



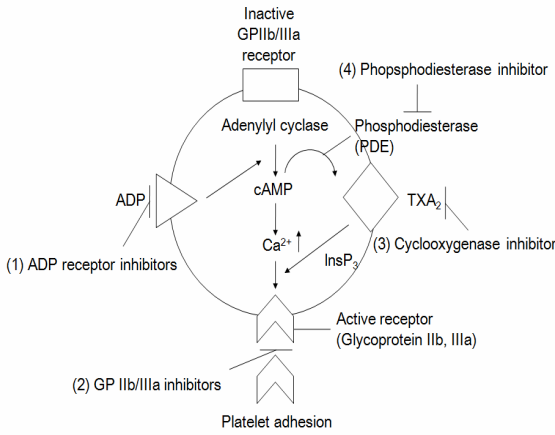
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Population Pharmacokinetic(PK)/Pharmacodynamic(PD)  
 modeling of anti-platelet agents


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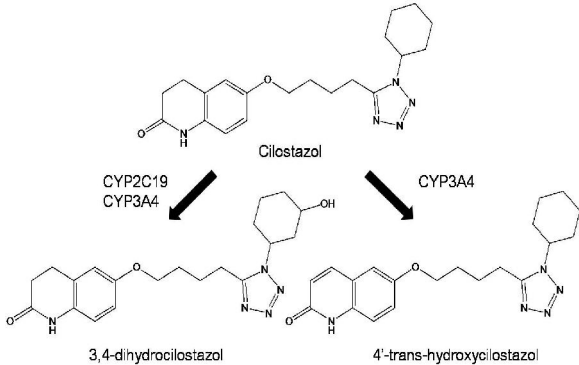
Pharmacological mechanism of anti-platelet agents



	Agents (Market share)
(1)	Clopidogrel (29.87%) Ticlopidine
(2)	Abciximab Eprifibatide Tirofiban Defibrotide
(3)	Aspirin Triflusal (5.46%)
(4)	Cilostazol (9.70%) Dipyridamole



### Cilostazol



Cilostazol

CYP2C19  
CYP3A4


3,4-dihydrocilostazol

CYP3A4

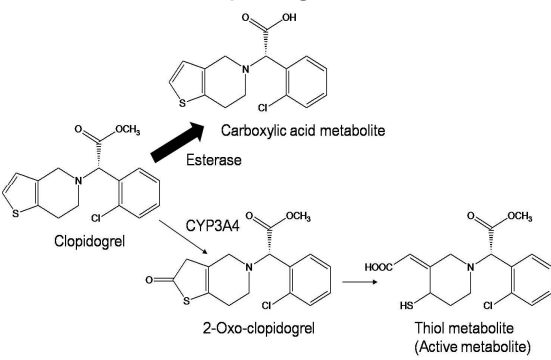
4'-trans-hydroxycilostazol

- Cilostazol(Pletal): Phosphodiesterase(PDE) inhibitor
- Dosage: 100mg twice a day
- Metabolism: hepatic CYP 2C19, CYP3A4
- 3,4-dihydrocilostazol: active metabolite, 4~7 times potent than cilostazol
- 4'-trans-hydroxy-cilostazol: active metabolite, 20% compared with cilostazol effect

Ikeda Y. *Thrombosis and Haemostasis*, 82(2): 435-438 (1999)  
Ikeda Y et al. *EJP*, 314: 197-202 (1996)



### Clopidogrel



Clopidogrel

Esterase

Carboxylic acid metabolite


CYP3A4

2-Oxo-clopidogrel

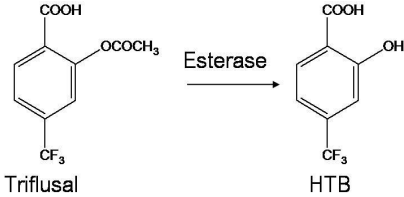
Thiol metabolite  
(Active metabolite)

- Clopidogrel(Plavix): Adenosine diphosphate(ADP) receptor inhibitor
- Dosage: 75mg once a day, loading dose 300mg
- Metabolism: Esterase, CYP3A4
- Prodrug
- Clopidogrel carboxyl metabolite : inactive metabolite, main metabolite
- Clopidogrel thiol metabolite: active metabolite

Taubert et al. *Thrombosis and Haemostasis*, 92(2): 311-316 (2004)  
Brandt JT et al. *AHJ*, 153(1): 66.e9-16 (2007)




### Triflusal



Triflusal  $\xrightarrow{\text{Esterase}}$  HTB

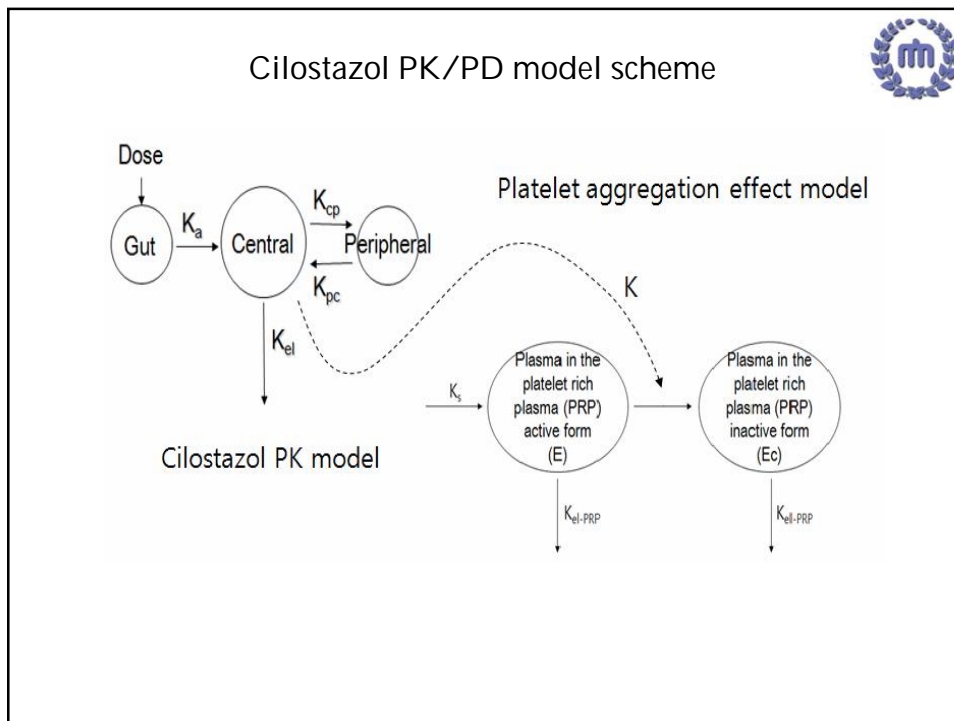
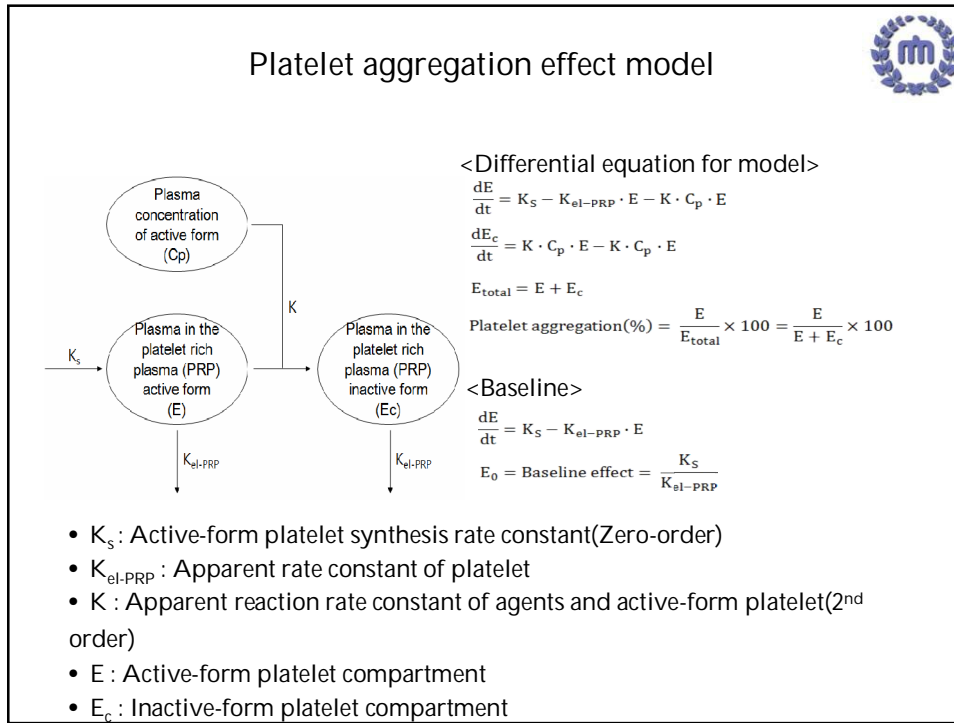
- Triflusal(Disgren): Cyclooxygenase(COX) inhibitor
- Dosage: 300mg three times a day, 600 or 900mg once a day
- Metabolism: Esterase
- Triflusal: Main pharmacological effect, short half-life ( $0.53 \pm 0.12$  hr)
- 2-hydroxy-4-trifluoromethylbenzoic acid(HTB): active metabolite, main metabolite, Long half-life ( $34.3 \pm 5.3$  hr)

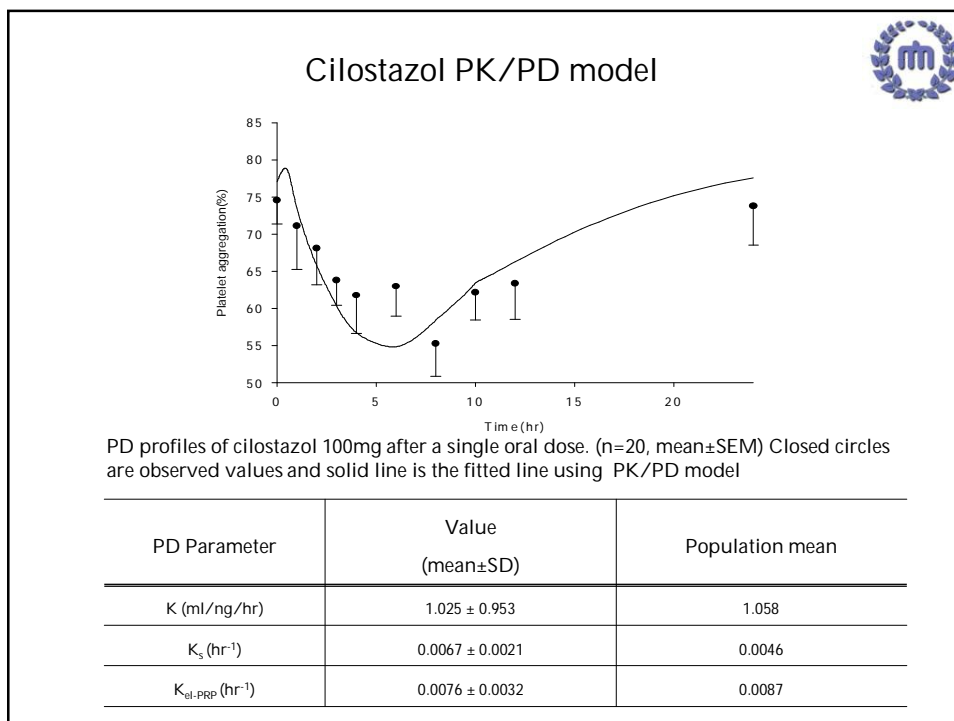
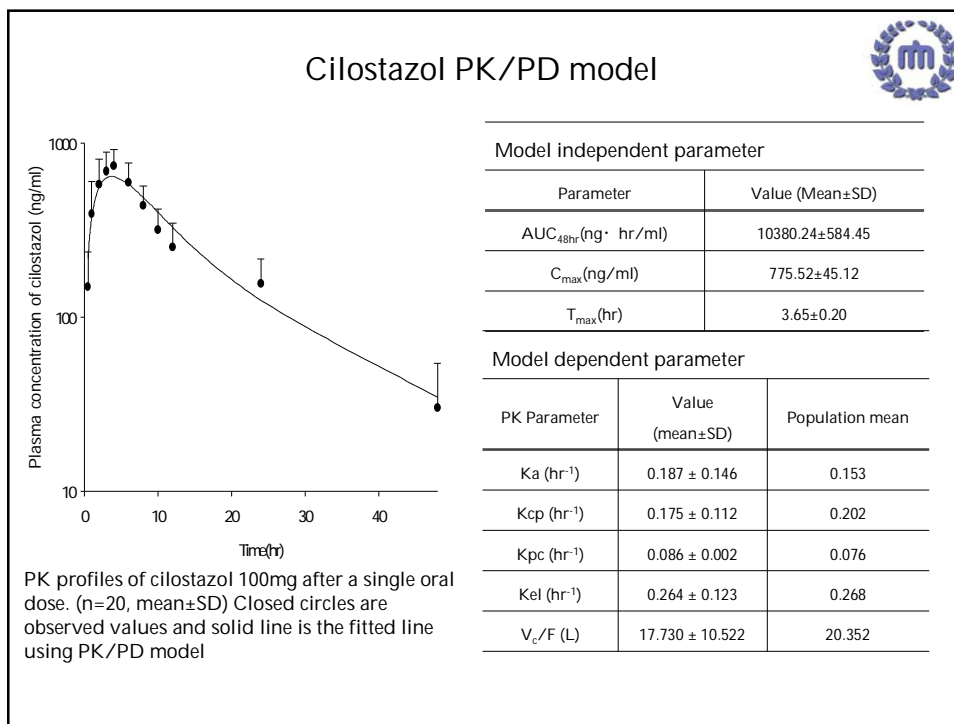
Rabasseda X et al. *Drugs of Today*, 29(Supple B):1-29 (1993)

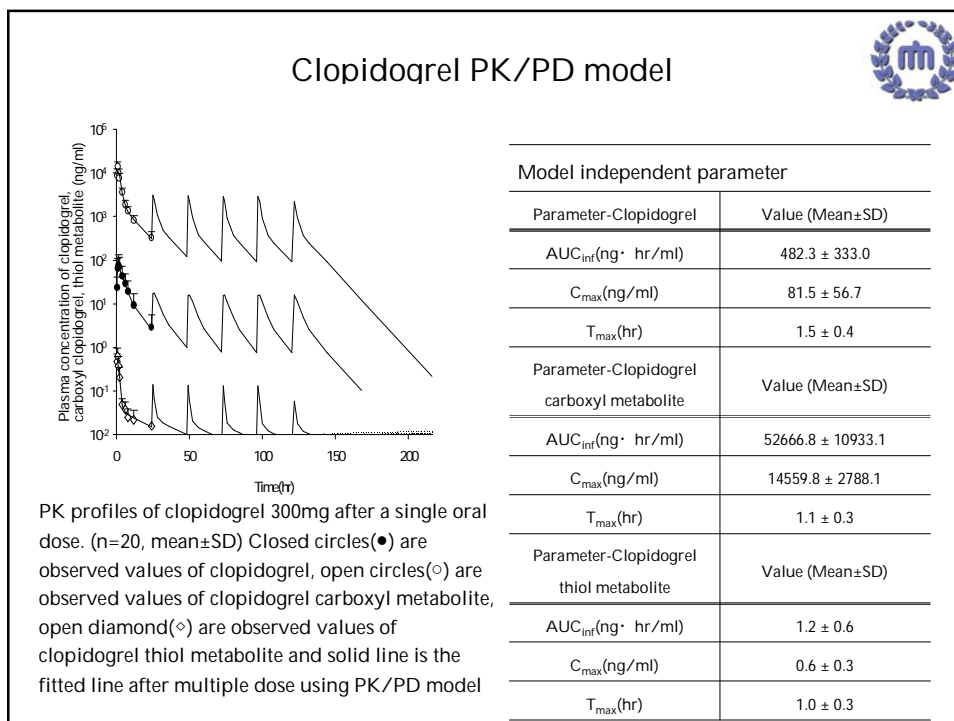
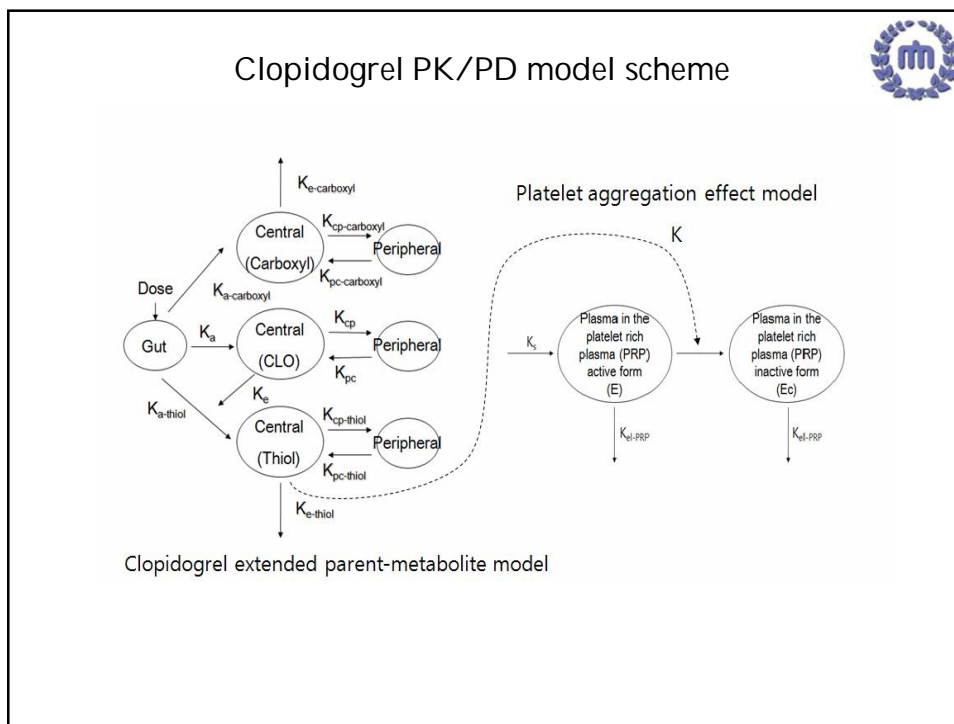


### Study Design


- Cilostazol
  - ✓ Cilostazol 100mg(Pletal) single oral dose
  - ✓ n=20
  - ✓ HPLC/UV(PK analysis), Platelet aggregation test(PD analysis)
- Clopidogrel
  - ✓ Clopidogrel (Plavix), Loading dose 300mg × 1day, 75mg × 6day
  - ✓ n=20
  - ✓ LC/MS/MS(PK analysis), Platelet aggregation test(PD analysis)
- Triflusal
  - ✓ Single dose
    - Triflusal 300mg × 3cap (disgren capsule) single oral dose
    - n=7
  - ✓ Multiple dose
    - Triflusal(disgren capsule), Loading dose: 900mg × 1day, 600mg × 8day
    - n=35
  - ✓ LC/MS/MS(PK analysis), Platelet aggregation test(PD analysis)







### Clopidogrel PK/PD model



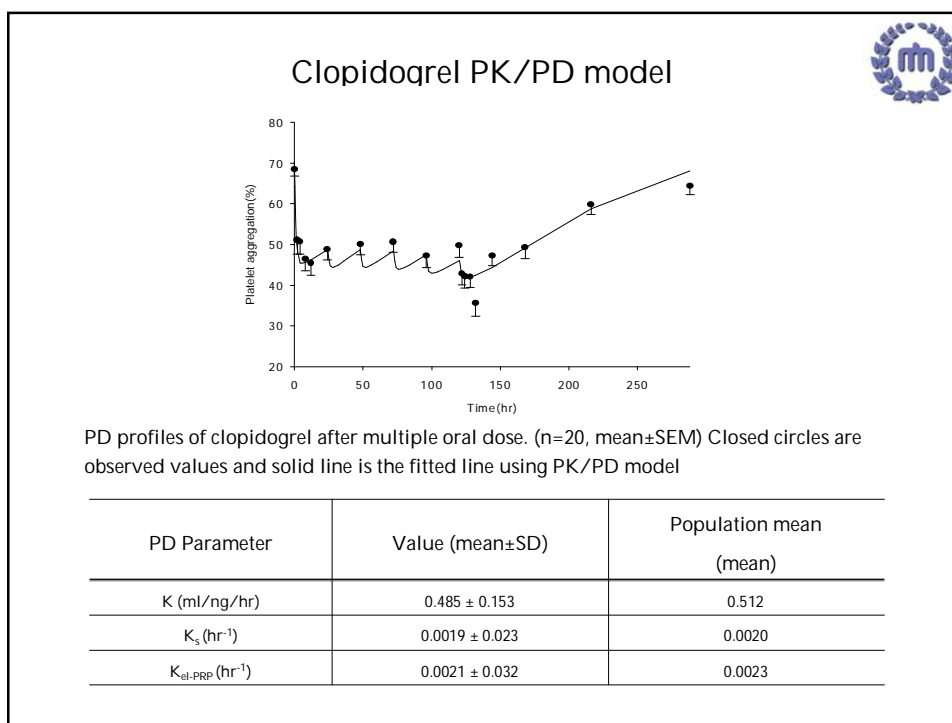
Model dependent parameter		
PK Parameter -Clopidogrel	Value (mean±SD)	Population mean (mean)
Ka (hr <sup>-1</sup> )	0.391 ± 0.125	0.294
Kcp (hr <sup>-1</sup> )	0.062 ± 0.053	0.054
Kpc (hr <sup>-1</sup> )	0.122 ± 0.095	0.094
Kel (hr <sup>-1</sup> )	0.206 ± 0.154	0.187
V <sub>c</sub> /F (L)	960.7 ± 650.2	900.57

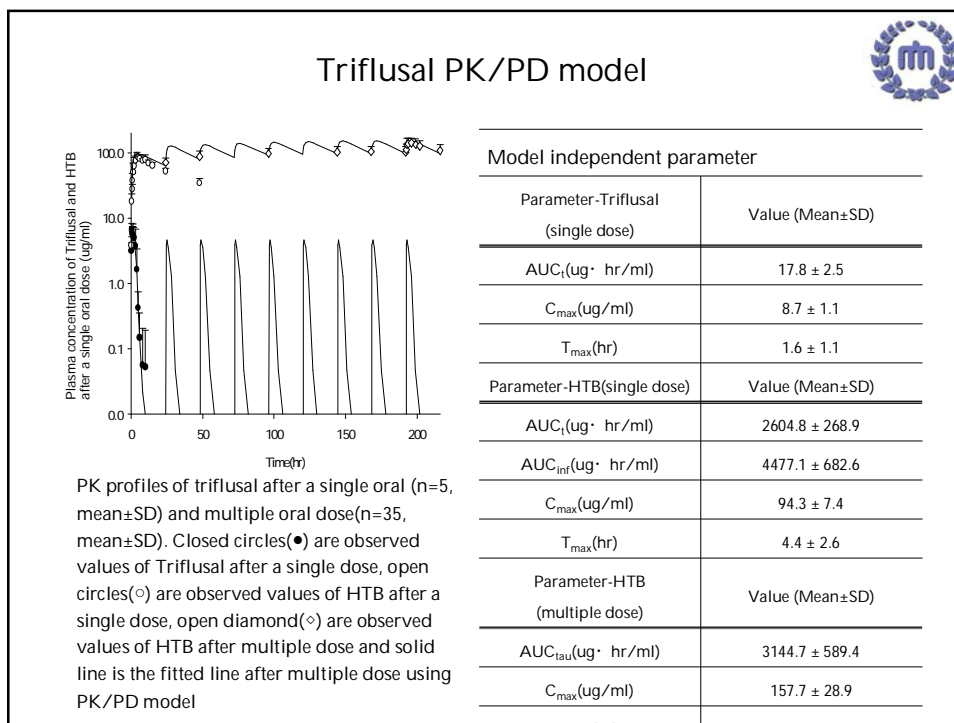
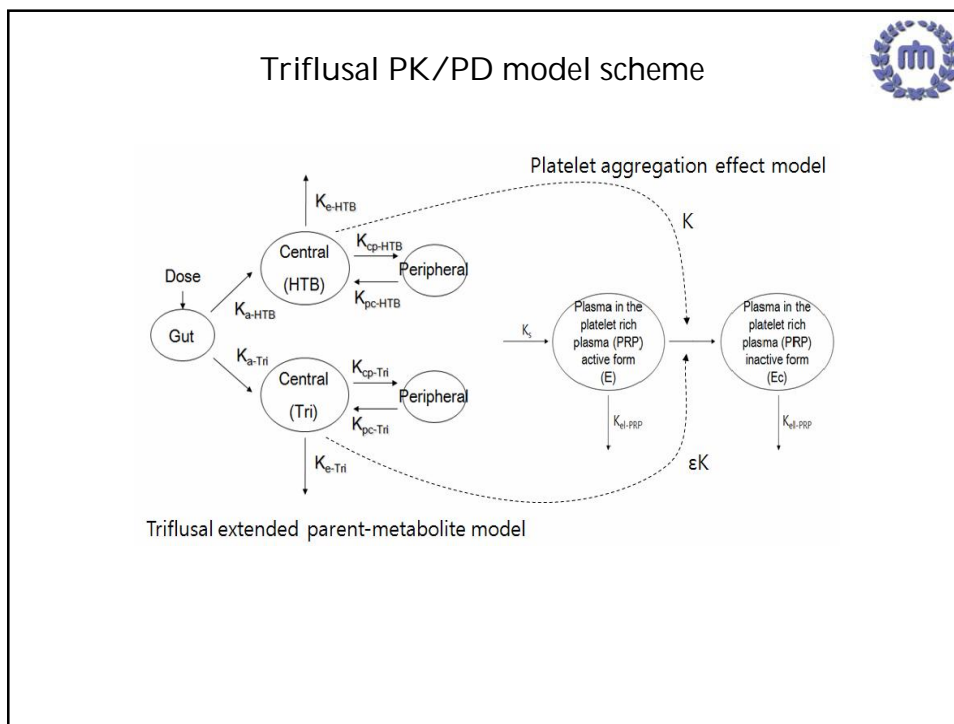
  

PK Parameter -Clopidogrel thiol metabolite	Value (mean±SD)	Population mean (mean)
Ka <sub>-thiol</sub> (hr <sup>-1</sup> )	0.314 ± 0.258	0.145
Kcp <sub>-thiol</sub> (hr <sup>-1</sup> )	1.121 ± 0.546	1.542
Kpc <sub>-thiol</sub> (hr <sup>-1</sup> )	0.078 ± 0.012	0.087
Kel <sub>-thiol</sub> (hr <sup>-1</sup> )	0.202 ± 0.154	0.158
V <sub>c</sub> /F <sub>-thiol</sub> (L)	3414 ± 1528	2576


  

PK Parameter -Clopidogrel carboxyl metabolite	Value (mean±SD)	Population mean (mean)
Ka <sub>-carboxyl</sub> (hr <sup>-1</sup> )	0.589 ± 0.352	0.486
Kcp <sub>-carboxyl</sub> (hr <sup>-1</sup> )	0.319 ± 0.158	0.213
Kpc <sub>-carboxyl</sub> (hr <sup>-1</sup> )	0.154 ± 0.084	0.258
Kel <sub>-carboxyl</sub> (hr <sup>-1</sup> )	0.464 ± 0.143	0.356
V <sub>c</sub> /F <sub>-carboxyl</sub> (L)	5.664 ± 4.586	3.258



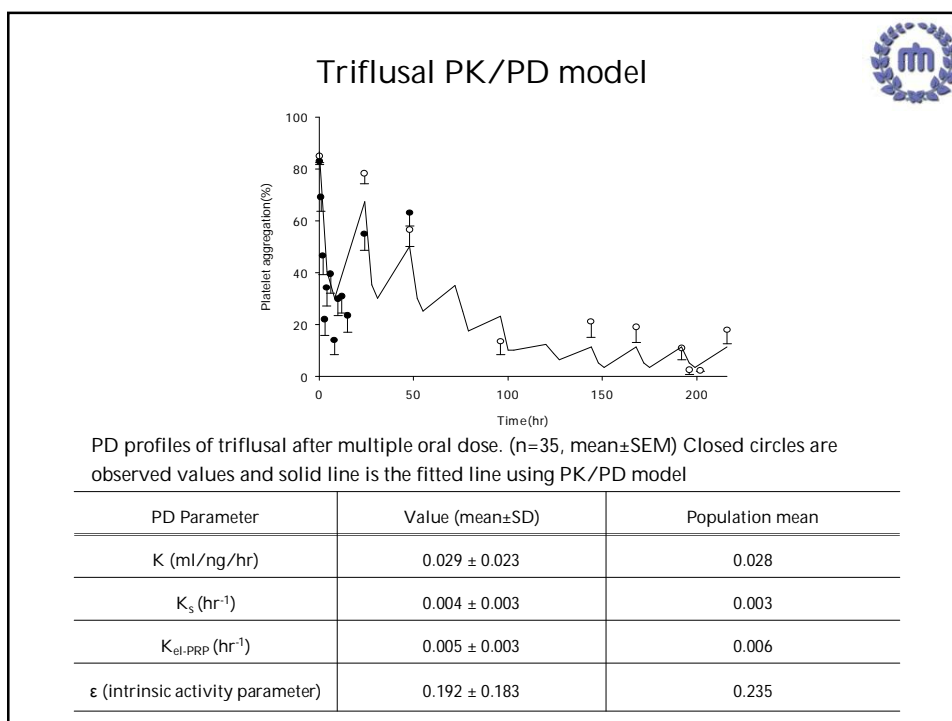


### Triflusal PK/PD model



Model dependent parameter

PK Parameter (Triflusal)	Value (mean±SD)	Population mean
Ka (hr <sup>-1</sup> )	0.774 ± 0.653	0.658
Kcp (hr <sup>-1</sup> )	0.531 ± 0.425	0.492
Kpc (hr <sup>-1</sup> )	0.021 ± 0.015	0.015
Kel (hr <sup>-1</sup> )	0.754 ± 0.325	0.879
V <sub>c</sub> /F (L)	40.180 ± 10.581	34.52
PK Parameter (HTB)	Value (mean±SD)	Population mean
K <sub>a-HTB</sub> (hr <sup>-1</sup> )	0.011 ± 0.005	0.009
K <sub>cp-HTB</sub> (hr <sup>-1</sup> )	3.930 ± 1.528	5.123
K <sub>pc-HTB</sub> (hr <sup>-1</sup> )	1.171 ± 10.546	0.956
K <sub>el-HTB</sub> (hr <sup>-1</sup> )	0.069 ± 0.012	0.048
V <sub>c</sub> /F <sub>HTB</sub> (L)	3.645 ± 2.358	2.698



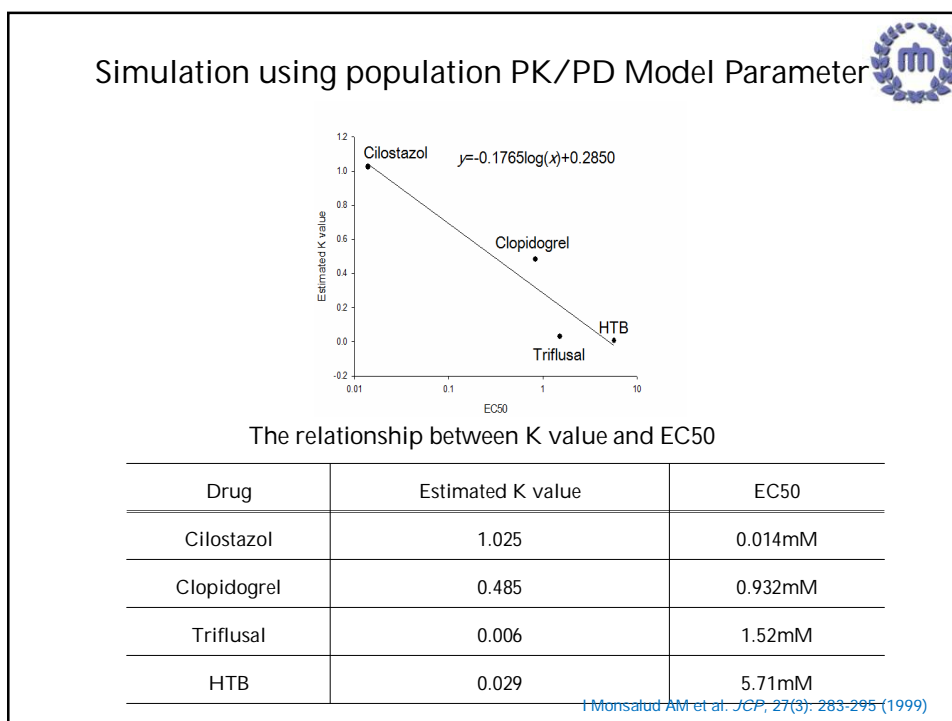
### Population PK/PD model parameter analysis

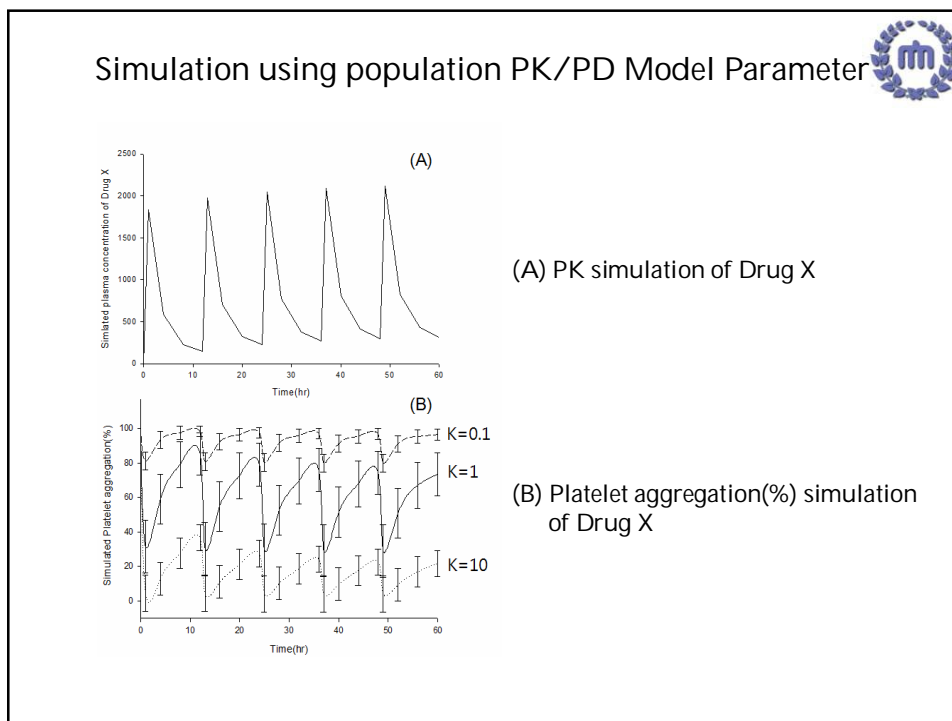
- Calculated  $E_0$  using  $K_s$  and  $K_{el-PRP}$

Drug	Equation	$E_0$ (observed)
Cilostazol	$(K_s/K_{el-PRP}) \times 100 = (0.0067/0.0076) \times 100$	88.15% (74.55%)
Clopidogrel	$(K_s/K_{el-PRP}) \times 100 = (0.0019/0.0021) \times 100$	90.47% (68.41%)
Triflusal	$(K_s/K_{el-PRP}) \times 100 = (0.0040/0.0050) \times 100$	80.00% (83.00%)

- Calculated platelet half life and  $K_{el-PRP}$

Drug	Equation	Half life(hr)
Cilostazol	$0.693/K_{el-PRP} = 0.693/0.0076$	91.18hr
Clopidogrel	$0.693/K_{el-PRP} = 0.693/0.0021$	330.00 hr
Triflusal	$0.693/K_{el-PRP} = 0.693/0.0050$	138.60 hr





## Conclusion

- We can be explained simultaneously the pharmacokinetic profiles of anti-platelet agents (Cilostazol, clopidogrel, triflusal) using extended parent-metabolite PK model based on 2-compartment model.
- The pharmacodynamics effects of the agents were fitted well to platelet aggregation effect model. The platelet aggregation effect model was made up following parameters:  $K_s$ , active-form platelet synthesis rate constant;  $K$ , apparent reaction rate constant of agents and active-form platelet;  $K_{el-PRP}$ , apparent rate constant of platelet;  $\epsilon$ , intrinsic activity parameters.
- The estimated PK parameters were well explained characteristics of absorption, distribution, metabolism and elimination of the agents and the estimated PD parameters have good correlations on platelet characteristics, such as platelet half-life and platelet aggregation base line effects.
- We observed the log linear relationship between estimated K value and EC50 of drugs. The linear equation was  $K \text{ value} = -0.1765 \log(\text{EC}_{50}) + 0.2850$ . Using the equation, we make more accurate and precise prediction, and actually used under various conditions.

The 8th Asian Conference on Clinical Pharmacy: "Toward Harmonization of Education and Practice of Asian Clinical Pharmacy"



Thank You