

# PHARMACOKINETICS AND DRUG DISPOSITION

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## A rational approach for selection of optimal covariate-based dosing strategies

**Background:** At present, there is no rational approach for choosing a dosing strategy for individualization based on a covariate. An approach to use in establishment of an a priori dosing strategy for individualization is presented. Factors influencing the choice of such a dosing strategy are identified.

**Methods:** The approach requires definition of the following: target variable, seriousness of deviations from the target (ie, risk function), population model, covariate distributions, and constraints. Minimizing the total risk yields an optimal dosing strategy, estimated as dose sizes for different subpopulations and covariate cutoff values at which doses are incremented or decremented. The method was illustrated with the use of simulated and real drug examples for the situation in which clearance is related to creatinine clearance.

**Results:** The estimated optimal cutoff(s) paralleled the median creatinine clearance in the population. The extent of variability in clearance explained by creatinine clearance was the main factor influencing the optimal ratios between adjacent dose sizes. An optimal dosing strategy was possible to estimate for the real drug.

**Conclusions:** The method is simple to perform, although one difficulty lies in defining the target variable and risk function. Our results imply that commonly used constraints in dosing strategies based on renal function (ie, dose ratio of 2 and predetermined cutoffs) are nonoptimal in the sense we propose. Because an optimal dosing strategy may not be practical to use, the therapeutic cost that would result with any constraint can be assessed by comparison of the outcome after the desired and the optimal strategy. (Clin Pharmacol Ther 2003;73:7-19.)

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A main goal for estimating population pharmacokinetic (PK) and pharmacodynamic (PD) characteristics for a drug is to optimize the dosing regimen in the patient population, including an assessment of the need for dosing individualization. Dosing strategies can be

grouped into a priori dosing regimens, individualized or not, and adaptive control dosing regimens, individualized by definition. An a priori dosing regimen is based on patient characteristics such as age, body size, or renal function. An adaptive control dosing regimen involves first an a priori dosage regimen, followed by feedback from patients (eg, plasma concentration [therapeutic drug monitoring] or effect and adverse effect), leading to subsequent dose adjustment for each individual.<sup>1,2</sup>

The dosing strategy used for a specific drug depends on the PK fate and the PD features of that drug in the target population. The PD features of a drug include the desired pharmacologic effect and the adverse event profile. By combining PK and PD information, relationships between the dose and effect or adverse events, respectively, can be described. Subsequently, weighing the beneficial effects versus the adverse effects results

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Received for publication Jan 28, 2002; accepted Sept 11, 2002.

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0009-9236/2003/\$30.00 + 0

doi:10.1067/mcp.2003.2

in finding a target concentration or effect with the greatest probability of overall treatment success.<sup>3</sup>

Several authors have established a priori dosage regimens using population PK-PD models as a starting point. A dosing strategy may be derived by simulation—that is, for a number of possible (and practical) dosing regimens, the outcome (desired target variable [eg, plasma concentrations or effect]) is simulated from a population model.<sup>4-6</sup> On the basis of a drug-specific criterion, one regimen is chosen as the most appropriate. Even under the assumption that the population model is correct, this method cannot be expected to provide the optimal solution for situations in which several aspects of the dosing strategy are to be simultaneously optimized.

An optimal dosing strategy can only be derived by estimation of the different aspects involved in the strategy, and some methods have been published.<sup>7-17</sup> The estimation necessitates a definition of the target that meets clinical demands. One part of the target definition is the establishment of a target variable. This variable may be pharmacokinetic (eg, area under the plasma concentration versus time curve) or pharmacodynamic (eg, a biomarker level). There are several examples in which PK<sup>7,9-12,15-17</sup> and PD<sup>8,13,14</sup> targets have been used. Consideration also needs to be given to whether the optimization with respect to the target variable should be made for several or all time points or only at a specific time point (eg, at steady state). For example, the therapeutic target could be systolic blood pressure at 36 hours after the dose,<sup>13</sup> serum concentrations over a whole dosing period,<sup>11</sup> or maximum and trough concentrations.<sup>12</sup> Furthermore, the target definition needs a specification of the seriousness of deviations from the target. This can be achieved by using a risk function that quantifies the risk associated with any deviation from the target. The optimal dosing strategy is then obtained by minimizing the overall expected risk. Wakefield<sup>17</sup> and several other authors<sup>7-9,11,14-16</sup> have used this approach.

The estimation of the dosing strategy is a multidimensional problem, and estimation of all aspects of the dosing strategy would yield a truly optimal strategy, given the target definition and assuming correctness of the PK-PD model and agreement of the covariate distribution with the intended patient population. However, often only a single aspect of the strategy is estimated, most commonly, the dose, and other aspects, for example, the dosing interval, are fixed or constrained to a few values.<sup>8,10-12,15-17</sup> Other examples of constraints are that the dose ratio is fixed<sup>11</sup> or that the dose size is allowed to take only some predefined values,<sup>8,16</sup> is

limited by a maximum value,<sup>14</sup> or is discretized.<sup>17</sup> There are few examples in which multiple aspects of a dosing strategy (for example, loading and maintenance infusion rates), which are the same for all subjects, are estimated without constraints.<sup>9,10</sup>

Designing individualized covariate-based dosing regimens without constraints, such as dosing per kilogram of body weight, is relatively straightforward and requires little or no estimation. However, when individualization is to be part of the (constrained) a priori dosing strategy, the subpopulations that should receive different doses could either be determined beforehand and fixed in the estimation<sup>11,17</sup> or be a part of the estimation. To our knowledge, the latter has not been presented previously.

In this work we describe and explore a method that estimates the entire dosing strategy; that is, both dosing and individualization aspects are estimated simultaneously, under given constraints. The purpose of the investigation was to propose and illustrate a rational approach to use in the establishment of an a priori dosing strategy for individualization and identify factors influencing the choice of such a dosing strategy. A real drug example is presented to show the use of this method during drug development. In this article the term *optimal dosing strategy* is understood to be optimal, conditional on target definition, constraints, the PK-PD model, and agreement of the covariate distribution with that of the intended patient population (ie, not a truly optimal dosing strategy).

## METHODS

We chose to illustrate the optimization of a dosing strategy by using a common situation—when the clearance (CL) of a drug depends on the patient's renal function and doses are, therefore, to be adjusted on the basis of creatinine clearance (CLCR). Clearance was assumed to be linearly related to renal function.

If only  $n$  discrete dose sizes or rates ( $D_1, D_2, \dots, D_n$ ) can be made available (as is common with oral therapy), an optimal dosing strategy requires simultaneous estimation of the dose sizes and the  $n - 1$  CLCR cutoff values ( $CO_1, CO_2, \dots, CO_{[n-1]}$ ). The COs are the CLCR values at which doses are incremented or decremented.

The strategy was illustrated by use of a simulation with a set of default conditions. The PK characteristics, the dosing strategy constraints or target definition, were thereafter varied to investigate factors governing the selection of key features (DRs and COs) in the dosing strategy. DR is the ratio between two adjacent dose rates (higher over the adjacent lower). Finally, the

**Table I.** Factors investigated for influence on selection of dosing strategy

Dosing categories estimated (No.)					Pharmacokinetic characteristics			CLCR characteristics		
1	2	3	4	5	$f_{e_{pop}}$	$CV_{CLR}$ (%)	$CV_{CLNR}$ (%)	Range*	$CLCR_{pop}$ (mL/min)	$CV_{CLCR}$ (%)
x	x	x	x	x	<b>1</b>	<b>20</b>	<b>NA</b>	<b>20-150</b>	<b>75</b>	<b>35</b>
x	x	x	x	x	1	5, 15, 25, 30, 50	NA	20-150	75	35
x	x				1	5, 15, 30	NA	20-150	50, 60, 90, 110	35
x	x	x	x	x	1	20	NA	5-150, 50-150	75	35
x	x	x			1	20	NA	20-150	50, 60, 70, 80, 90, 100, 110	35
x	x				1	20	NA	20-150	50, 60, 75, 90, 100	20, 50
x	x	x	x	x	0.9	20	40	20-150	75	35
x	x	x	x	x	0.9	20	40	20-150	50, 70, 90, 110	35
x	x				0.9	20	40	20-150	60	35
x	x				0.9	20	30	20-150	75	35
x	x	x	x	x	0.8	20	40	20-150	75	35
x	x				0.8	20	30	20-150	75	35
x	x	x	x	x	0.7	20	40	20-150	75	35
x	x	x	x	x	0.7	20	40	20-150	50, 70, 90, 110	35
x	x				0.7	20	40	20-150	60	35
x	x				0.7	20	30	20-150	75	35
x	x	x	x	x	0.6	20	40	20-150	75	35
x	x				0.6	20	30	20-150	75	35
x	x	x	x	x	0.5	20	40	20-150	75	35
x	x	x	x	x	0.5	20	40	20-150	50, 70, 90, 110	35
x	x				0.5	20	40	20-150	60	35
x	x				0.5	20	20, 30, 50	20-150	50, 60, 75, 90, 110	35
x	x	x	x	x	0.33	20	40	20-150	75	35
x	x				0.33	20	40	20-150	50, 60, 70, 90, 110	35
x	x				0.33	20	30	20-150	75	35

Nominal values of pharmacokinetic and CLCR characteristics used for simulation of data sets are shown, as well as all data sets simulated and dosing strategies estimated with each data set (eg, the second line describes 5 simulated data sets in which  $CV_{CLR}$  was varied and dosing strategies with 1 to 5 dosing categories were estimated for each data set). Settings for the default data set are given in boldface type.

CLCR, Creatinine clearance;  $f_{e_{pop}}$ , ratio of renal clearance to clearance in typical subject with typical CLCR value;  $CV_{CLR}$ , coefficient of variation for renal clearance;  $CV_{CLNR}$ , coefficient of variation for nonrenal clearance;  $CLCR_{pop}$ , creatinine clearance in typical subject;  $CV_{CLCR}$ , coefficient of variation for CLCR.

\*The distributions for CLCR were truncated at 20 and 150 mL/min.

approach was applied to the estimation of a dosing strategy for a real drug under development.

### Simulated data sets

Individual estimates of CL and CLCR were simulated for a large number of hypothetical subjects ( $n = 5000$  for each data set, arbitrarily chosen) according to the following equations:

$$CLCR_i = CLCR_{pop} \cdot e^{(\eta_{CLCR} \cdot CV_{CLCR})} \quad (1)$$

$$CLR_i = \theta_1 \cdot CLCR_i \cdot e^{(\eta_{CLR} \cdot CV_{CLR})} \quad (2)$$

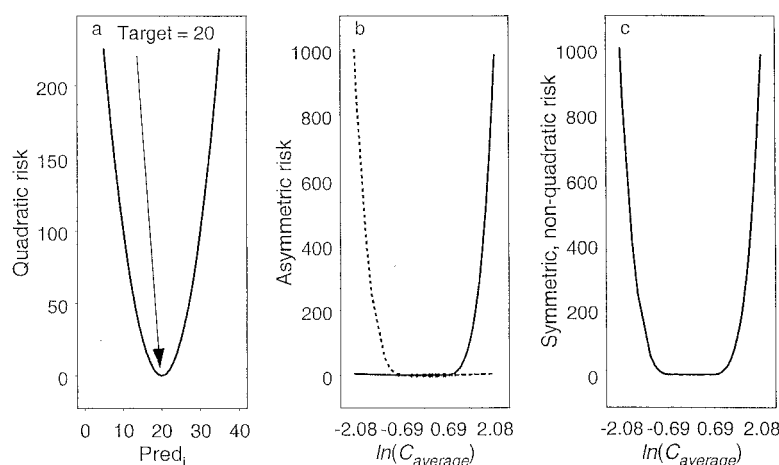
$$CLNR_i = \left( \frac{\theta_1 \cdot CLCR_{pop} - \theta_1 \cdot CLCR_{pop}}{f_{e_{pop}}} \right) \cdot e^{(\eta_{CLNR} \cdot CV_{CLNR})} \quad (3)$$

$$CL_i = CLR_i + CLNR_i \quad (4)$$

in which  $CLCR_{pop}$  is the typical value of CLCR in the population, CLR is renal clearance, CLNR is nonrenal

clearance,  $f_{e_{pop}}$  is the ratio of CLR to CL in a typical subject with a typical CLCR value, and  $CLCR_i$ ,  $CLR_i$ ,  $CLNR_i$ , and  $CL_i$  are the  $i$ th individual's parameter values. Without loss of generality,  $\theta_1$  was set to 1 throughout the study.  $\eta_{CLCR}$ ,  $\eta_{CLR}$ , and  $\eta_{CLNR}$  are normally distributed, zero-mean unit-variance variables truncated at  $\pm 3$ , and  $CV_{CLCR}$ ,  $CV_{CLR}$ , and  $CV_{CLNR}$  are the coefficients of variation. Default values of the parameters, as well as alternative values, are given in Table I. It should be noted that  $f_{e_{pop}}$  for a drug often is defined for healthy subjects, leading to a higher value compared with our definition here.

As a sensitivity analysis and to confirm the adequacy of approximating CLCR to a truncated log-normal distribution, 4 CLCR distributions were simulated to mimic, with respect to median and percent CV of CLCR, 4 real distributions obtained from clinical studies in patients with cardiovascular diseases ( $n = 75$ ,



**Fig 1.** Examples of risk functions. **a**, Quadratic risk function. **b**, Asymmetric risk function in log domain, in which  $W_{\text{high}} = 1$ , slope = 10, and  $a = \ln(0.5)$  (dotted line) or  $W_{\text{low}} = 1$ , slope = 10, and  $b = \ln(2)$  (solid line). **c**, Symmetric nonquadratic risk function in log domain, in which slope = 10,  $a = \ln(0.5)$ , and  $b = \ln(2)$ . (See Table III for explanations of  $W_{\text{high}}$ ,  $W_{\text{low}}$ , slope, and  $a$  and  $b$ .)

902, 1445, and 1490). In these studies the ranges of median CLCR and percent CV values were 63 to 75 mL/min and 32% to 43%, respectively. All individual values in the real distributions were replicated to reach  $n > 5000$ . The optimal dosing strategies based on real and matching simulated CLCR distributions were compared.

### Estimation of optimal dosing strategy

The principle of the approach can be described as follows:

$$\text{Target value} = \text{Pred}_i + \epsilon_i \quad (5)$$

in which  $\text{Pred}_i$  is the prediction of the target variable in the  $i$ th individual.  $\text{Pred}_i$  is given by individual PK parameters (which relate the dose to the target variable) and the estimated optimal Ds and COs. The individual PK parameters are simulated on the basis of a population PK model and a relevant covariate distribution. Hence  $\epsilon_i$  represents the individual deviation from the target value. The estimated optimal Ds and COs are those minimizing the sum of the squared deviations, that is, minimizing the total risk. Fig 1, *a*, shows a graphic description of this risk function. This estimation procedure is different compared with commonly used analyses; in commonly used procedures the dosing regimen (Ds and COs) is a given independent variable and the PK variables are estimated. In our method the PK parameters are independent variables and the Ds and COs (dosing regimen) are the parameters being estimated.

Several key issues need to be considered in the process of selecting a dosing strategy. In Table II the steps involved in the development of a dosing strategy are presented in a general perspective, together with the definitions made in this work. This scheme can be applied for estimating many types of dosing strategies, not only covariate-based dosing strategies. The estimation does not require a nonlinear mixed effects model, but all simulations and estimations (including the real drug example) were conveniently performed with use of the NONMEM program.<sup>18</sup> The optimal dosing strategy was considered as the one giving the lowest objective function value.

**Target definition (steps 1 and 2).** A prerequisite for estimating a dosing strategy is the therapeutic target definition that should reflect what is to be achieved, which is represented by the first 2 steps in Table II. The target variable may be a single PK variable (eg, steady-state concentration) or PD variable or a more complex variable demanding the use of a utility function or a responder concept, which combines multiple effects and side effects (ie, the weighted contribution of effect and side effect). The target variable can be the same in the entire population or can vary between subpopulations (eg, elderly patients may be more sensitive to a drug and, therefore, need a lower systemic exposure to reach the same effect). Once the target variable is defined, the seriousness of deviations from the target should be specified with use of a risk function. The shape of the risk function is driven by clinical consid-

**Table II.** Key issues to consider in development of an a priori dosing strategy

Step	Action	Conditions for simulated data sets	Conditions for real drug example
1	Definition of target variable	$C_{\text{average}}$ at steady state = 1	$C_{u, 1h}$ (loading infusion) = 70 $\mu\text{mol/L}$ , $C_{u,ss}$ (maintenance infusion) = 70 $\mu\text{mol/L}$
2	Definition of risk function	Quadratic risk in log domain	Quadratic risk in log domain
3	Definition of population PK-PD model	Population model for $C_{\text{average}}$ $C_{\text{average}} = \text{Dose rate}/\text{CL}$ Linear relationship between CL and CLCR Unexplained variability component in CLR and CLNR	Population model for $C_{1h}$ and $C_{ss}$ , see Table IV; fraction unbound set to 0.61 for all patients
4	Definition of covariate distribution	CLCR distributions as given by Table I	Empiric distributions of CLCR and WT from a previous phase 3 study in the target population (n = 902)
5	Definition of constraints	Default constraints: Discrete number of dose sizes (n = 1, 2, 3, 4, or 5), CO values restricted to multiples of 5 mL/min Alternative constraints: either DR or CO, or both, fixed to 2 and 50 mL/min, respectively, for default data set	Loading: Individualization based on WT or CLCR, up to 2 dosing categories Maintenance: Individualization based on CLCR, up to 4 dosing categories Patients with CLCR less than 30 mL/min should not be included
6	Estimation of dosing strategy	Estimation according to steps 1-5 plus sensitivity analysis with respect to steps 2 and 4 (risk function, CLCR distribution) and estimation method (direct versus stepwise)	Estimation according to steps 1-5 plus sensitivity analysis with respect to step 3 (uncertainty in population estimates)
7	Selection of final dosing strategy	No selection made but relative tradeoff made by comparison between overall variability in $C_{\text{average}}$ and number of dosing categories	Quality of therapy: Dosing strategy considered acceptable if at least 90% of target population reached unbound concentration greater than 50 $\mu\text{mol/L}$ and less than 5% of patients reached unbound concentrations greater than 100 $\mu\text{mol/L}$ Practical consideration: Lowest number of dose sizes

$C_{\text{average}}$ , Average plasma concentration at steady state;  $C_{u,1h}$ , unbound plasma concentration at 1 hour;  $C_{u,ss}$ , unbound plasma concentration at steady state; PK-PD, pharmacokinetic-pharmacodynamic; CL, clearance; CLR, renal clearance; CLNR, nonrenal clearance;  $C_{1h}$ , plasma concentration at 1 hour;  $C_{ss}$ , plasma concentration at steady state; WT, body weight; CO, cutoff; DR, ratio between 2 adjacent dose rates.

erations regarding the seriousness of deviation from the target. For example, if the main concern is reaching effective exposure of the drug, an asymmetric penalty function should be used in which the penalty for a negative deviation from the target is higher than for a corresponding positive deviation.

The target variable for the simulated data was average plasma concentration at steady state ( $C_{\text{average}}$ ), arbitrarily set to 1 for all patients. Accordingly, PD variability was not considered, which assumes the PD variability to be relatively low and that plasma concentrations are a sufficient surrogate for the pharmacologic

**Table III.** Description of investigated risk functions

$R = \begin{cases} ([\ln(C_{\text{average,T}}) - \ln(C_{\text{average,i}})] \cdot W_{\text{low}})^2 & \text{for } \ln(C_{\text{average,i}}) < a \\ ([\ln(C_{\text{average,T}}) - \ln(C_{\text{average,i}})]^2 & \text{for } a \leq \ln(C_{\text{average,i}}) \leq b \\ ([\ln(C_{\text{average,T}}) - \ln(C_{\text{average,i}})] \cdot W_{\text{high}})^2 & \text{for } b < \ln(C_{\text{average,i}}) \end{cases}$		
$W_{\text{low}} = 1 - \text{slope} \cdot (\ln[C_{\text{average,i}}] + a)$		
$W_{\text{high}} = 1 + \text{slope} \cdot (\ln[C_{\text{average,i}}] - b)$		
Values of $a$ , $b$ , and slope investigated*		
Slope	$a$	$b$
0†, 1, 2, 5, 10, 20, 50	$\ln(0.5)$ , $\ln(0.707)$	$\ln(2)$ , $\ln(1.41)$

$C_{\text{average,T}}$ ,  $C_{\text{average,i}}$  Target average concentration and expected individual average concentration given the estimated dose rates, respectively; R, risk function;  $W_{\text{low}}$ , weighting of downward deviations from the target;  $W_{\text{high}}$ , weighting of upward deviations from the target.

\*Constants giving shape of risk function. Setting either  $W_{\text{low}}$  or  $W_{\text{high}}$  equal to 1 while slope is nonzero yields asymmetric risk functions.

†Corresponds to quadratic risk function.

response. A quadratic risk function in the log domain was used as the default, but in addition, as a sensitivity analysis, the impact of using other risk functions, asymmetric and with other shapes, was investigated, as given in detail in Table III. Risk functions with other shapes are illustrated in Fig 1,  $b$  and  $c$ .

**Definition of PK-PD model and covariate distribution (steps 3 and 4).** The expected individual outcome given a dose input is based on a population PK-PD model relevant for the intended population, together with relevant covariate distributions. Uncertainty in estimated population parameters may be taken into account. The purpose of the PK-PD model is to describe the relationship between dose input and the selected target variable, including models for variability and covariate relationships. Accordingly, only parts of a full population model may be needed (eg, if the target variable is  $C_{\text{average}}$ , as in our simulations, then only a population model for clearance is required). Covariates that are relevant to define are those that are part of the target definition or PK-PD model. The covariate distribution may be obtained by parametric simulation, as in the simulation study, or from an empiric database, as in the real drug example and some simulations. Whatever the source, the important point is that the covariate characteristics reflect those of the intended patient population.

**Constraints (step 5).** The introduction of constraints may have its background in, for example, safety or practical considerations.<sup>7,14</sup> The optimization of the dosing strategy is then made under those constraints. Usually, several sets of constraints are considered in parallel. Constraints may be categorized into the following: (1) dosing constraints such as number of dose sizes available, actual dose size(s) available, dose ratio(s) allowed, dosing interval(s) allowed, and allowing only a constant dose within subjects; (2) individualization constraints, for example,

number of subpopulations and COs; and (3) covariate constraints, for example, patients with a CLCR less than 20 mL/min should not be treated.

Commonly used dosing strategies based on renal function involve some of the exemplified constraints (ie, DR of 2 and CO of 50 mL/min). To further explore how close commonly used dosing strategies are to optimal strategies and to estimate the loss adhering to certain DRs and COs, dosing strategies with the following constraints were estimated: (1) DR fixed to 2 (size of doses and CO estimated), (2) CO fixed to 50 mL/min (DR not fixed and dose sizes estimated), or (3) DR and CO fixed to 2 and 50 mL/min, respectively (dose sizes estimated). The constrained strategies 1 to 3 were compared with an optimal dosing strategy (ie, no constraints on DR or CO) with 2 dosing categories.

**Estimation of dosing strategy (step 6).** Once definitions have been set according to steps 1 through 5 in Table II, minimizing the expected total risk can optimize a dosing strategy. Sensitivity analyses with respect to assumptions made in steps 1 through 4 can be performed at this stage.

In the simulation and real drug example, the relationship between the target and dose rate was defined by different functions on different intervals with respect to CLCR, because the dose rate in an individualization strategy varies with subpopulation. Apart from the dose rates, the end points of the intervals (ie, COs) were estimated as shown in equation 6, in which  $n$  equals the number of dosing categories.

$$\text{Pred}_i = C_{\text{average},i} = \begin{cases} D_1 / \text{CL}_i & \text{CLCR}_i \leq \text{CO}_1 \\ D_2 / \text{CL}_i & \text{CO}_1 < \text{CLCR}_i \leq \text{CO}_2 \\ \cdot & \cdot \\ \cdot & \cdot \\ D_n / \text{CL}_i & \text{CO}_{n-1} < \text{CLCR}_i \end{cases} \quad (6)$$

The estimation of so-called change-point parameters such as the COs is numerically troublesome because the derivative of the function is not defined across all CLCR values.<sup>19</sup> To overcome this problem, 2 types of estimation procedures were used. (1) A stepwise search for the optimal dosing strategy allowing COs to take on values that are multiples of 5 mL/min, which was thought to result in practical dosing strategies, was done. Thus  $D_1 \dots D_n$  were estimated several times; each time, a different CO value (25, 30, . . . 145) or combination of CO values (if more than 2 dosing categories) was used and not estimated. The number of estimations depends on the range of CLCR values and number of dosing categories. The fit providing the lowest objective function value was identified as the optimal dosing strategy. This method was the default method for dosing strategies with 2 dosing categories. (2) The second method was a direct estimation method, in which the change-point model was substituted with a Hill equation relating D to CLCR by a continuous function, as given in equation 7. By fixing the shape factor ( $\gamma$ ) to a high value, the model approximated a change-point model without experiencing the numeric difficulties.

$$D = D_1 + \sum_{j=2}^n \frac{(D_j - D_{j-1}) \cdot \text{CLCR}_i^\gamma}{\text{CLCR}_i^\gamma + \text{CO}_{j-1}^\gamma} \quad (7)$$

In this parameterization,  $n$  equals the number of dosing categories. Thus in this procedure COs are directly estimated. This method was the default method for optimization of dosing strategies involving more than 2 dosing categories.

**Selection of dosing strategy (step 7).** If the optimal dosing strategy is estimated under more than one set of constraints, a selection between rival strategies must be made. This could (in theory) be achieved by a formalized function in which the practical considerations and therapeutic quality are weighted. However, we believe that a less formalized selection procedure is more easily implemented. In such a selection procedure, the practicality of a dosing strategy would be compared with the deviation from the target expressed either in terms of the risk function or by some other criteria (as in the real drug example; Table II).

From a practical perspective, it is often desirable to have as few dosing categories as possible, given the safety profile of the drug. Therefore the benefit achieved by increasing the number of dosing categories is an important issue to evaluate. One of the constraints in the simulation study was the number of dosing categories. To assess the gain from adding dosing categories to the strategy, a comparison was made of the

resulting overall variability in  $C_{\text{average}}$  after optimal dosing strategies involving different numbers of dosing categories. The change in overall variability relative to a dosing strategy with no individualization (ie, using one dose for the whole population) was calculated for each individualized strategy.

### Application to dosing strategy estimation of a real drug

As an illustration, the optimal dosing strategy, given certain constraints, was estimated for NXY-059 (disodium 4-[(*tert*-butylimino)methyl]benzene-1,3-disulfonate *N*-oxide), a nitrene-based free radical-trapping agent under development for the treatment of acute stroke as an alternative to thrombolytic therapy. NXY-059 will be administered as a 2-step infusion starting with a 1-hour loading infusion followed by a 71-hour maintenance infusion. The definitions of the target, population PK model, covariate distributions, constraints, and selection of optimal strategy are given in Tables II and IV.

An individualized dosage regimen was deemed to be necessary to attain the target exposures for NXY-059, because the drug is expected to dose-dependently affect a condition with a high risk of irreversible morbidity, as well as a high incidence of associated renal impairment. At present, no biomarkers are available for NXY-059, and therefore the unbound plasma concentration of NXY-059 was considered the most suitable target. On the basis of preclinical data, reaching effective concentrations was important, and therefore a quadratic risk function in the log domain (which penalizes a concentration at half the target as much as one at twice the target) was judged appropriate. A population PK model for NXY-059 has been characterized with use of the NONMEM program, on the basis of phase 2 study data from 92 patients.<sup>20</sup> A 2-compartment model adequately described the data, in which CL was linearly related to CLCR and central volume of distribution was linearly related to body weight (WT) (Table IV). According to this model, individualization based on either renal function or WT, or both, was considered. The empiric distribution of CLCR had a median of 63 mL/min and a coefficient of variation of 38% and ranged from 30 to 183 mL/min. The corresponding figures for the empiric WT distribution were 72 kg, 19%, and 36 to 153 kg. CLCR was calculated according to the Cockcroft-Gault formula.<sup>21</sup> The estimations of the optimal loading and maintenance infusions were done separately. The search for the optimal infusion rates was performed with the stepwise method.

In the above-described calculations, the uncertainty in population parameter estimates was not taken into ac-

**Table IV.** Population parameter estimates for NXY-059

<i>Parameter</i>	<i>Estimate (%RSE)</i>	<i>Interpatient variability* as %CV (%RSE)</i>
CL (L/h)	4.64 (2.5)†	22.0 (20)
Central volume of distribution (V1)(L)	7.20 (15)‡	38.0 (40)
Intercompartmental clearance (Q)(L/h)	15.9 (24)	NE§
Peripheral volume of distribution (V2)(L)	8.40 (13)	NE§
Proportional residual error ( $\sigma_1$ ) (%CV)	9.70 (25)	NA
Additive residual error ( $\sigma_2$ ) (SD, $\mu\text{mol/L}$ )	5.8 (19)	NA
Fractional change in CL with CLCR	0.0145 (8.3)	NA
Fractional change in V1 with WT¶	0.0178 (19)	NA

RSE, Relative standard error; CV, coefficient of variation; NE, not estimated; NA, not applicable.

\*Modeled with exponential error models. The RSE relates to the corresponding variance term.

†Refers to patient with renal function of 70.75 mL/min.

‡Refers to patient with body weight of 77 kg.

§Model fitting did not improve by inclusion of interpatient variability on this parameter.

||CL =  $4.64 \cdot (1 + 0.0145 \cdot [\text{CLCR} - 70.75])$ .

¶V1 =  $7.22 \cdot (1 + 0.0178 \cdot [\text{WT} - 77])$ .

count. Therefore the dosing strategy for the maintenance infusion (3 dosing categories) was re-estimated 200 times, and the uncertainty of the population parameters was taken into account. In each simulation of individual PK parameters, new samples of population parameters were used. The population parameters were sampled from the covariance matrix of the estimates. For each set of individual PK parameters, dosing strategy estimation was done. Each estimated dosing strategy was applied to new populations (individual PK parameters generated with uncertainty in population estimates taken into account as given) to obtain predictions of  $C_{u,ss}$ . The root mean square error (RMSE) was estimated for each dosing strategy.<sup>22</sup> Eventually, the RMSEs were compared with the RMSE for the optimal dosing strategy, without uncertainty taken into account, to assess the potential error made by not considering uncertainty.

## RESULTS

### Factors influencing optimal dosing strategy

For a population based on the default conditions (Table I), the optimal dosing strategy (2 dosing categories) resulted in a DR of 1.7 and a CO value of 70 mL/min, which was close to the median CLCR in the population (ie, 74 mL/min). The estimated optimal CO for a dosing strategy with 2 dosing categories paralleled the median CLCR in the population, with little or no influence of  $fe_{pop}$  (Fig 2). Similarly, for dosing strategies involving more than 2 dosing categories, the estimated COs paralleled median CLCR in the population but estimates were shifted upward and downward, respectively. The results for strategies with 2 or 3 dosing categories are given in Fig 2. The main factor influencing the selection of the optimal DR was  $fe_{pop}$ , which is

closely linked to the extent of variability in CL that can be explained by CLCR. The same tendency was obvious regardless of the number of dosing categories, as shown in Fig 3, although the size of the DR between adjacent doses decreased with increasing number of dosing categories. In addition to  $fe_{pop}$ , the distribution of CLCR had some impact on the choice of DR; the estimated DR correlated positively with range and variability in CLCR (results not shown). The magnitude of the unexplained variability in CL or CLNR had no effect or only a minor effect on the choice of COs and DRs (results not shown).

### Comparison of dosing strategies with different constraints

The gain from adding dosing categories to the strategy for drugs with  $fe_{pop}$  ranging from 0.33 to 1 are shown in Fig 4, *a*. The gain was large when individualization involved 2 or 3 dosing categories. However, further individualization resulted in a marginal decrease in overall variability. As can be expected, a population with a wide range of CLCR values gained more by individualization than did a population with a narrow range (results not shown); in addition, the gain from individualization was low in a population in which variability not explained by the covariate contributed markedly to total variability (Fig 4, *a*). In Fig 4, *b*, the results for dosing strategies in which DR or CO was fixed to commonly used values are shown in comparison with the results for an optimal dosing strategy. These resulted in less gain, and fixing both DR and CO even yielded an increase in overall variability for drugs in which  $fe_{pop}$  was lower than 0.6.

### Sensitivity analysis

The comparison of optimal dosing strategies based on 4 real and 4 matching simulated distributions of CLCR confirmed that the simulated CLCR distributions mimic real distributions satisfactorily for the purpose of dosing strategy estimation. The estimated DRs and COs did not differ in any case by more than 0.1 and 5 mL/min, respectively.

The effect of using nonquadratic or asymmetric risk functions was investigated for a dosing strategy with 2 dose levels with the use of the default data set. Using different risk functions did not have a marked impact on the choice of dosing strategy in terms of DR and CO. Regardless of risk function used, DR was in the range of 1.7 to 2 and CO was in the range of 60 to 75 mL/min. However, an asymmetric risk function that penalizes upward deviations from target more than corresponding downward deviations resulted in lower estimates of the dose sizes and vice versa.

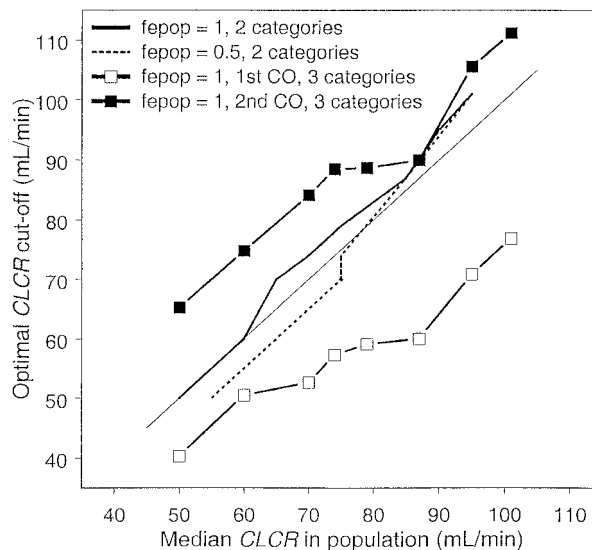
The 2 different estimation methods (stepwise versus direct) were compared for 1 series of simulated data sets in which  $fe_{pop}$  varied from 0.33 to 1. Comparison of the estimated dose sizes, COs, and overall variability by each method revealed good agreement, as shown for a dosing strategy involving 4 dosing categories in Fig 5.

### Real drug example

For the loading infusion, it was found that individualization based on either WT or CLCR did not result in appreciable benefit and that the same loading infusion was sufficient to fulfill the final dose selection criterion acceptably.

For the maintenance infusion, a dosing strategy involving 4 dosing categories was required to fulfill the final dose selection criterion acceptably (Table V). However, weighting quality of therapy versus practical considerations resulted in the conclusion that the improvement in overall results by addition of a fourth category was not substantial. Therefore the final dosing strategy involved 3 dosing categories. The results are presented in Table V. The results with respect to DRs and COs are in agreement with the results based on the simulated data, given the features of the population PK model and the CLCR distribution.

In these calculations it has been assumed that the point estimates of the population parameters correctly describe the PK characteristics of the target population. The sensitivity analysis with use of the covariance matrix of these estimates was made to produce the range of likely values of the performance of a dosing strategy, expressed as RMSE of achieved compared with target concentrations, when the uncertainty of the

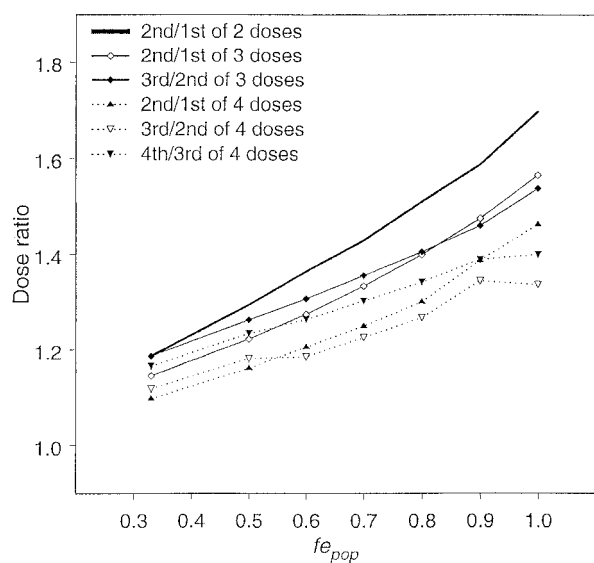


**Fig 2.** Relationship between estimated optimal cutoff (CO) values and median creatinine clearance (CLCR) in population. Results are shown for a dosing strategy with 2 dosing categories for a drug in which the ratio of renal clearance (CLR) to clearance in a typical subject with a typical CLCR value ( $fe_{pop}$ ) is either 1 or 0.5, as well as for a dosing strategy with 3 dosing categories ( $fe_{pop} = 1$ ). The *thin solid line* is the line of identity. Data sets were simulated by using default nominal values for other pharmacokinetic (PK) and CLCR characteristics (see Table I).

parameter estimates are taken into account. It may be surprising that the default strategy, when the performance of the method is evaluated with use of the same point estimates as used to derive the dosing strategy, did not result in the lowest RMSE (Fig 6). However, the main factor determining the overall deviation from the target was the value of the coefficient of variability in CL ( $CV_{CL}$ ). A linear regression of RMSE versus  $CV_{CL}$  showed a positive slope, with an  $r^2$  value of 0.69. The introduction of uncertainty in population estimates resulted in a range of estimated dosing strategies. The median values of the key features (infusion rates and COs) involved in the dosing strategy were close to those obtained when uncertainty was not taken into account.

### DISCUSSION

We have presented a rational approach to selection of an a priori dosing strategy comprising a simple method for the estimation of dosing aspects including individualiza-



**Fig 3.** Relationship between estimated optimal dose ratio (DR) and  $fe_{pop}$ . The results are shown for strategies with 2 to 5 dosing categories. The ratios are given as the high dose over the low dose for two adjacent doses, and doses are numbered in order of increasing renal function. Data sets were simulated by using default nominal values for other PK and CLCR characteristics (see Table I).

tion. The real drug example demonstrated that this approach could be implemented in drug development.

We believe that the method can be generally applied for the establishment of a priori individualized dosing strategies, not only under the conditions studied. Our simulation example was simple to demonstrate the dosing estimation method. It was based on a single covariate, a linear PK model, a linear parameter-covariate relationship, a PK target variable and population invariant target, and risk function. However, a situation with nonlinear pharmacokinetics, a nonlinear relationship between a PK parameter and covariate, and a PD target requires solely that the population model describing the relationship between dose input and the selected target variable is extended accordingly. For example, if PD variability had been clinically significant and plasma concentrations not adequate as a surrogate for drug effect, then a PD target variable should have been used and a PK-PD model would have been needed. With a linear relationship between plasma concentration and PD variable, no change in estimated COs or Ds would be expected, but the benefit of individualization would decrease with increasing PD variability. With a nonlinear relationship between plasma concentration and PD variable, both COs and Ds would be estimated to other values. In addi-

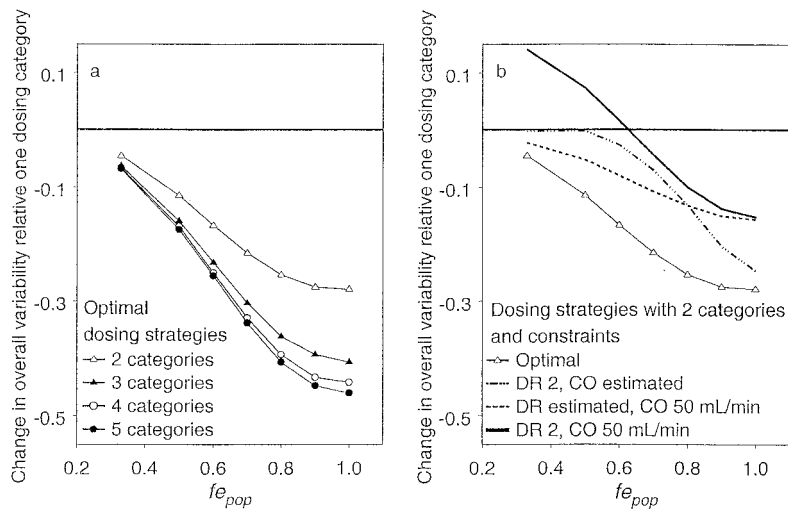
tion, if subpopulations demanding different targets or penalty functions can be defined on the basis of some available patient characteristic, the estimation could be modified to take this into account. Although addition of more complexity to the model or the target definition is possible in theory, it may lead to computational difficulties and therefore optimization under other conditions needs further investigation. With respect to individualized dosing strategies based on 2 or more covariates, those are estimable, although likely to result in complicated and impractical dosing strategies.

We do not suggest that these results can be extrapolated to other situations, apart from the fact that the distribution of the covariate is important for the CO and the shape of the parameter-covariate relationship is likely to be important for the magnitude of the DRs. The results would be applicable for situations in which the distribution of CLCR values is comparable with those studied and in which the PK relationships and target variable are the same. It is reasonable to believe that similar results would also be true for other covariates (eg, body weight or age) as long as the distribution is comparable.

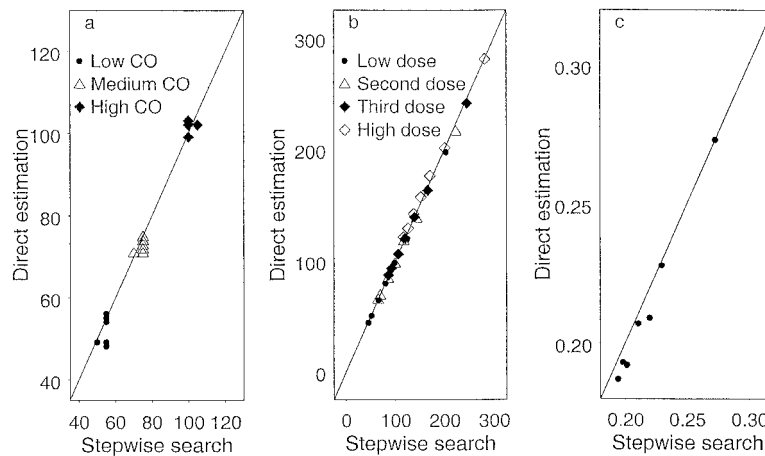
The re-estimation of the optimal dosing strategy for NXY-059, when uncertainty of the population estimate was taken into account, yielded results similar to those of the estimation without uncertainty considerations. In this specific case, the population estimate of CL and the interindividual variability of CL were estimated with high certainty, and the results are therefore not unexpected. With higher uncertainty, it can be expected that the truly optimal dosing strategy may deviate more from the one derived on the basis of the point estimates. However, for the performance of the dosing strategy, the estimates of unexplained variability appear to be the most important determinant.

One obstacle in the proposed approach for development of an a priori dosing strategy is the target definition (target variable and risk function). Although the definition may be implicitly present in the mind of the drug developer, the definition of the target is seldom explicitly expressed, as our method requires. However, we believe that the necessity to define a target is beneficial even in the absence of dosing strategy estimation and can therefore be advocated, because it may reveal different opinions about the goal of the treatment within the project team, make clinical trial simulations more focused, guide collection of information, and allow a more precise profiling against competitor drugs.

At present, there is no rational approach for choosing a dosing strategy based on a covariate. Dosing strategies based on renal function are often established by tradition, and a DR of 2 combined with a low CO is



**Fig 4.** Plots showing gain with individualization for optimal dosing strategies (2 to 5 dosing categories) (a) and dosing strategies with certain constraints (b). Gain is expressed as the change in overall variability for each dosing strategy relative to the overall variability for a dosing strategy with only 1 dose. Data sets were simulated by using default nominal values for other PK and CLCR characteristics (see Table I).



**Fig 5.** Comparison of optimal dosing strategies (4 dosing categories) based on either the direct estimation method or the stepwise search method as follows: optimal CO values (a), optimal dose sizes (b), and estimated standard deviation in residuals (c). The *solid line* in each plot is the line of identity. Data sets were simulated with  $f_{e_{pop}}$  varying from 0.33 to 1 and by using default nominal values for other PK and CLCR characteristics (see Table I).

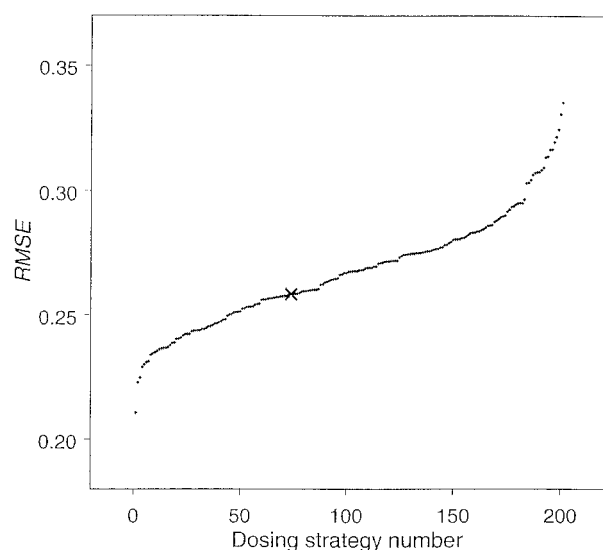
common. A survey of the labeling of drugs mainly excreted unchanged via the kidneys, which was performed for drugs (oral and intravenous administration) marketed in Sweden in 1999,<sup>23</sup> supports this statement. In total, 53 dosage regimens individualized by CLCR were possible to evaluate. Dosing categories numbering 2, 3, 4, 5, and more than 5 were used in 23%, 45%,

13%, 13%, and 6% of the regimens, respectively. In 10 of 12 strategies with 2 dose levels, the chosen DR was 2. For regimens with 3 dosing categories, lower dose increments were used, in particular, for the DR between the medium and lower dose, in which 10 of 24 ratios equaled 2 and 11 of the remainder had a lower ratio. However, for the ratio between the higher and medium

**Table V.** Estimated optimal maintenance infusion rates for NXY-059

No. of dosing categories	Infusion rate ( $\mu\text{mol/h}$ )				Cutoff (mL/min)			Overall variability (%CV)	% of population expected to be	
	First	Second	Third	Fourth	First	Second	Third		>50 $\mu\text{mol/L}$	>100 $\mu\text{mol/L}$
1	472	—	—	—	—	—	—	0.444	76.3	22.2
2	348	676	—	—	65	—	—	0.296	88.6	9.1
3	299	478	776	—	50	80	—	0.258	92.9	6.2
4	279	404	585	836	45	65	90	0.236	93.0	5.0

Infusion rates and cutoffs are numbered in order of increasing renal function. Dash, Not estimated.



**Fig 6.** Root mean square error (RMSE) for each dosing strategy applied to new population, sorted by RMSE. X, RMSE for the optimal DS without uncertainty taken into account.

dose, the DR was 2 in 20 of 24 cases. For regimens with 2 dosing categories, the CO ranged from 10 to 60 mL/min, with a median of 30 mL/min. Median values for the 2 COs used in the 3-dose strategies were 20 and 50 mL/min, respectively. This individualization is probably not based on the CLCR distribution in the target population. This was substantiated indirectly by a literature review of CLCR distributions in population PK-PD studies. The survey included CLCR distributions ( $n = 26$ ) from patients included in formal clinical studies or routinely visiting the clinic. The mean or median CLCR was not equal to or less than 30 mL/min in any of the studies, and it was less than or equal to 50 mL/min in only 3 cases. Altogether, these findings imply that recommended dosing strategies are nonoptimal in the sense we propose.

However, there may be reasons for fixing dose ratios or cutoff values in the dosing strategy. With respect to the DR, a ratio of 2 is perceived to be easier to communicate and has been used by tradition. In principle, with a DR of 2, a single tablet size could be marketed. However, this is seldom the case in practice. In addition, there may be a concern that using dose sizes that are nonmultiples (eg, 29 and 73 mg) could possibly give the impression that the drug has a narrow therapeutic index, which does not necessarily have to be the case. By using a low CO, one dose can be documented for the major part of the population. Subsequent studies may be performed to extend the treatment to the remainder of the population. The commonly used COs are also related to the clinical definitions of severe and moderate renal impairment. Although all of these reasons may be legitimate, the introduction of the constraints is not without cost, and not paying attention to the choice of dosing strategy may lead to a worse therapy than necessary, as implied by the simulation study that used different constraints. For example, for a drug with an  $fe_{\text{pop}}$  value of 0.65, the constrained dosing strategy (DR of 2 and CO of 50 mL/min) resulted in no decrease in the overall variability. It is recognized that several aspects of a dosing strategy may be restricted for practical reasons. Although a truly optimal dosing strategy may not be feasible, it is worthwhile to assess the cost each constraint results in, described as the decrease in benefit from treatment. This is achieved by comparison of the outcome after the desired (more constrained) and the estimated optimal (less constrained) strategy. The performance of the different dosing strategies is then evaluated in relation to any acceptable overall target definition, possibly leading to reassessment of the predefined constraints.

In conclusion, optimization of a priori dosing strategies for individualization has been illustrated with one common situation, but the method is applicable for other situations in which a desired target is related to a covari-

ate, which therefore would be used as a basis for dosing (eg, CL related to body weight or  $E_{max}$  related to age). The simulation study revealed the information that is crucial in the establishment of dosing individualization based on renal function, mainly  $fe_{pop}$  and CLCR, which will have implications on study design and collection of data. A dosing strategy evolves during drug development, and to obtain an adequate a priori dosing strategy, this method should be introduced as early as possible in the development (ie, before late confirming studies [phase 3 studies]), as illustrated by the real drug example. In addition, a review of commonly used CLCR-based dosing strategies showed that they are not optimal under the constraint of the number of dose sizes used.

We thank AstraZeneca Research and Development, Södertälje, Sweden, for providing us with the real drug example.

The following investigators involved in the NXY-059 study in stroke patients are gratefully acknowledged:

Sweden: N. G. Wahlgren, Karolinska Hospital, Stockholm; V. Kostulas, Huddinge; H.-G. Hårdemark, and A. Terent, Uppsala; S. Bornhov, Helsingborg; P. Palmqvist, Kalmar; and T. Olsson, Östersund.

United Kingdom: K. R. Lees, Western Infirmary, Glasgow; A. Sharma, Liverpool; D. Grosset, Southern General Hospital, Glasgow; D. Barer, Gateshead; G. A. Ford, Newcastle; L. Kalra, King's College, London; P. Tyrrell, Hope Hospital, Manchester; T. G. Robinson, Leicester; and J. Barrett, Wirral.

AstraZeneca is developing NXY-059 under a license agreement with Centaur Pharmaceuticals, Inc (Santa Clara, Calif).

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