

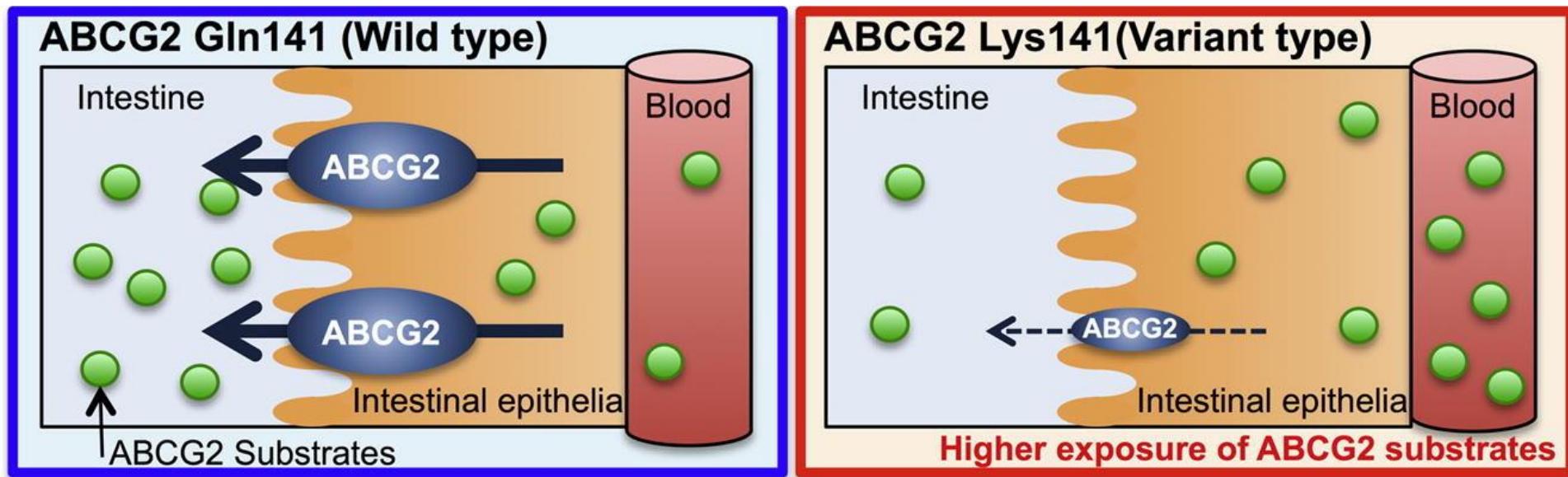
# Proposal for a CPIC Guideline for Rosuvastatin Therapy and *ABCG2* Genotype

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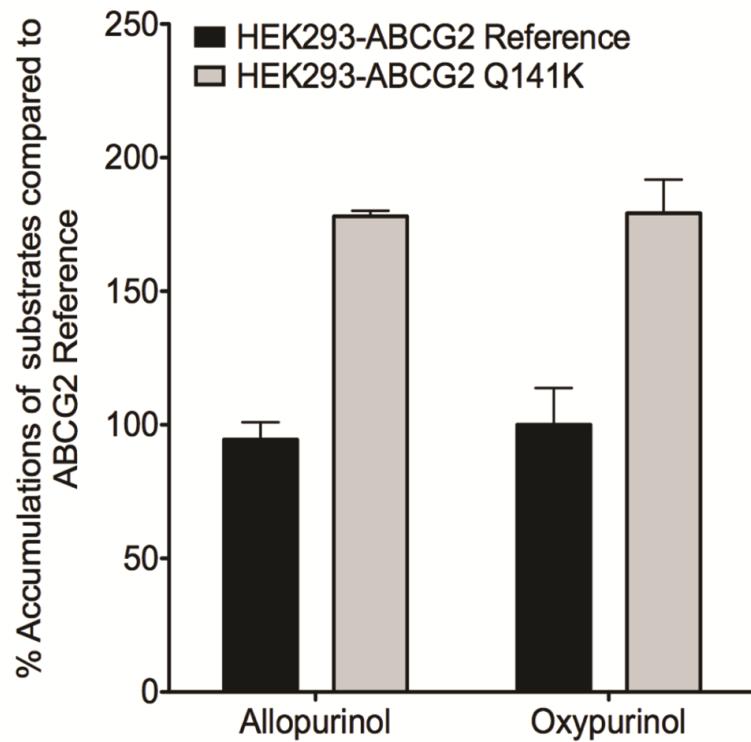
# *ABCG2* encodes the efflux transporter BCRP

- Active efflux transporter with a long list of diverse substrates
- Expressed ubiquitously, but especially in ADME tissues
- BCRP Q141K (ABCG2 Lys141) is a reduced function variant with approximately half expression of wild type



# BCRP Q141K causes the accumulation of *ABCG2* substrates

- Allopurinol and oxypurinol are *ABCG2* substrates
- Accumulation in the cell increases as efflux decreases with the Q141K variant

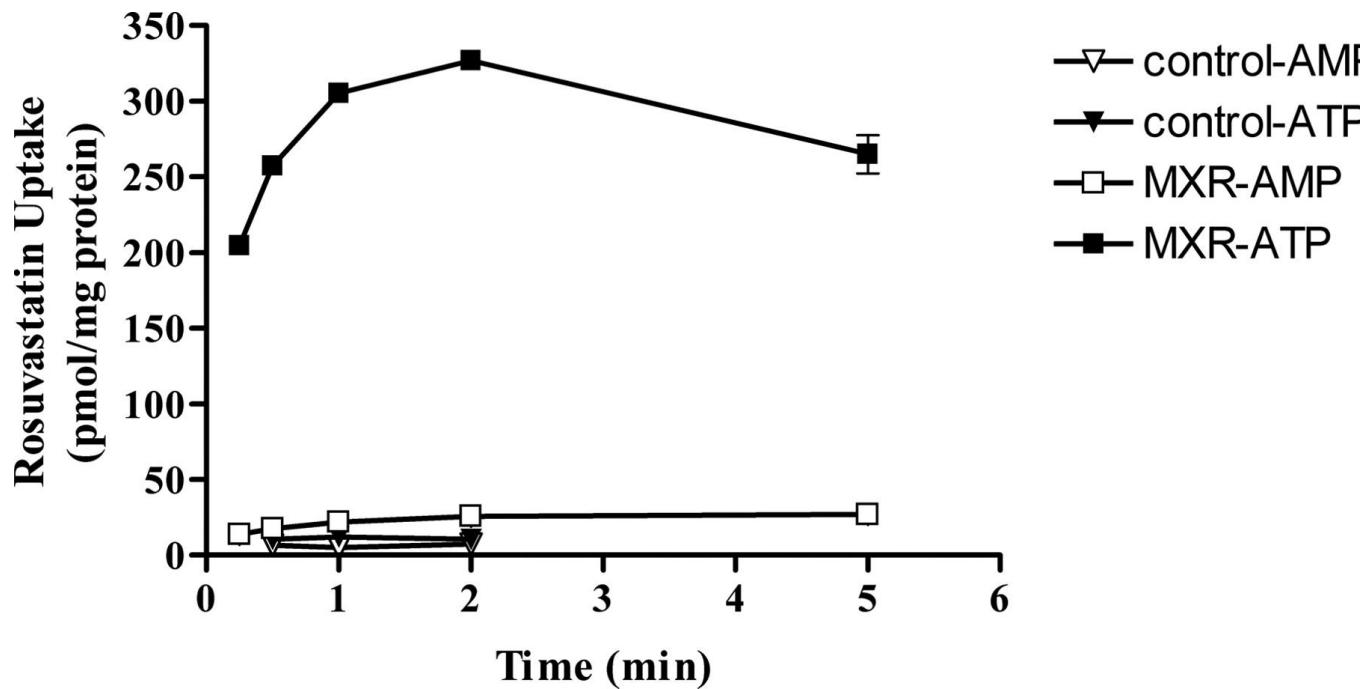


# BCRP Q141K is a common variant that can affect the PK-PD of many drugs

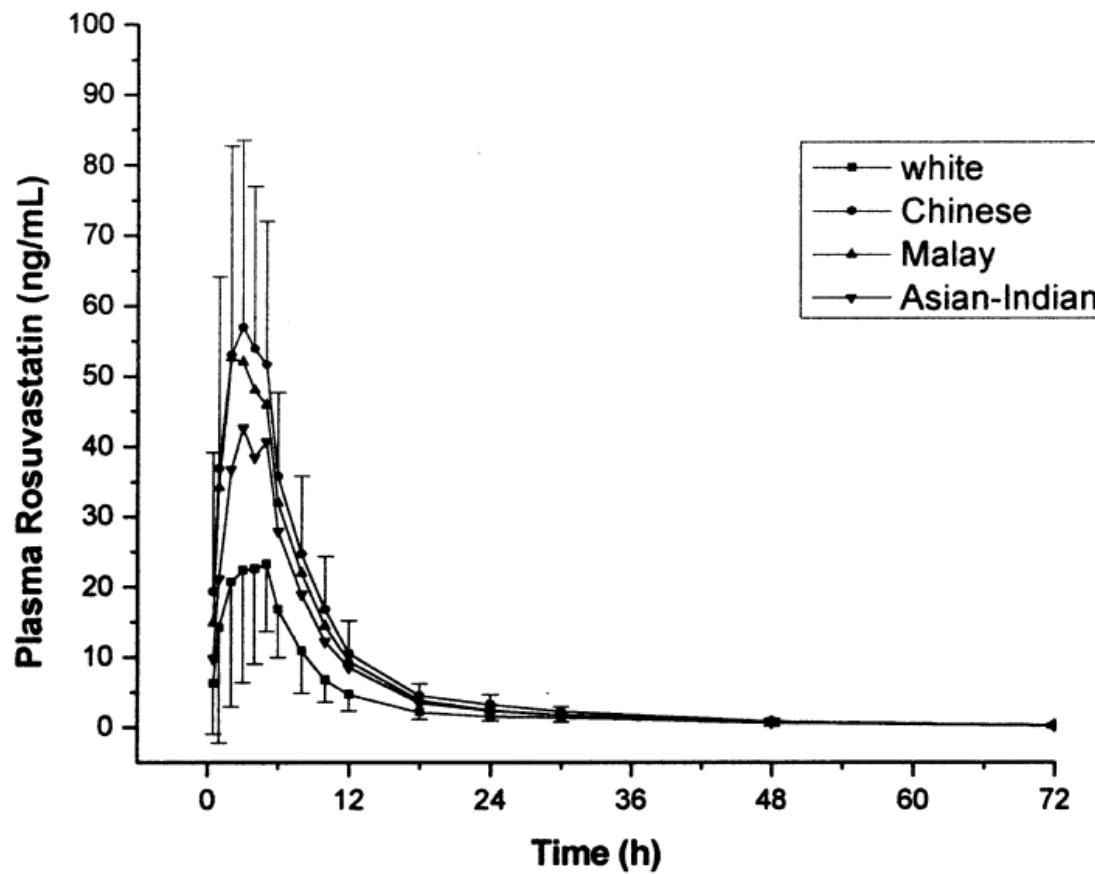


# Rosuvastatin is transported by BCRP

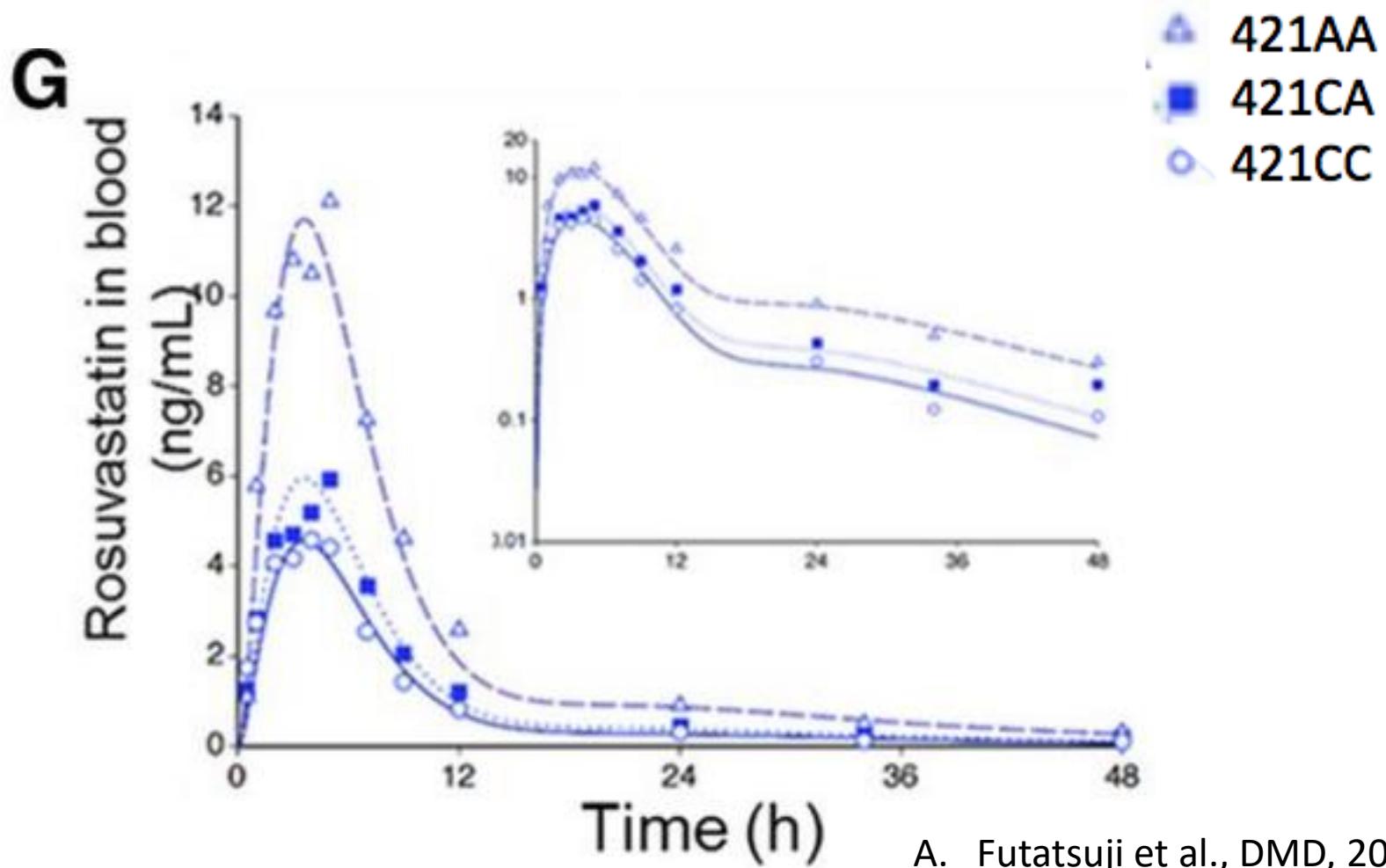
- Microsomes expressing BCRP (MXR) transport rosuvastatin in an ATP-dependent manner



# Rosuvastatin exposure is higher in Asian subjects



# Rosuvastatin exposure is higher in patients with 421AA



A. Futatsuji et al., DMD, 2019  
PMID: 29440178

# FDA and EMA recommend dosing rosuvastatin according to ethnicity

## HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use CRESTOR safely and effectively. See full prescribing information for CRESTOR.

**CRESTOR (rosuvastatin calcium) tablets**

Initial U.S. Approval: 2003

### 2.4 Dosage in Asian Patients

**FDA**

Initiation of CRESTOR therapy with 5 mg once daily should be considered for Asian patients [*see Use in Specific Populations (8.8) and Clinical Pharmacology (12.3)*].

## Race

Increased systemic exposure has been seen in Japanese and Chinese subjects (see section 4.4 Special warnings and special precautions for use and section 5.2 Pharmacokinetic properties). The recommended start dose is 5 mg for patients of Japanese and Chinese ancestry. The 40 mg dose is contraindicated in Japanese and Chinese patients (see sections 4.3 Contraindications and 5.2 Pharmacokinetic properties).

**EMA**

A number of published studies suggest that BCRP Q141K may be a better indicator for dose selection

<u>Study</u>	<u>Ethnicities</u>	<u>AUC<sub>Het/Ref</sub></u>	<u>AUC<sub>Alt/Ref</sub></u>	<u>Cmax<sub>Het/Ref</sub></u>	<u>Cmax<sub>Alt/Ref</sub></u>
Kashihara <sup>et al</sup>		1.96		2.04	
Zhou <sup>et al</sup>	Chinese	1.08	1.58	1.01	1.41
	Chinese, Filipino, Korean, Vietnamese, Japanese				
Birmingham <sup>et al</sup>	Japanese	1.40	2.44	1.38	2.55
Birmingham <sup>et al</sup>	Asian-Indian	0.99	1.44	0.95	2.47
Birmingham <sup>et al</sup>	Caucasian	1.12		1.04	
Keskitalo <sup>et al</sup>	Caucasian	1.22	2.44	1.11	2.31
<b>TOTAL</b>		<b>1.30<math>\pm</math>0.4</b>	<b>1.97<math>\pm</math>0.5</b>	<b>1.26<math>\pm</math>0.4</b>	<b>2.19<math>\pm</math>0.5</b>

Results for atorvastatin are similar and will be gathered for analysis as well

# Proposed Dosing Guideline

<i>Genotype</i>	<i>Implication</i>	<i>Therapeutic Recommendation</i>	<i>Classification of Recommendation</i>
CC	Normal exposure of rosuvastatin and atorvastatin	Initiate therapy with recommended dose	strong
CA	Slightly elevated exposure of rosuvastatin and atorvastatin, increased potential for side effects	Initiate therapy with recommended starting dose	strong
AA	Increased exposure of rosuvastatin and atorvastatin, increased plasma levels lead to increased probability of side effects	Decrease starting dose or prescribe alternative statin	strong

# Proposed Team of Authors

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