptin [158–161].

Sitagliptin is only minimally metabolized in the liver, with over 80% being excreted intact in urine [161]. Minor metabolic pathways are mediated mainly by CYP3A4 and to a lesser extent by CYP2C8. Still, a few case reports have suggested the possible inhibition of CYP3A4 and/or p-glycoprotein as well as sitagliptin-mediated impairments in renal function as causes of potential interactions [162–165]. Sitagliptin had no significant impact on simvastatin pharmacokinetics in one crossover study, increasing the AUC of the active simvastatin by only 1% [166]. Further studies are necessary to assess the in vivo impact of sitagliptin on the CYP3A4 enzyme system and to explore additional mechanisms that may contribute to these DDIs.

While selected, higher-risk individuals may experience a greater-than-average interaction between these agents, possibly explaining these few observed cases, it seems at least equally plausible that other factors, besides a sitagliptin–statin interaction, account for the toxicity observed in these cases.

Saxagliptin undergoes metabolism to an active metabolite via CYP3A4/5 enzymes. When co-administered with potent CYP3A4/5 inhibitors (e.g., ketoconazole, diltiazem) or inducers (e.g., rifampicin, dexamethasone), the exposure to saxagliptin and its primary metabolite is significantly altered [167]. In such cases, careful monitoring of glycemic control is essential.

6. Discussion

Metabolic syndrome represents a major global health challenge in today's world. The need to manage its risk factors and complications often leads to polypharmacy, significantly increasing the potential for undesirable outcomes such as ADRs, DDIs, DDGIs, poor treatment adherence, and medication errors. Furthermore, the financial burden of therapy rises with the number of medications prescribed, a cost that escalates further in the event of ADRs.

After a clear correlation has been established between genetic defects in drug-metabolizing enzymes and drug transporters and their impact on the efficacy and toxicity of certain drugs, some clinical guidelines for healthcare professionals have been developed and published by different working groups and organizations (CPIC, DPWG, PharmGKB). Depending on the scientific evidence, these guidelines and recommendations can be included in Patient Information Leaflets (PILs) and Summaries of Product Characteristics (SmPCs) by regulatory agencies such as the FDA and EMA. These guidelines significantly contribute to the transfer and implementation of pharmacogenetic knowledge into clinical practice.

Regarding clinical practice recommendations based on clinical pharmacogenetics, among the medications reviewed for MetS, we identified only the CPIC guideline for statins, considering the SLCO1B1, ABCG2, and CYP2C9 genotypes. This guideline provides statin recommendations (preferred intensity and dose) based on the SLCO1B1 phenotype and the risk of statin-associated muscle symptoms (SAMSs). For instance, in a patient

with poor SLCO1B1 function requiring high-intensity statin therapy, simvastatin and atorvastatin are to be avoided due to their elevated SAMSs risk. Rosuvastatin (5–10 mg) or pitavastatin (2–4 mg) are recommended as safer alternatives. Recommendations for ABCG2 are specific to rosuvastatin, suggesting a starting dose of ≤20 mg for individuals with a poor ABCG2 function. If a higher dose is necessary, an alternative statin or combination therapy (e.g., statin + ezetimibe) is advised. CYP2C9 phenotype-based recommendations pertain to fluvastatin, with intermediate metabolizers avoiding doses > 40 mg and poor metabolizers avoiding doses > 20 mg. If higher doses are required, an alternative statin is recommended. If fluvastatin is necessary, combination therapy (40 mg for intermediate metabolizers, 20 mg for poor metabolizers) with a non-statin lipid-lowering agent is suggested. This guideline exemplifies an ideal approach to consider pharmacokinetics, adverse drug reactions (ADRs), and drug–drug interactions (DDIs) when prescribing. It would be beneficial to have more guidelines focused on MetS drugs in the future.

In daily MetS management, clinicians frequently prescribe overlapping regimens of lipid-lowering drugs, antihypertensives, and antihyperglycemic drugs. For this reason, it is of great relevance to identify and understand the potential DDIs and DDGIs within these regimens (Tables 1 and 2).

Table 2. Drug–drug interactions based on the Lexidrug database.

Substrate	Inhibitor	Relevant Genotype	Effect	Reference	Risk Rating
SLCO1B1-mediated					
gliclazide glimepiride glipizide gliquidone	gemfibrozil	*SLCO1B*	increased risk of hypoglycemia	[142]	C
atorvastatin fluvastatin lovastatin pitavastatin pravastatin	gemfibrozil	*SLCO1B*	increased risk of myopathy	[63,155,156]	X
repaglinid	gemfibrozil	*SLCO1B* *CYP2C8*	increase the serum concentration of repaglinide	[63]	X
Various cytochrome P450 (CYP) enzymes					
pioglitazone rosiglitazone *	gemfibrozil	*CYP2C8*	decreased blood glucose, evidence of edema or hepatotoxicity	[131–133]	D/C *
simvastatin	diltiazem	*CYP3A5*3/*3*	increased risk of myopathy	[99]	D
atorvastatin lovastatin simvastatin	amlodipine diltiazem verapamil	*CYP3A4*	increase the serum concentration of simvastatin acute kidney injury, hyperkalemia	[99]	D
saxagliptin	diltiazem	*CYP3A4*	may increase the serum concentration of saxagliptin	[67]	C
sitagliptin	simvastatin	*CYP3A4*	increased risk of myopathy	[162–166]	C
atorvastatin, fluvastatin lovastatin pitavastatin pravastatin rosuvastatin simvastatin	fenofibrate	Uncertain (possible additive effect)	increased risk of myopathy	[61]	C

X, avoid combination; A, no known interaction; B, no action needed; C, monitor therapy; D, consider therapy modification. The * for rosiglitazone means rosiglitazone was withdrawn from the market.

With lipid-lowering drugs, ADRs such as SAMSs, with the use of PGx testing, are preventable. In the MetS population, the concomitant use of statins and calcium channel blockers is frequent. Simvastatin and amlodipine share the same metabolic pathway

through the enzyme CYP3A4. The product label advises against using them together if the dose of simvastatin exceeds 20 mg per day due to the risk of adverse effects. Similar caution should be applied to co-therapy involving amlodipine or losartan with atorvastatin and lovastatin, as both medications are also metabolized by CYP3A4 in the liver [157]. Despite existing statin clinical PGs practice guidelines recommendations, are focused primarily on polymorphisms of the SLCO1B1, ABCG2, and CYP2C9 genes. We have opted to include information on CYP3A4 polymorphisms in this text. This decision is based on the understanding that, while individual CYP3A4 variant effects may be modest, their cumulative impact or interactions with other factors (genetic, environmental, or drug-related) could hold clinical relevance.

Also, regarding statin-related toxicity, ABCG2 polymorphism should be taken into consideration when prescribing co-therapies. Potential interactions can arise between substrates (atorvastatin) and ABCG2 inhibitors (such as amlodipine, lacidipine and lercanidipine). For attending physicians, it is advisable to opt for drugs that do not inhibit the ABCG2 gene [41].

ABCG2 plays a crucial role in regulating the absorption of its substrates in the gut and facilitating their excretion into bile and urine, thereby decreasing the bioavailability of drugs that interact with it. There is a relatively common frequency of *ABCG2* polymorphisms in the population, with the genotype frequency for variants such as *ABCG2* c.421 C A reaching 10–15% among Caucasians [37]. Given the mentioned substrates, as well as inhibitors of ABCG2, there is a need for further research on the potential association of ABCG2 polymorphisms to avoid possible therapeutic difficulties.

Clinically relevant drug substrates of ABCG2 other than lipid-lowering drugs (rosuvastatin, atorvastatin, fluvastatin, ezetimibe, fibrates) are PPIs and anticoagulants (apixaban, rivaroxaban) [25–30]. Given that patients with metabolic syndrome are predisposed to cardiovascular disease (CVD), the potential DDGI is paramount, especially in prescribed anticoagulant drugs. This consideration underscores the importance of comprehensive medication management and genetic profiling in optimizing treatment efficacy and minimizing serious ADRs in this patient population.

For clinical practice, an important example of potential drug–drug interactions (DDIs) involving CYP2C9 genotypes could be the combined treatment of fluvastatin with medications commonly prescribed for comorbidities in patients with hyperlipidemia, such as losartan or valsartan (for hypertension) or glimepiride (for diabetes). While fluvastatin is a known CYP2C9 substrate, the co-administration of fluvastatin with other medications that interact with CYP2C9, such as losartan, valsartan, or glimepiride (whether as weak or moderate inhibitors or inducers), could potentially alter fluvastatin exposure. In the case of CYP2C9 inhibitors, this could lead to increased fluvastatin levels, particularly in individuals with CYP2C9 poor metabolizer genotypes, due to their inherently reduced CYP2C9 enzyme activity. This heightened exposure might increase the risk of dose-related adverse events such as myopathy. Conversely, if a co-administered medication induces CYP2C9 activity it could decrease fluvastatin levels, potentially leading to subtherapeutic concentrations.

Fibrates are dominantly favorable in the management of hypertriglyceridemia. Gemfibrozil, if given concomitantly with statin therapy, also has the potential to induce SAMSs [168–170]. On the other hand, gemfibrozil can interfere with pioglitazone. *CYP2C8*3* allele influences the variability of PK during the interaction between gemfibrozil, a CYP2C8 inhibitor, and pioglitazone, a CYP2C8 substrate. In a randomized, two-phase crossover study involving 30 healthy Caucasian participants, the findings revealed that the presence of the *CYP2C8*3* allele led to decreased plasma exposure of pioglitazone in vivo and significantly impacted the extent of the DDI between gemfibrozil and pioglitazone [139]. Furthermore, the observed effect of the genotype was consistent with findings from previous clinical studies, indicating approximately 25% to 30% lower plasma exposure of pioglitazone in carriers of the *CYP2C8*3* allele compared to individuals with the wild-type genotype [140].

Within our review, we searched for existing clinical recommendations and found that, although the PGs information of some drugs has been evaluated by CPIC and DPWG,

no dosing recommendations have been made for routine clinical practice in certain cases. Examples include carvedilol (CYP2D6), glimepiride (CYP2C9), and gliclazide, glimepiride, or glipizide (G6PD genotype) [7,8]. For instance, while the impact of CYP2D6 variations on carvedilol PK may not currently necessitate dose adjustments, ongoing research could reveal subtle differences in efficacy or safety profiles among different metabolizer phenotypes. Similarly, further investigation into the effects of CYP2C9 and G6PD genotypes on the metabolism and response to antidiabetic medications like glimepiride and glipizide could potentially identify subgroups of patients who may benefit from personalized dosing strategies. Therefore, the absence of current recommendations should not be interpreted as a lack of potential clinical relevance for PGs in these cases. Rather, it highlights the need for continued research and the importance of staying abreast of emerging evidence in this rapidly evolving field.

While the interactions between one drug and a polymorphic enzyme or transporter genes is documented in some cases, our knowledge about the role of PGx in polypharmacy is still insufficient. As can be seen from Table 1, many drugs used in the treatment of MetS often share the same metabolic and transport pathways. The presence of polymorphic low- or high-activity variants of relevant genes along with drug interactions represent a significant risk for the development of ADRs and/or ineffectiveness. These are important challenges for future research on the role of PGx in the treatment of MetS.

Pharmacogenetic testing has the potential to identify patients at risk, but its widespread adoption in clinical practice faces challenges such as center availability of genetic testing, patient selection, result interpretation, and incorporation into treatment decisions. Pre-emptive pharmacogenetic analysis, coupled with assessing DDGIs, could enhance personalized drug and dose selection, reducing the incidence of ADRs.

We advocate for the integration of pharmacogenetic testing into routine clinical practice to optimize medication management in complex patient populations. By elucidating how genetic variations influence drug responses and interactions, pharmacogenomic testing offers a promising avenue for personalized treatment approaches, optimizing treatment outcomes and enhancing patient safety in the face of complex medication regimens. Further larger studies are needed and would enable us to come closer to implementing personalized treatment for patients with MetS.

Author Contributions: Conceptualization, A.B., J.M.-P. and D.V.; investigation, S.K., F.F.-A., T.B. and A.B.; data curation, S.K., F.F.-A., T.B. and A.B.; writing—original draft preparation, S.K., F.F.-A., T.B. and A.B.; writing—review and editing, all authors; supervision, A.B., T.B., J.M.-P. and D.V.; project administration, S.K. and A.B. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

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