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Research Article

Genetic Variation in CYP2D6 and Adverse Effects in Cardiovascular Patients on Metoprolol Therapy

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Abstract

The CYP2D6 genetic variation seems to be important for several clinically used drugs including metoprolol. The frequency of adverse effects of metoprolol may vary depending upon the genotype of CYP2D6. However, how CYP2D6 genetic variation affects metoprolol's adverse effects is not well understood in the Pakistani population. In this study, we prospectively included Pakistani patients who started metoprolol treatment for cardiovascular indications. Decisions on inclusion and exclusion were made without awareness of the *CYP2D6* genotype. Before intake of the first metoprolol dose, detailed medical history, baseline clinical characteristics, and laboratory indices were obtained. For *CYP2D6* polymorphism examination, 5 ml of venous blood was collected and stored in a −80°C refrigerator until analysis. This study was approved by the Ethics Board of the Kohat University of Science & Technology and was conducted in line with the ethical guidelines of the 1975 Declaration of Helsinki. Our results showed that all the patients were wild type for this CYP2D6*6 (rs5030655) and no variant allele was found. For CYP2D6*4(rs1065852), 60 patients were wild type, 27 were heterozygous and only 3 patients were homozygous mutants for this single nucleotide polymorphism. Dizziness, bradycardia, and hypotension were more frequently observed adverse effects than lightheadedness and syncope. The frequency of adverse effects was hypotension (20), bradycardia (21), lightheadedness (16), dizziness (45), and syncope (13). The distribution of adverse effects in different genotypes of CYP2D6*4(rs1065852) reveals that this genetic variation is not associated with the adverse effects experienced by metoprolol users in a Pakistani cohort with cardiovascular indications.

Keywords: CYP2D6, metoprolol, genetic variation, adverse effects, single nucleotide polymorphism

1. Introduction

The cytochrome P450 2D6 (*CYP2D6*) is not only responsible for the expression of about 20% of all hepatic enzymes but also plays a critical role in the metabolism of a remarkable 25% of drugs (Zanger and Schwab 2013). Pharmacogenomic studies found growing evidence establishing causality between *CYP2D6* gene allelic variants and fluctuating responses to some therapeutic agents (Whirl-Carrillo et al. 2012). To date, more than 100 variations, primarily single nucleotide polymorphisms and copy number variants, have been reported (Zanger and Schwab 2013). These variations may lead to an increased CYP2D6 metabolic activity, thereby affecting drug metabolism and pharmacokinetic profiles across multiple drug classes (Swen et al. 2011). To characterize the *CYP2D6* metabolic activity of individuals, treatment guidelines classify four phenotypes: poor metabolizers (PM), intermediate metabolizers (IM), extensive metabolizers (EM), and ultra-rapid metabolizers (UM) (Swen et al. 2011, Crews et al. 2014, Hicks et al. 2015, Relling et al. 2011). The prevalence of *CYP2D6* phenotypes is predicted to be 0.4 to 5.4%, 0.4 to 11%, 67 to 90%, and 1 to 21% for PM,

Table 1: Baseline characteristics of the investigated sample.

Variable		Mean/n	SD/%
Age		52	12
Male		58	65
Smoking		27	30
BMI (kg/m²)		21	2.7
Systolic BP (mm Hg)		138	14
Diastolic BP (mm Hg)		79	10
Heart Rate (bpm)		76	11
Creatinine (mmol/L)		85	21.2
Metoprolol Indication			
	Hypertension	63	70
	Ischemic Heart Disease	32	36
	Heart Failure	31	35
	Other Indications	11	12
Concurrent Drugs			
	Ca Channel Blockers	47	52
	ACEI/ARB	46	51
	Diuretics	29	32
	Other Drugs	5	6

IM, EM, and UM respectively (Gaedigk et al. 2017).

Metoprolol is a cardio-selective β_1-blocker. It is widely regarded by physicians as a gold standard therapy for a number of cardiovascular diseases, which includes heart failure, coronary artery disease, and hypertension (McDonagh et al. 2021). Notably, CYP2D6 in the liver is responsible for metabolizing 70%–80% of orally administered metoprolol (Zisaki, Miskovic, and Hatzimanikatis 2015). However, the metabolites of this drug have minimal pharmacological effects. Strong evidence supports the notion that the highly polymorphic *CYP2D6* gene influences the therapeutic outcome to metoprolol (Anstensrud et al. 2020).

Additionally, numerous research papers reported a link between therapeutic response to metoprolol and *CYP2D6* phenotype. Reduced CYP2D6 function typically correlates with a more pronounced effect of metoprolol, such as lower blood pressure (Batty et al. 2014, Thomas et al. 2020) and a slowed heart rate (Batty et al. 2014, Thomas et al. 2020, Meloche et al. 2020). However, despite compelling evidence, a significant connection between directly-reported symptoms of clinical significance, by the patients receiving metoprolol, and *CYP2D6* phenotype remains obscure. This uncertainty is due to studies that reported both negative (Wuttke et al. 2002, Anstensrud et al. 2020, Bijl et al. 2009, Chen et al. 2022) and positive (Poulussen et al. 2019, Zineh et al. 2004, Fux et al. 2005, Hamadeh et al. 2014) associations. The Dutch Pharmacogenomics Working Group (DPWG) has issued guidelines for prescribing drugs affected by *CYP2D6* variations (Whirl-Carrillo et al. 2012). For PMs, DPWG guidelines recommend either a gradual increase in the metoprolol or prescribing less than a quarter of the usual dose. This indicates that there will be a 75% reduction in the dosage for patients who fall in the PM category for metoprolol. Therefore, in the present study, we investigated the influence of the CYP2D6*4 and CYP2D6*6 polymorphisms on the adverse effects of metoprolol in cardiovascular patients in a Pakistani cohort.

Table 2: Allelic and genotype frequencies of the investigated cohort.

SNP	Genotype	Frequency
CYP2D6*4(rs1065852)		
	CC	60
	CT	27
	TT	3
CYP2D6*6 (rs5030655)		
	TT	90
	T-	0
	--	0

2. Materials and Methods

Patients were enrolled in this prospective study from the Dr. Naeem Ur Rehman Clinic, starting April 2021 to July 2022, to be given metoprolol treatment for cardiovascular indications. The drug regimen was formulated and adjusted freely by the doctors according to the individual patient baseline and clinical basis. Furthermore, inclusion and exclusion criteria were defined without the *CYP2D6* genotype awareness. Prior to the first metoprolol dose, comprehensive medical records, clinically relevant baseline characteristics, and laboratory indices were taken into account. For examining *CYP2D6* polymorphism, venous blood (5ml from each subject) was extracted and stored at −80°C. This study was approved by the Ethics Board of the Kohat University of Science & Technology. Moreover, the practices in this study adhered to the 1975 Declaration of Helsinki ethical guidelines. Each subject of the study provided informed written consent. The corresponding author, upon reasonable request, can provide the datasets utilized and/or analyzed during this study.

Following metoprolol treatment initiation, follow-ups were done via interviews through telephone fortnightly, and for 12 weeks patients' electronic medical records were reviewed to assess the metoprolol dose and adverse events correlation, if any. Instances of polypharmacy, including treatment with antiarrhythmic drugs, antihypertensives, and CYP2D6 inhibitors while treating with metoprolol, were recorded.

Adverse events, cardiovascular and non-cardiovascular, related to metoprolol were documented. Cardiovascular events included bradycardia (heart rate <55 bpm), postural hypotension, and cold extremities were considered as cardiovascular, whereas lightheadedness and dizziness were categorized as non-cardiovascular adverse effects.

Furthermore, a manual method was used to isolate genomic DNA from lymphocytes in whole blood. The methods used for the detection of *CYP2D6* alleles 4 and 6 were derived from (Martin Hersberger 2000)

Variables of categorical nature were presented as frequencies (%), whereas continuous variables were presented as the mean standard deviation. For categorical variables, the group differences were evaluated by employing a chi-squared test. Hardy–Weinberg equilibrium departure was tested for each of the *CYP2D6* alleles through the chi-squared test. To perform statistical analyses, SPSS 26.0 software (IBM Corporation, Armonk, NY, United States) was used. A p-value of < 0.05 was considered significant.

3. Results

Notably, patients' average age in our study was 52+12 years, 65% were male, and 30% were active smokers. Their mean BMI was 21+2.7 kg/m^2. Their mean systolic BP was 138+14 and diastolic BP was 79+10 (mmHg). The average creatinine levels were 85+21.2 mmol/L (Table 1). About 70% of patients were prescribed

Table 3: Adverse effects in metoprolol users observed in the study.

Adverse Effect	Frequency	CC	CT	TT	p-value CC vs (CT&TT)
Hypotension	20	14	5	1	0.233
Bradycardia	21	13	7	1	0.170
Lightheadedness	16	11	5	0	0.091
Dizziness	45	33	10	2	0.301
Syncope	13	9	4	0	0.562

metoprolol for hypertension, 36% for ischemic heart disease, 35% for heart failure, and 12% for other indications. Along with metoprolol, 52% of patients were receiving a calcium channel blocker, 51% were receiving ACEI/ARB, 32% were receiving diuretics, and 6% patients were receiving other drugs (Table 1).

Investigation of *CYP2D6**6 (rs5030655) revealed that all the patients were wild type for this SNP and no variant allele was found. For *CYP2D6**4(rs1065852), 60 patients were wild type, 27 were heterozygous and only 3 patients were homozygous mutants for this SNP (Table 2). Dizziness, bradycardia, and hypotension were more frequently observed adverse effects than lightheadedness and syncope. The frequency of adverse effects was hypotension (20), bradycardia (21), lightheadedness (16), dizziness (45), and syncope (13). The distribution of adverse effects in different genotypes of CYP2D6*4(rs1065852) is shown in Table 3. It is evident from Table 3 that this SNP is not associated with the adverse effects experienced by metoprolol users.

4. Discussion

The CPIC as well as the Dutch Pharmacogenetics Working Group guidelines recommend clinical considerations based on the *CYP2D6* phenotype (Bank et al. 2018) for appropriate drug and dose selection for different patients, in line with the purpose of precision medicine, guided by pharmacogenetics. This underscores the significance of accurately defining the *CYP2D6* phenotype.

It is well known that mutations in the *CYP2D6* allele vary substantially across ethnicities (Bradford 2002, Zhou, Ingelman-Sundberg, and Lauschke 2017). Known to produce Ums, *CYP2D6* allele duplication (e.g., **1×N*, **2×N*), rarely occurs in East Asians, less than 1% (Zhou, Ingelman-Sundberg, and Lauschke 2017, Crews et al. 2021). Compared to other metabolizers, ostensibly, UMs have an improved safety profile, as they possess a considerably higher CYP2D6 enzymatic activity (Blake et al. 2013, Meloche et al. 2020). Following metoprolol administration, UMs clear out the drug at a higher rate, leading to lower plasma concentrations. Although ultrarapid metabolizers might experience limited therapeutic efficacy, they are less prone to metoprolol-induced adverse effects.

We designed a short-term, prospective clinical study to probe the association of *CYP2D6* genotypes (CYP2D6*4 and CYP2D6*6) with metoprolol adverse events in 90 Pakistani patients suffering from cardiovascular diseases. During the course of metoprolol treatment, the most frequently reported incidences were bradycardia, postural hypotension, syncope, dizziness, as well as lightheadedness. However, the correlation between the incidence of non-cardiovascular adverse events *and CYP2D6* phenotypes was not significant.

Numerous studies focusing on the differences between PMs and non-PMs failed to include UMs and PMs in the Pakistani population. (Goryachkina et al. 2008) conducted a study that revealed that unlike NMs, IMs developed not only postural hypotension but also severe brad-

ycardia, when metoprolol was coupled with paroxetine. These occurrences demonstrated that patients who experience reduced CYP2D6 enzyme activity following the use of potent CYP2D6 inhibitors are more prone to phenotypically become CYP2D6 poor metabolizers compared to those with typical enzyme activity levels.

Overall, incidences of metoprolol-associated adverse effects, reported in this study, are similar to those reported previously (Zineh et al. 2004, Fux et al. 2005, Hamadeh et al. 2014). The metoprolol therapeutic window is narrow in advanced-age patients with cardiovascular diseases compared to the general population (Fux et al. 2005, Hamadeh et al. 2014), particularly in IMs than in NMs. However, due to the absence of a placebo group, the trends observed in this study cannot accurately determine the true frequency of adverse events. Additionally, directly comparing the incidences of adverse events among these conditions may be inappropriate since adverse events could be counted multiple times.

Previous research has found that patients receiving β-blockers experience a slight drop in heart rate or blood pressure, which may be a factor behind the significant lowering in the frequency of cardiovascular events (Cucherat 2007, Fisker, Grimm, and Wehland 2015, Hardy et al. 2015). Despite the long-term cardiovascular benefits of metoprolol treatment, a pronounced drop in blood pressure and heart rate can lead to dire outcomes in elderly patients with cardiovascular diseases. Furthermore, this study revealed that higher incidences of bradycardia, postural hypotension, and syncope predispose patients to disturbance in hemodynamic parameters, falls, and hospital readmissions.

However, this study had a few limitations. The first limitation pertains to the gender imbalance among the recruited participants, as most were male. Notably, the studies about baseline differences in CYP2D6 activity between male and female patients have conflicting results (Walle et al. 1989, Tamminga et al. 1999, Hägg, Spigset, and Dahlqvist 2001). However, (Borobia et al. 2009) dismissed the clinical relevance of these differences. The findings of this study provide some representation of patients taking metoprolol; nonetheless, additional studies with a greater number of female participants are required to validate our results. Another constraint of this study was that we considered only *CYP2D6*4 and *6* to determine individual *CYP2D6* phenotypes. Furthermore, no structural variants were identified in the current study. Therefore, complete and detailed genotyping analyses, including structural variants, are crucial for improving the accuracy of genotype-to-phenotype translation, an important point to be considered in future studies. Another significant parameter (metoprolol plasma concentration) was not measured; therefore, the extent of metoprolol accumulation could not be determined when patients presented with adverse events.

5. Conclusion

This short-term, prospective, clinical trial used the *CYP2D6*4 and *6 in Pakistani* patients suffering from cardiovascular diseases. In conclusion, the study found that these SNPs are not associated with metoprolol-induced adverse events.

Conflict of Interest

The authors declare that they have no competing interests.

Funding

No separate funding was received for this project.

Study Approval

This study was approved by the ethical committee of Kohat University of Science & Technology, Kohat, Pakistan.

Consent Forms

Consent forms are available with the authors.

Data Availability

All the data related to this study are available with the authors.

Authors Contribution

NS and MR conceptualized the study, NS, and AN performed the experiments, AN and MR analyzed the data, and MR wrote the final manuscript.

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References

Anstensrud, Anne Kristine, Espen Molden, Hans Jørgen Haug, Rehman Qazi, Hysen Muriq, Linn E Fosshaug, Olav Spigset, and Erik Øie. 2020. "Impact of genotype-predicted CYP2D6 metabolism on clinical effects and tolerability of metoprolol in patients after myocardial infarction–a prospective observational study." *European Journal of Clinical Pharmacology* no. 76:673-683.

Bank, PCD, KE Caudle, JJ Swen, RS Gammal, M Whirl-Carrillo, TE Klein, MV Relling, and H-J Guchelaar. 2018. "Comparison of the guidelines of the clinical pharmacogenetics implementation consortium and the dutch pharmacogenetics working group." *Clinical Pharmacology & Therapeutics* no. 103 (4):599-618.

Batty, JA, AS Hall, HL White, J Wikstrand, RA De Boer, DJ Van Veldhuisen, P Van Der Harst, F Waagstein, Å Hjalmarson, and J Kjekshus. 2014. "An investigation of CYP2D6 genotype and response to metoprolol CR/XL during dose titration in patients with heart failure: a MERIT-HF substudy." *Clinical Pharmacology & Therapeutics* no. 95 (3):321-330.

Bijl, MJ, LE Visser, RHN Van Schaik, JA Kors, JCM Witteman, Albert Hofman, AG Vulto, Teun van Gelder, and BHCh Stricker. 2009. "Genetic variation in the CYP2D6 gene is associated with a lower heart rate and blood pressure in β-blocker users." *Clinical Pharmacology & Therapeutics* no. 85 (1):45-50.

Blake, Charlene M, ED Kharasch, M Schwab, and P Nagele. 2013. "A meta-analysis of CYP2D6 metabolizer phenotype and metoprolol pharmacokinetics." *Clinical Pharmacology & Therapeutics* no. 94 (3):394-399.

Borobia, Alberto M, Jesús Novalbos, Pedro Guerra-López, Rosario López-Rodríguez, Beatriz Tabares, Vanesa Rodríguez, Francisco Abad-Santos, and Antonio J Carcas. 2009. "Influence of sex and CYP2D6 genotype on mirtazapine disposition, evaluated in Spanish healthy volunteers." *Pharmacological research* no. 59 (6):393-398.

Bradford, L DiAnne. 2002. "CYP2D6 allele frequency in European Caucasians, Asians, Africans and their descendants." *Pharmacogenomics* no. 3 (2):229-243.

Chen, Jianqiao, Jin Zheng, Zifan Zhu, Benchuan Hao, Miao Wang, Huiying Li, Yulun Cai, Shiqi Wang, Jun Li, and Hongbin Liu. 2022. "Impact of the CYP2D6 genotype on metoprolol tolerance and adverse events in elderly Chinese patients with cardiovascular diseases." *Frontiers in Pharmacology* no. 13:876392.

Crews, Kristine R, Andrea Gaedigk, Henry M Dunnenberger, J Steve Leeder, Teri E Klein, Kelly E Caudle, Cyrine E Haidar, Danny D Shen, John T Callaghan, and Senthilkumar Sadhasivam. 2014. "Clinical Pharmacogenetics Implementation Consortium guidelines for cytochrome P450 2D6 genotype and codeine therapy: 2014 update." *Clinical*

Pharmacology & Therapeutics no. 95 (4):376-382.

Crews, Kristine R, Andrew A Monte, Rachel Huddart, Kelly E Caudle, Evan D Kharasch, Andrea Gaedigk, Henry M Dunnenberger, J Steven Leeder, John T Callaghan, and Caroline Flora Samer. 2021. "Clinical pharmacogenetics implementation consortium guideline for CYP2D6, OPRM1, and COMT genotypes and select opioid therapy." *Clinical Pharmacology & Therapeutics* no. 110 (4):888-896.

Cucherat, Michel. 2007. "Quantitative relationship between resting heart rate reduction and magnitude of clinical benefits in post-myocardial infarction: a meta-regression of randomized clinical trials." *European heart journal* no. 28 (24):3012-3019.

Fisker, Filip Y, Daniela Grimm, and Markus Wehland. 2015. "Third-generation beta-adrenoceptor antagonists in the treatment of hypertension and heart failure." *Basic & clinical pharmacology & toxicology* no. 117 (1):5-14.

Fux, Richard, Klaus Mörike, Anne MT Pröhmer, Ursula Delabar, Matthias Schwab, Elke Schaeffeler, Gernot Lorenz, Christoph H Gleiter, Michel Eichelbaum, and Kari T Kivistö. 2005. "Impact of CYP2D6 genotype on adverse effects during treatment with metoprolol: a prospective clinical study." *Clinical Pharmacology & Therapeutics* no. 78 (4):378-387.

Gaedigk, Andrea, Katrin Sangkuhl, Michelle Whirl-Carrillo, Teri Klein, and J Steven Leeder. 2017. "Prediction of CYP2D6 phenotype from genotype across world populations." *Genetics in Medicine* no. 19 (1):69-76.

Goryachkina, Ksenia, Aleksandra Burbello, Svetlana Boldueva, Svetlana Babak, Ulf Bergman, and Leif Bertilsson. 2008. "Inhibition of metoprolol metabolism and potentiation of its effects by paroxetine in routinely treated patients with acute myocardial infarction (AMI)." *European journal of clinical pharmacology* no. 64:275-282.

Hägg, Staffan, Olav Spigset, and Rune Dahlqvist. 2001. "Influence of gender and oral contraceptives on CYP2D6 and CYP2C19 activity in healthy volunteers." *British journal of clinical pharmacology* no. 51 (2):169-173.

Hamadeh, Issam S, Taimour Y Langaee, Ruti Dwivedi, Sofia Garcia, Ben M Burkley, TC Skaar, AB Chapman, JG Gums, ST Turner, and Y Gong. 2014. "Impact of CYP2D6 polymorphisms on clinical efficacy and tolerability of metoprolol tartrate." *Clinical Pharmacology & Therapeutics* no. 96 (2):175-181.

Hardy, Shakia T, Laura R Loehr, Kenneth R Butler, Sujatro Chakladar, Patricia P Chang, Aaron R Folsom, Gerardo Heiss, Richard F MacLehose, Kunihiro Matsushita, and Christy L Avery. 2015. "Reducing the blood pressure–related burden of cardiovascular disease: impact of achievable improvements in blood pressure prevention and control." *Journal of the American Heart Association* no. 4 (10):e002276.

Hicks, J Kevin, Jeffrey R Bishop, Katrin Sangkuhl, Daniel J Müller, Yuan Ji, Susan G Leckband, J Steven Leeder, Rebecca L Graham, Dana L Chiulli, and Adrián LLerena. 2015. "Clinical Pharmacogenetics Implementation Consortium (CPIC) guideline for CYP2D6 and CYP2C19 genotypes and dosing of selective serotonin reuptake inhibitors." *Clinical Pharmacology & Therapeutics* no. 98 (2):127-134.

Martin Hersberger, Marti-Jaun, Jacqueline Rentsch, Katharina Hänseler, Edgar. 2000. "Rapid detection of the CYP2D6* 3, CYP2D6* 4, and CYP2D6* 6 alleles by

tetra-primer PCR and of the CYP2D6* 5 allele by multiplex long PCR." *Clinical Chemistry* no. 46 (8):1072-1077.

McDonagh, Theresa A, Marco Metra, Marianna Adamo, Roy S Gardner, Andreas Baumbach, Michael Böhm, Haran Burri, Javed Butler, Jelena Čelutkienė, and Ovidiu Chioncel. 2021. "2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC." *European heart journal* no. 42 (36):3599-3726.

Meloche, Maxime, Michael Khazaka, Imad Kassem, Amina Barhdadi, Marie-Pierre Dubé, and Simon de Denus. 2020. "CYP2D6 polymorphism and its impact on the clinical response to metoprolol: a systematic review and meta-analysis." *British journal of clinical pharmacology* no. 86 (6):1015-1033.

Poulussen, Fenna CP, Bas J Peters, Ken Ho Hua, Patrick Houthuizen, Rene J Grouls, and Maarten J Deenen. 2019. "The effect of the CYP2D6 genotype on the maintenance dose of metoprolol in a chronic Dutch patient population." *Pharmacogenetics and Genomics* no. 29 (7):179-182.

Relling, MV, EE Gardner, WJ Sandborn, K Schmiegelow, C-H Pui, SW Yee, CM Stein, M Carrillo, WE Evans, and TE Klein. 2011. "Clinical Pharmacogenetics Implementation Consortium guidelines for thiopurine methyltransferase genotype and thiopurine dosing." *Clinical Pharmacology & Therapeutics* no. 89 (3):387-391.

Swen, Jesse J, M Nijenhuis, Albert de Boer, L Grandia, Anke-Hilse Maitland-van der Zee, H Mulder, GAPJM Rongen, RHN Van Schaik, Talitha Schalekamp, and DJ Touw. 2011. "Pharmacogenetics: from bench to byte—an update of guidelines." *Clinical Pharmacology & Therapeutics* no. 89 (5):662-673.

Tamminga, WJ, J Wemer, B Oosterhuis, J Wieling, B Wilffert, LFMH De Leij, RA De Zeeuw, and JHG Jonkman. 1999. "CYP2D6 and CYP2C19 activity in a large population of Dutch healthy volunteers: indications for oral contraceptive-related gender differences." *European journal of clinical pharmacology* no. 55:177-184.

Thomas, Cameron D, Scott A Mosley, Sarah Kim, Karthik Lingineni, Nihal El Rouby, Taimour Y Langaee, Yan Gong, Danxin Wang, Siegfried O Schmidt, and Philip F Binkley. 2020. "Examination of metoprolol pharmacokinetics and pharmacodynamics across CYP2D6 genotype-derived activity scores." *CPT: Pharmacometrics & Systems Pharmacology* no. 9 (12):678-685.

Walle, Thomas, U Kristina Walle, T Douglas Cowart, and Edward C Conradi. 1989. "Pathway-selective sex differences in the metabolic clearance of propranolol in human subjects." *Clinical Pharmacology & Therapeutics* no. 46 (3):257-263.

Whirl-Carrillo, Michelle, Ellen M McDonagh, JM Hebert, Li Gong, K Sangkuhl, CF Thorn, Russ B Altman, and Teri E Klein. 2012. "Pharmacogenomics knowledge for personalized medicine." *Clinical Pharmacology & Therapeutics* no. 92 (4):414-417.

Wuttke, Henrike, Thomas Rau, Roland Heide, Klaus Bergmann, Michael Böhm, Joachim Weil, Dierk Werner, and Thomas Eschenhagen. 2002. "Increased frequency of cytochrome P450 2D6 poor metabolizers among patients with metoprolol-associated adverse effects." *Clinical Pharmacology & Therapeutics* no. 72 (4):429-437.

Zanger, Ulrich M, and Matthias Schwab. 2013. "Cytochrome P450 enzymes in drug metabolism: regulation of gene expression, enzyme activities, and impact of genetic variation." *Pharmacology & therapeutics* no. 138 (1):103-141.

Zhou, Yitian, Magnus Ingelman-Sundberg, and Volker M Lauschke. 2017. "Worldwide distribution of cytochrome P450 alleles: a meta-analysis of population-scale sequencing projects." *Clinical Pharmacology & Therapeutics* no. 102 (4):688-700.

Zineh, Issam, Amber L Beitelshees, Andrea Gaedigk, Joseph R Walker, Daniel F Pauly, Kathleen Eberst, J Steven Leeder, Michael S Phillips, Craig A Gelfand, and Julie A Johnson. 2004. "Pharmacokinetics and CYP2D6 genotypes do not predict metoprolol adverse events or efficacy in hypertension." *Clinical Pharmacology & Therapeutics* no. 76 (6):536-544.

Zisaki, Aikaterini, Ljubisa Miskovic, and Vassily Hatzimanikatis. 2015. "Antihypertensive drugs metabolism: an update to pharmacokinetic profiles and computational approaches." *Current pharmaceutical design* no. 21 (6):806-822.