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Predicting Interactions between Rifampin and Antihypertensive Drugs Using the Biopharmaceutics Drug Disposition Classification System

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Predicting interactions of antihypertensive drugs and rifampin in tuberculosis patients using BDDCS

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Abstract

Background Lack of blood pressure control is often seen in hypertensive patients concomitantly taking antituberculosis (TB) medications due to the complex drug-drug interactions between rifampin and antihypertensive drugs. Therefore, it is of clinical importance to understand the mechanism of interactions between rifampin and antihypertensive drugs, thereby allowing predictions and recommendations on the use of antihypertensive drugs in such co-medicated patients.

Objective To predict interactions between antihypertensive drugs and rifampin under the theory of the Biopharmaceutics Drug Disposition Classification System (BDDCS), taking into consideration the role of drug transporter and metabolic enzyme interactions, and to give guidance on the selection of antihypertensive drugs for patients with TB.

Methods Antihypertensive drugs approved by the FDA and the China FDA were included in this study. The drugs were classified into 4 categories under BDDCS. Detailed information of Cytochrome P450 enzymes and/or drug transporters of antihypertensive drugs were searched in Pubmed and electronic databases. Predictions were made under the theory of BDDCS according to the collected information. Then a systematic literature search for interventional and observational studies was carried out; studies published in Pubmed and two Chinese databases (CNKI and WanFang) through Jan 28, 2016 were included and data were extracted for validation of the predictions.

Results Pharmacokinetic or pharmacodynamic data for 15

antihypertensive drugs dosed together with rifampin were found and most of the antihypertensives are BDDCS Class 1 and 2 drugs. Under BDDCS theory, Class 3 active drugs, but excluding β blockers, are predicted to exhibit minimal interactions with rifampin. Taking into consideration transporter and metabolic enzyme information, olmesartan, telmisartan, angiotensin-converting enzyme inhibitors (ACEIs), spironolactone and hydrochlorothiazide may be recommended for patients concomitantly using rifampin without concern for clinically relevant interactions. A systematic literature search revealed 12 case reports and 18 before and after studies of relevance. Most of the studies involved calcium channel blockers (CCBs) and β blockers. The effects of rifampin on the reported drugs were in line with our predictions. The pharmacokinetic profiles and/or pharmacodynamic outcomes associated with CCBs were decreased markedly.
Conclusions Using BDDCS theory, we predicted the interactions between rifampin and antihypertensive drugs. When hypertensive patients start to take antituberculosis medications that include rifampin, it is recommended that the use of CCBs and β blockers should be avoided. ACEIs, olmesartan, telmisartan, spironolactone and hydrochlorothiazide would be preferable since interactions would not be expected.

Key Points

Using the theory of the Biopharmaceutics Drug Disposition Classification System (BDDCS), the interactions

between antihypertensive drugs and rifampin were predicted, taking into consideration drug transporters and metabolic enzymes.

Use of calcium channel blockers (CCBs) and β blockers should be avoided in hypertensive patients taking rifampin. Angiotensin-converting enzyme inhibitors (ACEIs), olmesartan, telmisartan, spironolactone and hydrochlorothiazide are recommended.

1 Introduction

Tuberculosis (TB) is one of the leading causes of morbidity and mortality worldwide. According to 2013 Global Burden of Disease estimates, the number of HIV-negative tuberculosis cases increased from 5.0 million in 1990 to 7.1 million in 2013 [1]. In addition, a survey in China in 2010 showed that among the individuals with TB, 56.6% (346 in 611 patients) were older than 60 years [2]. As the incidence of hypertension increases with age, it is likely that elderly people may have a greater chance to experience TB together with hypertension. A 2009 study reported that among 80 old individuals with TB, 39 (48.75%) also had hypertension [3]. Therefore, there is a high prevalence of patients concomitantly taking anti-TB medications and antihypertensive drugs and it is more likely for these patients to have drug-drug interactions. In clinical practice we found that blood pressure in patients with both TB and hypertension was difficult to control and the choice of antihypertensive drugs required elucidation.

Among the frequently-used anti-TB agents, rifampin, a

potent inducer of hepatic microsomal enzymes, Cytochromes P450 (CYPs), is known to reduce blood concentrations of many classes of medications that are metabolized in the liver. These interactions have been particularly problematic in the concurrent use of rifampin with antihypertensive drugs. Many case reports document that blood pressure in these patients is more difficult to control [4-15], with the majority of drugs utilized being calcium channel blockers. However, rifampin can also affect the function of drug transporters, being an inhibitor of organic anion transporter polypeptides (OATP) and an inducer and inhibitor of P-gp. By inhibiting OATP, rifampin could block OATP substrates from getting into the hepatocyte for further metabolism or biliary excretion, causing an increase in blood concentrations. For drugs that are dual substrates of CYPs and OATPs, the direction and extent of the interaction has not be systematically analyzed. A volunteer study revealed that rifampin had a different influence on both the pharmacokinetics and pharmacodynamics of glyburide when given in various ways of coadministration by inducing CYPs and/or inhibiting OATPs [16]. Induction of P-gp could have an effect on drug absorption, decreasing drug absorption and therefore decreasing systemic concentrations. Inhibition of P-gp will yield the opposite effects.

Therefore it should be highlighted that not only metabolic interactions but also transporter-based drug-drug interactions (tDDI) as well as transporter-enzyme interactions are ongoing between rifampin and antihypertensive drugs, which makes these DDIs more

complex and hard to predict. Previous case reports and human pharmacokinetic and pharmacodynamic studies have reported the interactions between rifampin and antihypertensive drugs. However, no systematic summary or prediction of these interactions has been presented. Recently te Brake et al. have evaluated the inhibitory potential of tuberculosis drugs on efflux transporters [17] and provide a listing in the supplementary material of potential drug substrates that could be affected. However, the only antihypertensive drug listed was verapamil, and no predictions were provided. Here we utilize the Biopharmaceutics Drug Disposition Classification System (BDDCS) to predict the direction of both tDDIs and metabolic interactions. BDDCS is an extension of the Biopharmaceutics Classification System (BCS) classifying drugs into four categories using the extent of metabolism or passive membrane permeability and solubility [18]. BDDCS is a useful system for predicting enzyme and/or transporter interplay based on a compound's in vitro characteristics.

In the present study, we used BDDCS to predict DDIs between rifampin and antihypertensive drugs, in order to give recommendations on the choice of hypertensive drugs. A thorough systematic literature review was carried out and all the published human studies and case reports were summarized for the validation of our predictions.

2 Methods

2.1 BDDCS Classification

Five main classes of antihypertensive drugs were included

in the study: angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), calcium channel blockers (CCBs), β blockers and diuretics. Drugs were searched in the database of FDA and China FDA (CFDA). Inclusive criteria were 1) oral administration; 2) indicated for hypertension; 3) marketing status was “prescription”. Drugs were BDDCS classified according to published literature [19, 20]. Four further antihypertensive drugs approved in South Korea and Europe were identified in clinical case reports or pharmacokinetic interactions studies and are included here. We have determined the BDDCS class of these drugs to be: tertatolol-Class 1; barnidipine and manidipine-Class 2; and fimasartan-Class 4.

2.2 CYP and transporter information

To identify CYP and transporter information for each drug, electronic databases including charite.bioinformatics.superCYP, UCSF-FDA TransPortal, and PubChem Compound were searched. Drugs without BDDCS classification were excluded, although for four drugs where relevant clinical data were available, we classified these compounds, as stated above. CYP and transporter information for rifampin was also collected.

2.3 Theoretical predictions

Based on BDDCS classification, the combined effect of CYPs and drug transporters for drugs in different BDDCS classes were predicted. Combined with the effects of rifampin on CYPs and transporters and the detailed

information of antihypertensive drugs, predictions of the direction and extent of rifampin effects on antihypertensive drugs were made.

2.4 Literature confirmation

Human studies were systematically searched in Pubmed and two Chinese databases (CNKI and WanFang) through Jan 28, 2016 using the strategy of “(rifampin OR rifampicin) AND (antihypertensive drugs OR amlodipine OR barnidipine OR benidipine OR felodipine OR manidipine OR nicardipine OR nifedipine OR nimodipine OR nisoldipine OR nitrendipine OR verapamil OR diltiazem OR benazepril OR captopril OR enalapril OR fosinopril OR imidapril OR lisinopril OR perindopril OR quinapril OR ramipril OR trandolapril OR candesartan OR eprosartan OR irbesartan OR losartan OR olmesartan OR telmisartan OR valsartan OR acebutolol OR atenolol OR betaxolol OR bevantolol OR bisoprolol OR carvedilol OR celiprolol OR labetalol OR metoprolol OR nadolol OR oxprenolol OR pindolol OR propranolol OR timolol OR hydrochlorothiazide OR indapamide OR spironolactone OR furosemide OR torasemide OR bumetanide)”, and limited to “human”.

Citations were eligible for possible inclusion if there were in agreement with the following inclusion criteria: 1) case reports or case series with clinical outcomes; 2) randomized controlled trials (RCTs), cohort studies or before and after studies with pharmacodynamic or pharmacokinetic outcomes.

Potential studies of interests were first screened by titles

and abstracts, then the full-text articles were acquired for detailed information. All the included studies were summarized, and the direction and extent of the DDI was applied to validate and further improve our predictions.

3 Results

3.1 BDDCS Classification

The FDA and CFDA databases were searched for the five main classes of antihypertensive drugs, and 58 drugs were included. In Table 1 we list these antihypertensive drugs approved by the FDA and CFDA plus the 4 drugs approved in South Korea or Europe for which we have clinical rifampin interaction data and 9 ACEI active metabolites (italicized). Of these 71 compounds, BDDCS categorization was known or determined for 53 antihypertensive drugs and 7 ACEI active metabolites.

3.2 CYP and transporter information

Rifampin is a dual inducer of CYPs and intestinal P-glycoprotein [21, 22]. We could find no studies that confirmed that rifampin may also induce intestinal BCRP in humans, but this has recently been confirmed in chickens [23], and because of regulatory overlap in humans, we expect that rifampin also induces BCRP, as so indicated in Table 2. Rifampin is a potent inhibitor of OATP and OAT [24], but not a strong inhibitor of P-gp and BCRP, IC_{50} values of 29 and 56 μM, respectively [17]. However, since the potential interaction between antihypertensive drugs and efflux transporters will occur in the gut, high concentrations of

rifampin at this site following oral dosing may still result in a significant interaction when rifampin is dosed orally. Therefore it is important to determine whether the antihypertensive drugs are substrates for all of these transporters. The corresponding information for 53 antihypertensive drugs were collected (Table 2).

It was shown that most of CCBs and β blockers are substrates of CYPs and/or P-gp. For ACEIs, only captopril and enalapril are substrates of CYPs.

Detailed CYP isoform information of antihypertensive drugs that are substrates of CYPs is listed in Table 3.

3.3 Theoretical predictions

3.3.1 Predicting combined effects of CYPs and transporters under BDDCS theory

As Benet and others have predicted, transporter effects on different classes of drugs following oral administration are different (Fig. 1). For Class 1 drugs, the effect of transporters can be ignored clinically. For Class 3 drugs, the effect of uptake transporters should be mainly considered, but efflux transporters can also have an effect on drug that is taken up. For Class 2 and Class 4 drugs, both uptake and efflux transporters could affect drug concentrations.

Thus, we could make predictions of DDIs taking into consideration BDDCS classes, transporters and CYPs profiles (Fig. 2). For Class 1 drugs, we should mainly consider CYP effects when co-administrated with enzyme inducers or inhibitors. For Class 2 drugs, both the effect of CYPs and transporters should be considered. Due to the low extent of

metabolism of Class 3 drugs, we should mainly consider the absorptive transporter effects, but once drug is taken up efflux transporter effects can be observed, whereas CYP effects will be minimal. For Class 4 drugs, transporter effects also predominate.

3.3.2 Predicting effects of rifampin on antihypertensive drugs

After predicting CYPs and transporter effects of different BDDCS classes of drugs, we could make predictions about the direction and extent of DDIs between rifampin and antihypertensive drugs (Fig. 3).

Since rifampin is a dual inducer of CYPs and P-gp as well as an inhibitor of OATP, we could predict that:

1) For **Class 1** drugs, when co-administrated with rifampin, if the drug is a substrate of CYPs, its concentration will be decreased. For drugs that are only a substrate of OATP, OAT or P-gp/BCRP, the effect could be ignored and rifampin should not affect their blood concentration.
2) For **Class 2** drugs, both the effect of CYPs and transporters should be considered. As a result, if the drug is a substrate of CYPs (and/or P-gp/BCRP) and not a substrate of OATP, its concentration will still be decreased by rifampin as for Class 1 drugs. Furthermore, for drugs that were both substrates of CYPs and P-gp/BCRP, the decreased effect may be greater. If the drug is a substrate of OATP but not CYPs, rifampin will increase its concentration if rifampin concentrations are measurable in the systemic fluids. That is, when rifampin dosing is

stopped the effect on OATP will end, although the induction effects on CYP enzymes and P-gp/BCRP will remain. However, if it is both a substrate of CYPs and OATP, because the opposite effects may counteract each other, the final concentration is hard to predict.

3) For **Class 3** drugs, induction of P-gp and inhibition of OATP should be the primary concern. Rifampin may increase the concentration of drugs that are substrates of OATP in the liver, but decrease the concentration of drugs that are substrates of OATP2B1 in the intestine (e.g., celiprolol and probably talinolol). Drugs in this class may also be substrates of CYPs, although their extent of metabolism is low. Therefore if CYPs are induced by rifampin, these drugs' concentration may decrease, too, although the decrease should be slight. For substrates of P-gp, such as β blockers, induction of P-gp will yield decreased concentrations. However, an oral dose of rifampin could also inhibit P-gp in the intestine while rifampin is present in the intestine. For continuous dosing of rifampin in TB we expect that the inducing effect on P-gp would be greater than the inhibition, although this has not been tested.
4) For **Class 4** drugs, the effects of CYPs and transporters should be similar to that seen for Class 3 drugs.

For drugs that are neither substrates of CYPs nor transporters, rifampin may not affect the concentration of these drugs.

According to the above predictions, there were three possible effects of rifampin on antihypertensive drugs:

1) **Decreased exposure**: CCBs, most β blockers and losartan;
2) **Increased exposure**: fimasartan, olmesartan, telmisartan, valsartan
3) **Unaffected**: ACEI active species, spironolactone hydrochlorothiazide, furosemide and candesartan

3.4 Literature confirmation

Reviewing actual pharmacokinetic and pharmacodynamic data, our predictions could be tested and confirmed. Therefore, a systematic literature search for both interventional and observational studies was carried out. The search of electronic databases resulted in 224 records in Pubmed, 52 records in CNKI and 51 records in WanFang, of which 37 were duplicate and 253 were not relevant. Within the remaining 37 records, seven studies were excluded through the full-text screening, due to the lack of PK data, full text not available or recalculation of a previous study [35-41]. As a result, 12 case reports and 18 before and after studies were included (Fig. 4).

The detailed information of the case reports and before and after studies between antihypertensive drugs and rifampin are summarized in Tables 4 and 5.

Of these case reports (Table 4), 55% of the drugs reported were CCBs, primarily nifedipine (Fig. 5). β blockers and ACEIs were also reported.

The before and after studies showed that rifampin reduced the area under the plasma concentration–time curve (AUC) of most antihypertensive drugs (Table 5). As shown in

Fig. 6, CCBs, β blockers and ARBs were affected by rifampin. The drugs were found to be in Class 1, 2 and 3 in BDDCS. For fimasartan, rifampin caused an increase in exposure [58] due to inhibition of hepatic uptake for this Class 4 drug primarily eliminated into the bile.

Among these drugs, verapamil was affected most, resulting in very poor blood pressure control, followed by nifedipine. The AUC of CCBs after pretreatment of rifampin decreased to 3.28% -35.7% of that found for control drug alone. The pharmacodynamic effects (e.g. blood pressure) were also statistically significant. AUC of the Class 2 drug, carvedilol, decreased to 37%-43% with significant decreased pharmacodynamic effects. Class 3 drugs exhibited different pharmacokinetic and pharmacodynamic results. For example, the AUC of the Class 3 drug celiprolol decreased 55.6%, with no significant pharmacodynamic changes reported [54], whereas atenolol's AUC decreased by 19% but the decrease in blood pressure was significant between groups [56]. We believe that the decreased AUC and effects for celiprolol and atenolol are due to P-gp induction by rifampin. Among these studies, fimasartan is the only studied antihypertensive drug with increased concentration by 4.60 fold [58], we suspect due to inhibition of OATP.

According to these pharmacokinetic data from before and after studies, we analyzed our predictions. Among the 53 drugs we included, 10 drugs had human pharmacokinetic data. For 6 of the 10 drugs with human pharmacokinetic data there were corresponding pharmacodynamic results. Pharmacodynamic effects were reported for an additional 3

drugs. The results of the rifampin effects on the 13 drugs are summarized in Fig. 7. Pharmacodynamic data appear to be available for captopril, lisinopril and perindopril in the case studies in Table 4, but these drugs were dosed together with and stopped with nifedipine, and thus their independent effect cannot be assessed.

4 Discussion

4.1 Why using BDDCS

Due to the complexity of drug-drug interactions, i.e., not only hepatic metabolism but also drug transporters are involved, it is important to find useful tools to give directions and a way of distinguishing potential DDIs. BDDCS is such a useful tool. One of the advantages of BDDCS is the prediction of transporter effects. The application of the predictions has been well demonstrated in several fields, such as the development of new molecular entities, biowaiver and the prediction of the brain disposition [18, 59, 60]. Therefore we made DDIs predictions under the BDDCS theory.

4.2 Explanation of the predictions

4.2.1 The direction and extent of the effects

The combined effects of CYPs and transporters were predicted based on the theory of BDDCS. Thus after classifying the antihypertensive drugs into BDDCS classes, we could make a prediction about the direction and potentially the extent of rifampin effects on these drugs. To confirm our predictions, we searched published

pharmacokinetic data that could document the actual extent of rifampin effects.

For drugs that were both substrates of CYPs and transporters, the complex interactions may be difficult to predict.

4.2.2 Active species must be considered when predicting effects

It should be noted that except for captopril and lisinopril, the other listed ACEIs are prodrugs. They are rapidly metabolized mainly by liver carboxylesterases to the active metabolites (although as indicated in Table 3, enalapril is a substrate of CYP3A4), which fall into Class 3 or 4 in BDDCS [19]. For these drugs, we use the active metabolites to predict potential DDIs. For class 3 and 4 drugs, the effect of rifampin on CYPs is minimal. Thus, it might be expected that class 3 and 4 drugs would be preferable versus highly metabolized class 1 and 2 drugs when rifampin is coadministered. However, there still could be transporter effects such as the induction of the efflux transporter P-gp or inhibition of OATP2B1 in the intestine both causing decreased drug absorption.

4.2.3 Extent of induction on different CYP isoforms

To better forecast the interactions, we should also consider the specific CYP isoforms of each drug. As shown in Table 3, drugs may be substrates of several CYP isoforms, while the extent of rifampin induction on CYP isoforms is different, as presented in Table 6 for *in vitro* studies. The

induction effect of rifampin was greatest for CYP2C19 and CYP3A4 isoforms and CYP2D6 may not be induced *in vitro*, although it was listed to be induced in one database (http://medicine.iupui.edu/flockhart/). Another review showed that CYP2D6 was largely uninducible by rifampin [61]. Madan *et al.* [62] have investigated the induction effect of rifampin on CYP isoforms in primary human hepatocytes, and found that CYP2D6 was not significantly induced by rifampin. Therefore, for drugs that are primarily substrates of CYP2D6, e.g. captopril, labetalol and pindolol, the rifampin effect may be too slight to be clinically relevant.

4.3 Actual effects of rifampin on antihypertensive drugs

Through the case reports and before and after studies reported here, we could see actual effects of rifampin on different antihypertensive drugs as presented in Fig. 7. Thus, we could test the reliability of our prediction. Furthermore, the extent of AUC change of drugs evaluated in before and after studies may help us have a better concept on probable dose adjustment.

As shown in Figs. 5 and 6, CCBs were reported to exhibit the greatest decrease in efficacy when co-administrated with rifampin, especially verapamil and nifedipine. The marked influence of rifampin on CCBs in Fig. 7 (barnidipine, manidipine, nifedipine and verapamil) is in accord with our prediction.

All of the seven β blockers where clinical data are

available (atenolol, bisoprolol, carvedilol, celiprolol, metoprolol, nadolol, propranolol) are substrates of CYPs and/or P-gp or intestinal OATP. Thus the reduced efficacy/lower AUC that is confirmed may result from reduced absorption and induced metabolism. It is interesting to note that the reduction in response results from three different interactions of rifampin, induced P-450 metabolism, induction of intestinal P-gp (or BCRP) or inhibition of intestinal OATP2B1.

Losartan and fimasartan are the only ARBs for which we have confirmatory data. Losartan is a Class 2 drug and a substrate of CYPs and P-gp, and as expected we observed a reduction of AUC in the before and after study [50]. Fimasartan is a Class 4 drug and a substrate of OATP, and yields the expected increase in AUC in the before and after study [58].

Amongst ACEIs, only captopril and enalapril were metabolized by CYPs. The Class 1 drug enalapril is a substrate of CYP3A4 and was reported in one case to exhibit decreased formation of the active metabolite enalaprilat when coadministered with rifampin [5]. The other ACEIs were all reported in cases together with CCBs and the reason for the loss of blood pressure control is difficult to distinguish.

Therefore, among the 53 drugs included here, the effects of all 13 drugs with published data were in line with our predictions.

Among frequently-used antihypertensive drugs reported in the before and after studies, the AUC of CCBs decreased markedly to below 10% after pretreatment by rifampin. The

AUC of metoprolol, losartan and carvedilol were also decreased. Thus the clinical effect should be observed and these drugs should be avoided.

4.4 Recommendations of coadministration

According to BDDCS theory, for antihypertensive drugs co-administrated with rifampin, Class 3 drugs, but not Class 3 β blockers, would be recommended. Documented decreases in systemic concentrations and pharmacodynamic effects with concomitant rifampin for the Class 3 β blockers atenolol, bisopralol, celiprolol and nadolol have been noted above. Thus, the frequently-used antihypertensive drugs bisoprolol, olmesartan, hydrochlorothiazide and ACEIs may be our first line of recommendation.

Thus in conclusion, when patients with tuberculosis are complicated with hypertension, it is inappropriate to use CCBs and β blockers when rifampin is included in the anti-TB regimen. Except for enalapril, ACEIs seem to be not affected by rifampin. Olmesartan and telmisartan are also recommended since efficacy may increase, provided blood pressure and adverse effects are monitored. Spironolactone, furosemide and hydrochlorothiazide may not be affected by rifampin. In summary, we would choose suitable drugs according to individual patients, and no matter which drug is used, blood pressure and adverse effects should be monitored regularly.

However, it should also be noted that the mode of co-administration is important. As for the above mentioned study of glyburide, the onset and duration of induction of

CYPs depends both on the kinetics of the drug and on the half-lives of CYP enzymes, which range from 1 to 6 days [66]. Usually it takes 4-14 days for peak induction. After withdrawing an inducer, increased enzyme activity will last for a period of time, and only returns to its original level in from 1-3 weeks [67]. However, the inhibition effect of transporters appears just after the administration when rifampin concentrations can be measured in the systemic circulation. As a result, for drugs that are both substrates of CYPs and drug transporters, such as fimasartan, co-administration of rifampin increases fimasartan blood concentration. However, several days after withdrawing rifampin, the inducing effect of enzymes still lasts so that blood pressure may rise and the dosage needs to be increased. As a result, we need to pay attention to dose adjustment in different periods, especially when starting and discontinuing rifampin treatment.

4.5 Limitations

By integrating the information concerning CYPs, transporters and BDDCS theory, we could make predictions of DDIs between rifampin and antihypertensive drugs. However, the predictions of the DDI directions and extents are general and only show a tendency, which cannot be guaranteed to occur. Also, it is difficult to quantify the effects followed by dose adjustment recommendations. More human studies are needed to be further investigated.

Since transport mechanisms are so complex in the human body, we recognize that there could be transporters and

substrates not yet discovered. So there may be further transporter information not yet discovered and collected in this study.

4.6 Making DDI predictions for other classes of drugs

Using BDDCS, we predicted the interactions between rifampin and antihypertensive drugs. This DDI prediction process could be also applied in general to other drug categories as follows: a. Classify drugs in BDDCS; b. Identify CYPs and transporter information for drugs of interest; c. Make DDI predictions under the theory of BDDCS; d. Give recommendations.

5 Application

We applied this way of considering DDIs in clinical practice, and made recommendations according to our study conclusions, resulting in a patients' blood pressure becoming under control.

A 65-year-old woman was referred to our hospital for the treatment of dyspnea and pleural effusion. The symptoms had persisted for one year and she was treated with anti-TB therapy one month before referral with levofloxacin 0.5 g qd, rifampin 450 mg qd, isoniazid 300 mg qd and ethambutol 0.75 g qd. She had a 6-year history of essential hypertension, which had been well-controlled with amlodipine 5 mg qd, losartan 50mg qd and hydrochlorothiazide 12.5 mg qd with her blood pressure (BP) under 140/90 mmHg. However, her BP rose to 188/80 mmHg on the day she came to our hospital. To control BP, long-

acting nifedipine 30 mg qd was prescribed to replace amlodipine. Her BP remained high, so sublingual nifedipine 10 mg and captopril 12.5 mg were prescribed. Her BP was 161-148/71-64 mmHg in four days.

As her BP was still out of control, the physician turned to us. In consideration of the interaction between rifampin and nifedipine, we recommended olmesartan or telmisartan. As a result, olmesartan 20 mg qd, in addition to hydrochlorothiazide 12.5 mg qd were used. Her blood pressure decreased significantly on the next day and was maintained at 138-125/70-60 mmHg until discharge. We have added olemsartan to Fig. 7 as a 15th confirmatory example based on this result. Olmesartan systemic concentrations may have been increased (as firmasartan) or unchanged, but antihypertensive efficacy was achieved.

6 Conclusion

Under the theory of BDDCS, we made predictions about DDIs between rifampin and antihypertensive drugs in order to select more suitable drugs for patients with both TB and hypertension. We found that CCBs and β blockers were likely to be affected greatly so that for such patients, these drugs were not suitable. Rather, ACEIs, olmesartan, telmisartan and hydrochlorothiazide are recommended. Reviewing case reports and before and after studies, the predictions we made were found to be reliable. Therefore the method of predicting DDIs may be also used for other drugs. Based on the analysis presented here, we have recommended effective antihypertensive drugs for patients in clinical practice and

their blood pressure was well controlled. Our study further expands the application of BDDCS in predicting drug-drug interactions.

However, it should be noted that the CYPs and transporters information we collected could not differentiate the mechanisms of all of the interactions and the prediction is only based on theory. The real effect of rifampin on antihypertensive drugs needs to be further observed. Further studies both in animals and humans are needed in the future.

Compliance with Ethical Standards

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Table 1 Classification of antihypertensive drugs in BDDCS.

	Class 1	Class 2	Class 3	Class 4	Unclassified
CCBs	Amlodipine Benidipine Diltiazem Nicardipine Verapamil	Barnidipine Felodipine Manidipine Nifedipine Nilvadipine Nimodipine Nisoldipine Nitrendipine			Azelnidipine Cilnidipine Lacidipine Lercanidipine
ACEIs	Benazepril Enalapril Imidapril Perindopril Ramipril	Fosinopril Quinapril Trandolapril	Captopril Lisinopril *Benazeprilat* *Enalaprilat* *Imidaprilat* *Quinaprilat* *Ramiprilat*	*Fosinoprilat* *Trandolaprilat*	Moexipril *Moexiprilat* *Perindoprilat*
ARBs		Losartan Irbesartan Telmisartan	Olmesartan	Candesartan Eprosartan Fimasartan Valsartan	Allisartan Azilsartan
β blockers	Acebutolol Betaxolol Labetalol Metoprolol Oxprenolol Pindolol Propranolol Tertalolol Timolol	Bevantolol Carvedilol	Atenolol Bisoprolol Celiprolol Nadolol Talinolol		Arotinolol Nebivolol
Diuretics	Indapamide	Spironolactone Torasemide	Bumetanide Hydrochlorothiazide	Furosemide	

CCBs calcium channel blockers, ACEIs angiotensin-converting enzyme inhibitors, ARBs angiotensin receptor blockers. Italicized are active metabolites of ACEIs.

Table 2 CYPs and transporters information of rifampin and classes of antihypertensive drugs [17, 19, 20, 24-34].

		CYPs	Efflux transporters				Uptake transporters			
			P-gp	MRP	BCRP	MATE	OATP	OAT	OCT	PEPT
	Rifampin	S, ind	S, ind, inh	ind	ind, inh		S, inh	inh		
BDDCS Class 1										
CCBs	Amlodipine	S, inh	/		inh					
	Benidipine	S, inh								
	Diltiazem	S, inh	S, inh			inh				
	Nicardipine	S, inh, ind	inh		S, inh					
	Verapamil	S, inh	S, inh	inh		inh	inh		inh	
β blockers	Acebutolol	inh	S						inh	
	Betaxolol	S, inh								
	Labetalol	S, inh								
	Metoprolol	S, inh	S, inh						inh	
	Oxprenolol	inh							inh	
	Pindolol	S, inh, ind								
	Propranolol	S, inh	S, inh						inh	
	Tertatolol	S								
	Timolol	S, inh	S							
ACEIs	Benazepril									S
	Enalapril	S	inh				S	inh		S, inh
	Imidapril									
	Perindopril		inh							S
	Ramipril									S
Diuretic	Indapamide	S						inh		
BDDCS Class 2										
CCBs	Barnidipine	S, inh								
	Felodipine	S, inh	inh		inh					
	Manidipine	S, inh								
	Nifedipine	S, inh, ind	S, inh		S, inh					
	Nilvadipine	S								
	Nimodipine	S								

	Nisoldipine	S, inh	inh					
	Nitrendipine	S, inh	inh	inh				
ACEIs	Fosinopril							S, inh
	Quinapril						inh	S
	Trandolapril							S
ARBs	Irbesartan	S, inh	/					inh
	Losartan	S, inh	S	inh			inh	inh
	Telmisartan	inh		inh		S, inh	inh	
β blockers	Bevantolol							
	Carvedilol	S	S, inh				inh	
Diuretic	Spironolactone	inh, ind	inh	ind				
	Torasemide	S, inh						
BDDCS Class 3								
ARBs	Olmesartan			S		S	S, inh	
ACEIs	Captopril	S	inh	inh			S, inh	inh
	Lisinopril		inh					S
β blockers	Atenolol	S	S, inh					
	Bisoprolol	S	S, inh					
	Celiprolol	S	S			S		
	Nadolol		S					
	Talinolol	S	S			S		
Diuretic	Bumetanide	S				S	S, inh	
	Hydrochlorothiazide	/					inh	
BDDCS Class 4								
ARBs	Candesartan	S, inh		inh		inh	inh	
	Eprosartan	inh		ind				
	Fimasartan	S				S	S	
	Valsartan	S, inh		S		S, inh	inh	inh
Diuretic	Furosemide	S		inh			S, inh	

S substrate, inh inhibitor, ind inducer, / not substrate nor inhibitor nor inducer, blank in the table means lack of information in current studies. CCBs calcium channel blockers, ACEIs angiotensin converting enzyme inhibitors, ARBs angiotensin receptor blockers, CYPs Cytochromes P450, P-gp P-glycoprotein, BCRP breast cancer resistance-associated protein, MRP multidrug resistance protein, MATE multidrug and toxin extrusion protein, OATP organic anion transporter polypeptide, OAT organic anion transporter, OCT organic cation transporter, PEPT oligo-peptide transporter.

Table 3 Main CYP isoforms information of drugs that are substrates of CYPs.[a]

		1A2	2C9	2C19	2D6	3A4
CCBs	Amlodipine	inh	inh		inh	S,inh
	Barnidipine		inh	inh	inh	S,inh
	Benidipine		inh	inh	inh	S, inh
	Diltiazem		S,inh		S,inh	S,inh
	Felodipine		inh		inh	S,inh
	Manidipine		inh		inh	S,inh
	Nicardipine		inh,ind	inh	S,inh	S,ind,inh
	Nifedipine	inh	inh,ind		S,inh	S,ind,inh
	Nilvadipine					S
	Nimodipine					S
	Nisoldipine	inh				S, inh
	Nitrendipine					S,inh
	Verapamil	S	S,inh	S	inh	S,inh
ACEIs	Captopril				S	
	Enalapril					S
ARBs	Candesartan		S,inh			
	Fimasartan					S
	Irbesartan	inh	S,inh		inh	inh
	Losartan	inh	S,inh	inh		S,inh
	Valsartan		S,inh			
β blockers	Atenolol					S
	Betaxolol	S			S, inh	
	Bisoprolol				S	S
	Carvedilol	S	S		S	S
	Celiprolol					S
	Labetalol				S,inh	
	Metoprolol			S	S,inh	
	Pindolol				S, inh, ind	
	Propranolol	S,inh		S	S,inh	S
	Talinolol					S
	Tertatolol					S
	Timolol			S	S,inh	
Diuretics	Indapamide					S
	Torasemide		S	inh		

S substrate, inh inhibitor, ind inducer, blank in the table means lack of information in current studies. CCBs calcium channel blocke ACEIs angiotensin-converting enzyme inhibitors, ARBs angioten

receptor blockers.

The Class 3 and 4 drugs, bumet
hydrochlorothiazide are not listed in the table; furosemide is only
the substrate of CYP2E1, which is also indu
bumetanide is little metabolized and the CYP isoform is unknown.

[a]CYP isoforms here are demonstrated to be induced by rifampin.

Table 4 Case reports about the interactions between rifampin and antihypertensive drugs.

Cases	Age, Gender	Antihypertensive drugs and dosage	BP/ Symptom	Dosage of Rifampin	BP/Symptom after coadministration with rifampin	Intervention	Result of BP
1 [11]	/	Verapamil 480 mg q6h	SVT	/	recurrent symptomatic SVT	Discontinuation of rifampin and substitution of ethambutol	almost four-fold increase in verapamil levels with concurrent control of SVT
2 [10]	/	Nifedipine	angina pectoris	/	angina exacerbated; The peak plasma level and AUC were reduced and the apparent oral clearance of nifedipine was increased	/	/
3 [5]	35, man	Enalapril	/	/	BP rose significantly; AUC of enalapril wasn't alter, but AUC of enalaprilat reduced 31%	Discontinuation of rifampin	/

4 [6]	72, woman	Nifedipine 40 mg bid	140-160/80-90 mmHg	450 mg	200/110 mmHg after 2 weeks	Discontinuation of rifampin	160-170/80-90 mmHg in 10 days
5 [4]	70, man	Nifedipine 40 mg qd	140-150/60-70 mmHg	300 mg	180-210/70 mmHg after 9 days (nifedipine increased to 120 mg qd)	Withdrawal of rifampin	150/60 mmHg in 4 days with nifedipine 60 mg qd
6 [4]	77, woman	Manidipine 20 mg qd	130/70 mmHg	450 mg	Bp increased to 220/90 mmHg in 2 days	Manidipine 90 mg and lisinopril 5 mg qd	140-150/70-75 mmHg in 2 days
7 [4]	76, woman	Barnidipine 15 mg qd	/	300 mg	170/90 mmHg in 2 days	Withdrawal of rifampin; barnidipine 20 mg and bisoprolol 5 mg qd	135-140/85 mmHg in 4 days with barnidipine 10 mg and bisoprolol 2.5 mg qd
8 [12]	62, woman	Nifedipine 10 mg tid; Captopril 12.5 mg bid	135/90 mmHg	/	150-180/98-120 mmHg after 15 days	Discontinuation of rifampin	128-131/75-90 mmHg in 3 days

9 [13]	72, man	Nifedipine 10 mg tid, Metoprolol 50 mg tid; Lisinopril 20-40 mg qd	/	450 mg	195-210/120 mmHg	Withdrawal of rifampin	150/90 mmHg in 2 days; lisinopril 20 mg qd: 130/90 mmHg after 1 week
10 [7]	66, man	Atenolol 50 mg qd	well-controlled exertional angina	600 mg	exercise threshold for angina worsened	TB treatment was withheld	Symptoms resolved
11 [9]	71, /	Bisoprolol 3.75 mg qd	/	600 mg	BP increased and cardiac arrhythmia were seen	Bisoprolol 3.75 mg in the morning and 1.875 mg in the evening	BP was controlled
12 [8]	73, man	Nifedipine 30 mg qd	<140/90 mmHg	450 mg	150-210/70-90 mmHg after 3 weeks	Withdrawal of rifampin; substitution of irbesartan and hydrochlorothiazide, metoprolol, clonidine	140/90 after 1 week
13 [14]	75, man	Nifedipine 30 mg bid, Carvedilol 10 mg bid, Perindopril 4 mg qd	120-150/50-70 mmHg	/	140-184/78-86 mmHg in 10 days	Withdrawal of rifampin	120-134/70-80 mmHg in 7 days

14 [15]	80, man	Nifedipine 30 mg qd, Metoprolol 47.5 mg qd	130/70 mmHg	450 mg	158-164/85-100 mmHg after 7 days	Coadministration of enalapril 10 mg qd	154/87 mmHg in the 10th day

BP blood pressure, *SVT* supraventricular tachycardia, *AUC* area under the plasma concentration–time curve, *TB* tuberculosis, *q6h* every 6 hours, *qd* once daily, *bid* twice daily, *tid* three times daily, "/" indicates la information.

Table 5 Before and after studies between rifampin and antihypertensive drugs.

Studies	Study type[a]	Subject (n)[b]	Affected drug	BDDCS	Dose (mg/d)	Pretreatment of Rif (d)	Rif dose (mg/d)	Coadministration[c]	AUC[d] (%)	CL[e] (%)	AUC change[f]	PD[g]
Barbarash, 1988 [42]	NC	6	Verapamil	1	120	15	600	N	6.51	–*	↓↓↓	Y
Fromm, 1996 [43]	NC	8	Verapamil	1	240	14	600	Y	3.29	2772	↓↓↓	Y
Fromm, 1998 [44]	NC	8	Verapamil	1	240	12	600	Y	3.28	–	↓↓↓	Y
Bennett, 1982 [45]	NC	12†	Metoprolol	1	100	15	600	N	67.1	–	↓	–
Herman, 1983 [46]	NC	6	Propranolol	1	360	21	600	Y	–	269	↓↓	–
								N	–	299	↓↓	–
Holtbecker, 1996 [47]	NC	6	Nifedipine	2	20	7	600	N	8.18	1393	↓↓↓	–
Ndanusa, 1997 [48]	NC	6	Nifedipine	2	10	8h	1200	N	35.7	289	↓↓	–
Saima, 2002 [49]	NC	5	Nilvadipine	2	4	6	450	N	3.45	2994	↓↓↓	Y
Williamson, 1998 [50]	NC	10	Losartan	2	50	7	600	N	64.5	160	↓	–
Giessmann, 2004 [51]	NC	12	Carvedilol	2	25	9	600	Y	37-43	–	↓↓	Y
Kirch, 1986 [52]	NC	6	Bisoprolol	3	10	14	600	Y	66.5	151	↓	–

Westphal, 2000 [21]	NC	8	Talinolol	3	100	5	600	Y	64.7	154	↓	–
Zschiesche, 2002 [53]	NC	8	Talinolol	3	100	5	600	Y	65.5	141	↓	–
Lilja, 2004 [54]	C	10	Celiprolol	3	200	5	600	N	44.4	–	↓↓	N
Misaka, 2013 [55]	C	10	Nadolol	3	30	6	450	N	78[#]	127[#]	↓	N
Lilja, 2006 [56]	C	9	Atenolol	3	100	5	600	N	81	–	↓	Y
Kirch, 1990 [57]	NC	10[‡]	Tertatolol	1	5	6	600	Y	42.7	271	↓↓	N
Kim, 2013 [58]	NC	22	Fimasartan	4	240	10	600	Y	460	20.6	↑↑	–

Rif - rifampin, AUC - area under the plasma concentration–time curve, CL - clearance, PD - pharmacodynamics.

[a] NC non-controlled before and after study, C randomized cross-over study

[b] Subjects in these studies were healthy volunteers unless noted.

[c]"Y" coadministration of rifampin with antihypertensive drugs; "N" antihypertensive drugs dose given after stopping rifampin.

[d]AUC with rifampin induction/AUC control as a percentage.

[e]CL with rifampin induction/CL control as a percentage.

[f]The arrows show the direction and extent of AUC change: "↓" AUC decreased, "↑" AUC increased; one arrow indicates AUC change of 0~50%, two arrows indicates change of 50%~90%, three arrows indicates change of > 90%.

[g]"Y" pharmacodynamics of the interaction was statistically significant; "N" not significant.

[†]The subjects were volunteers, but plasma gamma glutamyl transpeptidase was abnormal (105 IU/L) in one subject, two subjects were smokers and another two consumed alcohol.

[‡]The subjects were patients with arterial hypertension.

[*]"–" data were not reported or not studied in the article.

[#]The changes in AUC and CL were **not** statistically significant. In all undesignated studies, the changes in AUC and/or CL were

statistically significant ($P < 0.05$).

Table 6 The extent of rifampin induction on different CYP isoforms (*in vitro* studies).

Studies	Rifampin Concen-tration	System	Activity of CYP isoforms (-fold increase)				
			1A2	2C9	2C19	2D6	3A4
Madan, 2003 [62]	20 or 50 µM	primary human hepatocytes	2.3	3.5	37	*	10
Mills, 2004 [63]	10 µM	Fa2N-4 cells		2			9
Sonesson, 2011 [64]	10 µM	primary human hepatocytes			3.6		
	25 µM	cryopreserved human hepatocytes		2.4			8.7
Paris, 2009 [65]	10 µM	primary human hepatocytes	1.8	2.1	6.8		3.9

*CYP2D6 was not significantly induced by rifampin

Figure legend

Fig. 1 Transporter effects predicted by BDDCS following oral dosing.

Fig. 2 CYP and transporter effects predicted under the theory of BDDCS following oral dosing.

Fig. 3 Predictions of the effects of rifampin on antihypertensive drugs. Arrows indicate an increase or decrease of drug efficacy when coadministrated with rifampin. “↔” indicates there may not be an interaction between rifampin and the drug. Italicized drugs represent active metabolites of ACEIs.

Fig. 4 Flow chart depicting the selection process of the studies.

Fig. 5 Distribution of case reports for involved antihypertensive drugs by BDDCS class.

Fig. 6 Distribution of before and after studies for involved antihypertensive drugs by BDDCS class.

Fig. 7 Results of the pharmacokinetic and pharmacodynamic effects of rifampin on antihypertensive drugs. Black arrows indicate a predicted increase or decrease of drug efficacy when coadministrated with rifampin. Red arrows indicate documented pharmacodynamic effects. Blue arrows indicate documented pharmacokinetic effects.

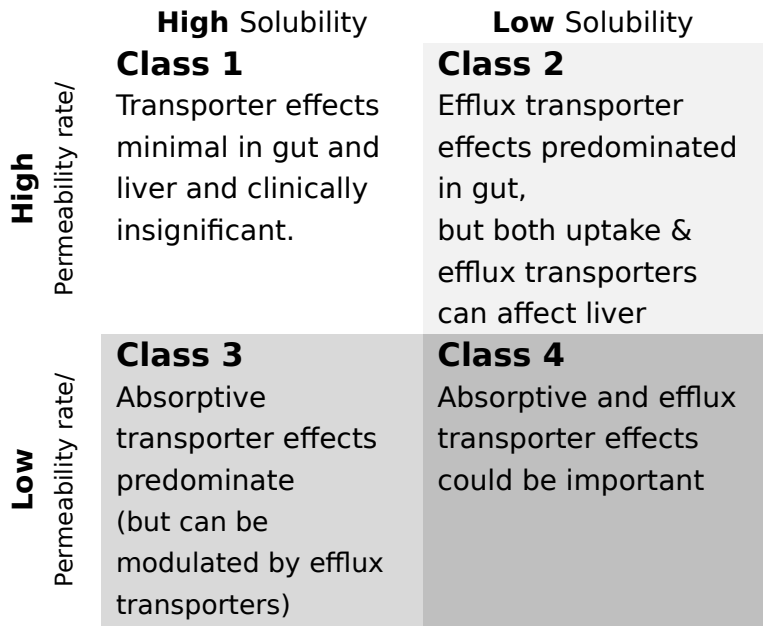

Fig. 1 Transporter effects predicted by BDDCS following oral dosing [25].

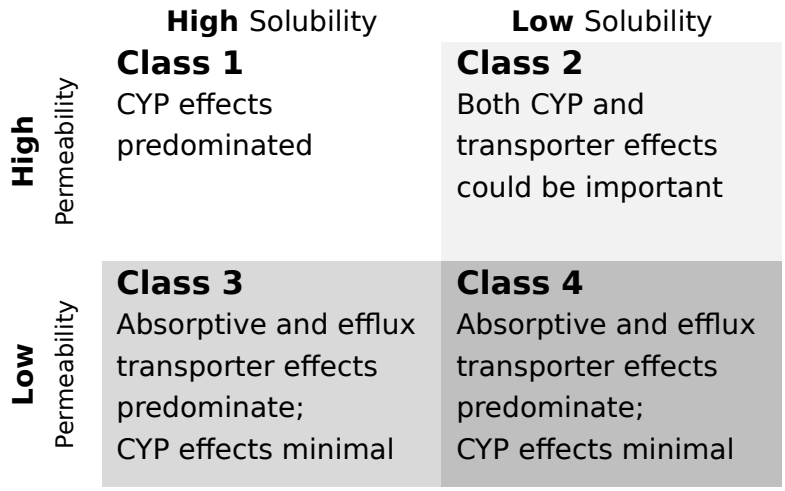

Fig. 2 CYP and transporter effects predicted under the theory of BDDCS following oral dosing.

	High Solubility	**Low** Solubility
High	**Class 1** **Substrate of CYPs:↓** Amlodipine Benidipine Betaxolol Diltiazem Enalapril Indapamide Labetalol Metoprolol Nicardipine Pindolol Propranolol Tertatolol Timolol Verapamil **Only substrate of P-gp/BCRP: ↔** Acebutolol **Not substrate of CYPs & OATP: ↔** Benazepril Imidapril Oxprenolol Perindopril Ramipril	**Class 2** **Substrate of CYPs: ↓** Barnidipine Felodipine Irbesartan Manidipine Nilvadipine Nimodipine Nisoldipine Nitrendipine Torasemide **Substrate of CYPs & P-gp/BCRP: ↓** Carvedilol Losartan Nifedipine **Substrate of OATP: ↑** Telmisartan **Not substrate of CYPs & OATP: ↔** Bevantolol Fosinopril Quinapril Spironolactone Trandolapril

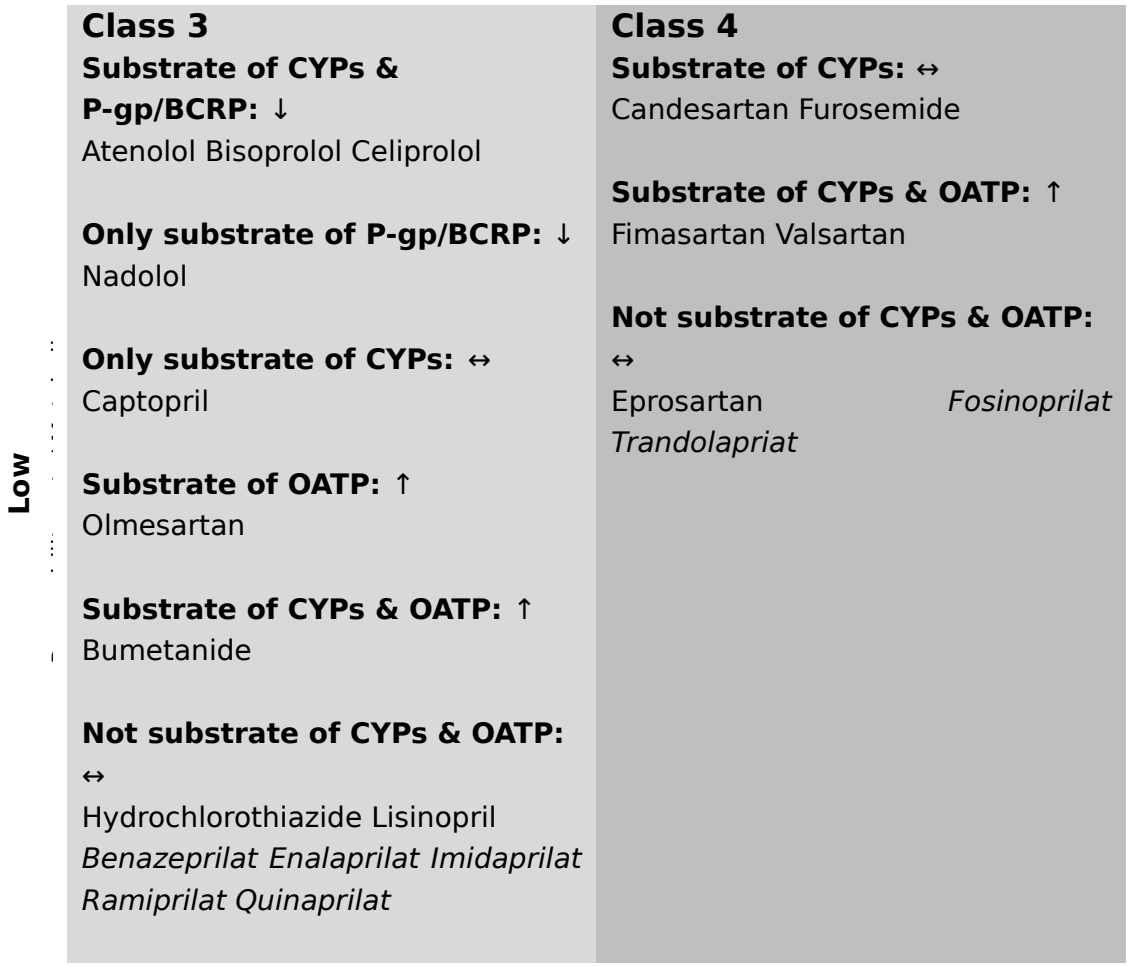

Fig. 3 Predictions of the effects of rifampin on antihypertensive drugs. Arrows indicate an increase or decrease of drug efficacy when coadministrated with rifampin. "↔" indicates there may not be an interaction between rifampin and the drug. Italicized drugs represent active metabolites of ACEIs

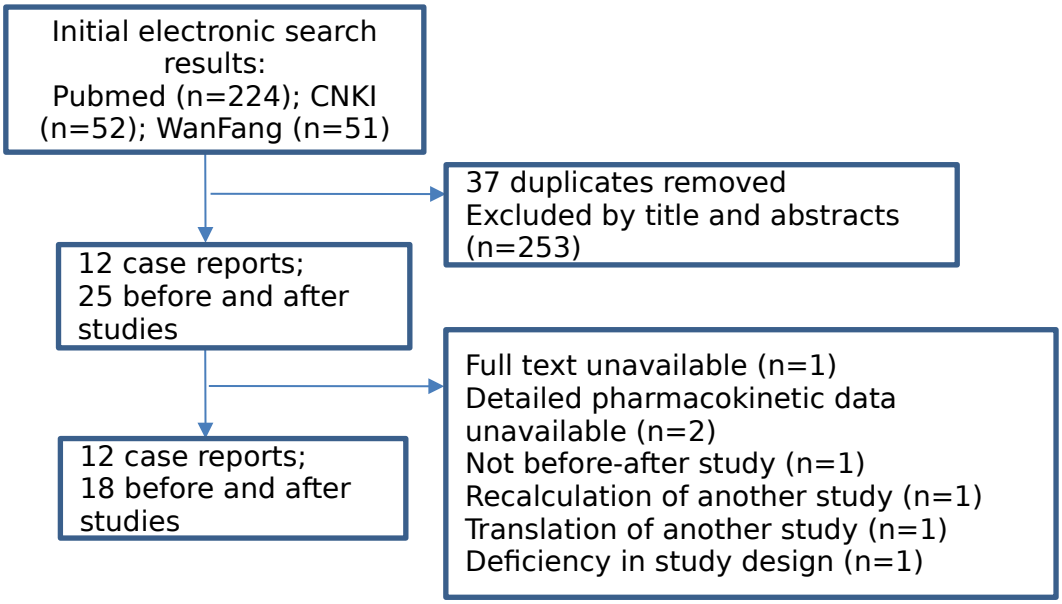

Fig. 4 Flow chart depicting the selection process of the studies.

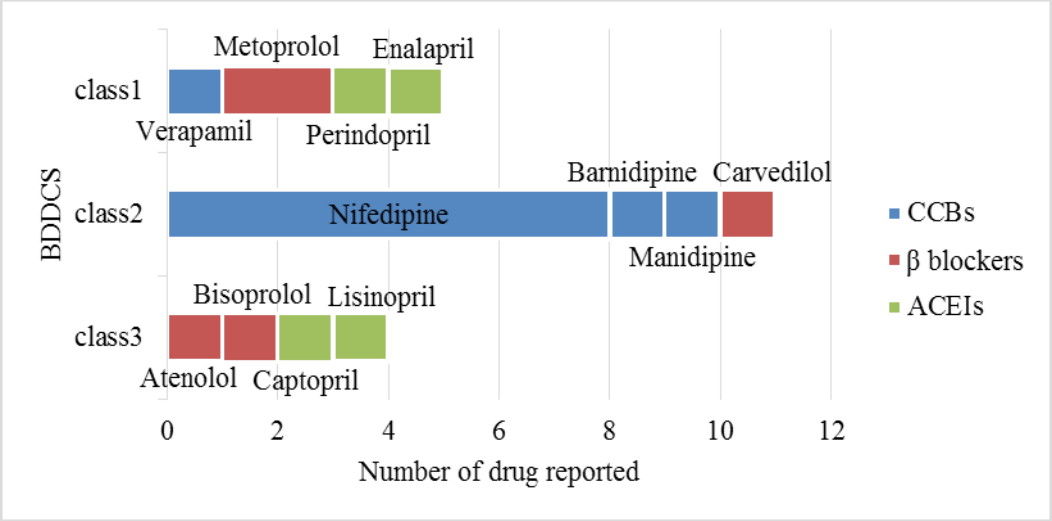

Fig. 5 Distribution of case reports for involved antihypertensive drugs by BDDCS class.

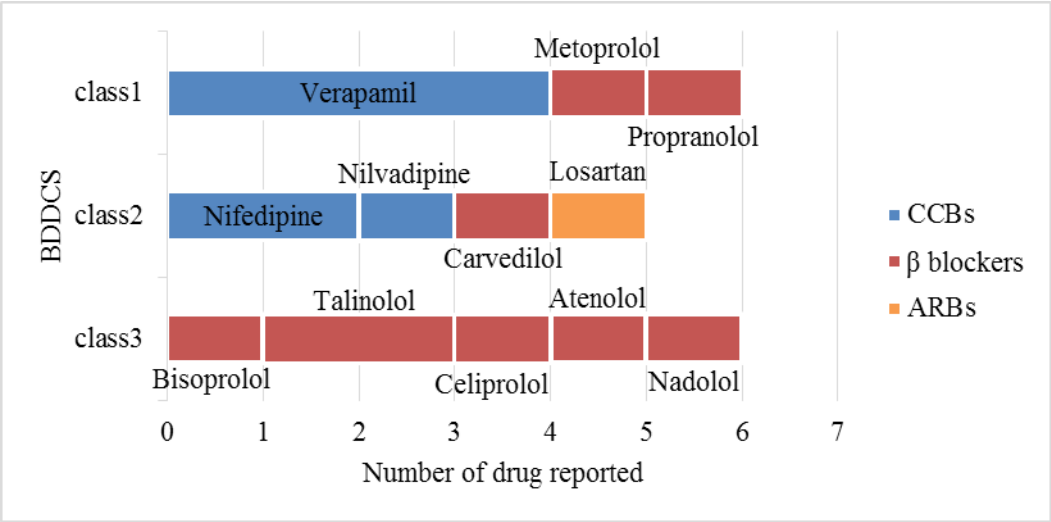

Fig. 6 Distribution of before and after studies for involved antihypertensive drugs by BDDCS class.

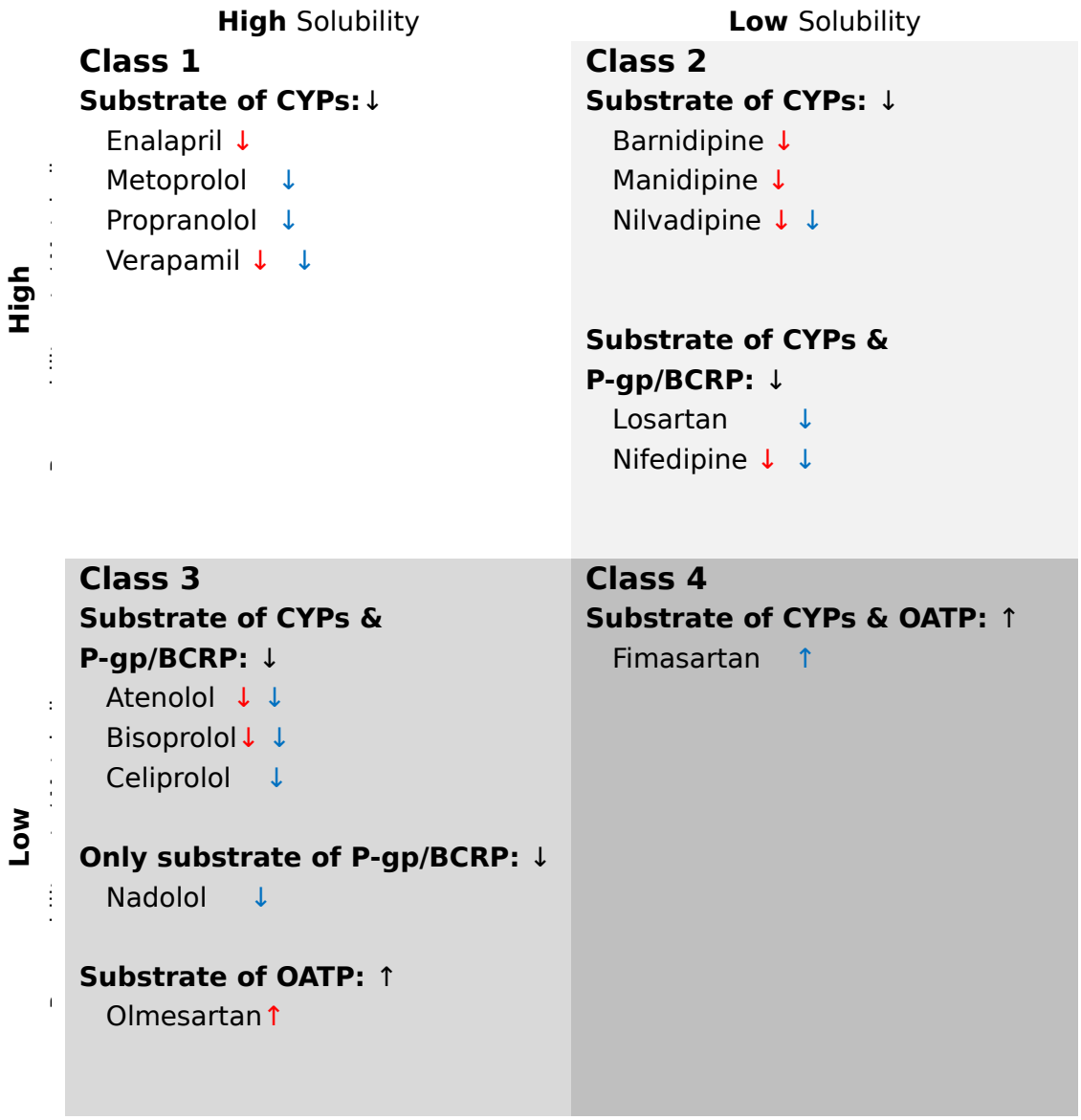

Fig. 7 Results of the pharmacokinetic and pharmacodynamic effects of rifampin on antihypertensive drugs. Black arrows indicate a predicted increase or decrease of drug efficacy when coadministrated with rifampin. Red arrows indicate documented pharmacodynamic effects. Blue arrows indicate documented pharmacokinetic effects.