Usefulness of Bnet, a Simple Linear Metric in Discerning Torsades De Pointes Risks in 28 CiPA Drugs

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The Comprehensive in vitro Proarrhythmia Assay (CiPA) project suggested the torsade metric score (TMS) which requires substantial computing resources as a useful biomarker to predict proarrhythmic risk from human ether-à-go-go–related gene (hERG) and a few other ion channel block data. The TMS was useful to predict low TdP risks of drugs blocking Na⁺ (ranolazine) and Ca²⁺ (verapamil) channels as well as the hERG channel. However, Mistry asserted that the simple linear metric, Bnet reflecting net blockade of a few influential ion channels has similar predictive power. Here we compared the predictability of Bnet and TMS for the 12 training and 16 validation CiPA drugs which were pre-classified into three categories according to the known TdP risks (low, intermediate, and high risk) by CiPA. Bnet at 5×Cmax (Bnet_5xCmax) was calculated using the ion-channel IC50 and Hill coefficients of CiPA drugs collected from previous reports by the CiPA team and others. The receiver operating characteristic curve area under curve (ROC AUC) values for TMS and Bnet_5xCmax as performance metrics in discerning low versus intermediate/high risk categories for the 28 CiPA drugs were similar. However, Bnet_5xCmax was much inferior to TMS at discerning between intermediate- and high-risk drugs. Dynamic Bnet, which used in silico hERG dynamic parameters unlike conventional Bnet, improved the misspecification. Thus, we propose that Bnet_5xCmax is used for quick screening of TdP risks of drug candidates and if the “intermediate/high” risk is predicted by Bnet_5xCmax, in silico approaches, such as dynamic Bnet or TMS, may be further considered.

Keywords: proarrhythmic risk, biomarker, torsade metric score, Bnet, ion channel, CiPA, ICH

INTRODUCTION

The International Council on Harmonization (ICH) established the guidelines, S7B for non-clinical evaluation and E14 for clinical evaluation of the proarrhythmic risk of drugs. As recommended by the guidelines, the conventional practice to evaluate the Torsades de Pointes (TdP) risks has been focused on the QTc interval from blockade of human ether-à-go-go–related gene (hERG) channel (Shah, 2005) that is associated with rapidly activating delayed rectifier potassium current Ikur. (Sager et al., 2014) Although ICH S7B and E14 regulatory guidelines have been successful in screening TdP risks of new drugs, there are several low TdP risk drugs with the prolonged action potential duration.
(APD) and QTc interval. Thus, the current practice according to ICH guidelines is sensitive but not specific enough to evaluate proarrhythmic (TdP) risks.

One of the major objectives of the Comprehensive in vitro Proarrhythmia Assay (CIPA) initiative was to improve the current ICH guidelines to avoid the misclassification of TdP risks by evaluating mechanistically based in vitro assays and in silico reconstruction of the cardiac action potential. The CIPA ion channel working group and in silico modeling group suggested qNet and the torsade metric score (TMS) as conclusive markers via the CiPAOrv1.0, the mechanistic in silico model (Li et al., 2019b) based on a series of modification of O’Hara-Rudy (ORd) human ventricular myocyte model (O’hara et al., 2011).

However, a few groups have raised questions on the superiority in accuracies of model-driven in silico approaches. (Mistry et al., 2015; Mistry, 2017; Parikh et al., 2017; Mistry, 2018; Parikh et al., 2019; Mistry, 2019a) Especially, Mistry asserted that Bnet, a simple linear metric using the net difference between inward and outward ion channel blocking, has predictive power similar to that of TMS. (Mistry, 2019a) Mistry questioned the usefulness of the complicated in silico approaches proposed by CIPA if the performance to assess the proarrhythmic risk is similar, although the CIPA researchers asserted the superiority of in silico approaches that consider the trapping of the hERG and other channels through rigorous validation of the model (Li et al., 2019b).

In this report, we compared the performance of Bnet and TMS in discerning TdP risks of the whole 28 CIPA drugs (12 training and 16 validation) to gain insight into potentials and limitations of in silico approaches by CIPA.

### METHODS

#### Channel Block Data to Calculate Bnet

The CIPA have chosen 12 training and 16 validation drugs which have been classified by a team of clinical cardiologists and electrophysiologists into three categories according to the known TdP risks (high, intermediate, and low risk) (Colatsky et al., 2016).

To compare the relationship between TMS and Bnet of the 28 drugs, we first collected the ion channel block data (IC50 and Hill coefficients by the drugs) that were used to estimate the TMS (Li et al., 2019b). They were used to calculate Bnet values. Because the CIPA aimed to automate the assays by using high-throughput patch-clamp systems (HTS) (Sager et al., 2014), hybrid patch-clamp data collected using both manual (for hERG channel) and automated (other channels) methods were compared with data from the manual method for all channels. The performance of the hybrid and manual methods seemed equivalent (Li et al., 2019b). However, we picked the TMS values obtained from the manual method that has long been used as a standard in patch clamp studies.

In the many ion channels, only the four channels that were finally chosen by CIPA as significantly influencing the qNet and TMS: rapidly activating delayed rectifier potassium current (I\textsubscript{Kr}), late sodium current (INaL), L-type calcium current (ICaL), and peak sodium current (INa) (Li et al., 2019b). Thus, for the calculation of Bnet, we used the IC50 and Hill coefficients for the four channels identical to those used to estimate qNet and TMS by CIPA. Those for the 12 training drugs were retrieved from the report by Crumb et al. (2016) that was utilized by Li et al. (2019). In the case of the 16 validation drugs, the CIPA researchers did not use published data but have performed patch-clamp studies on their own. (Li et al., 2019b) Thus, we retrieved the IC50 and Hill coefficients for INaL, ICaL, and INa channels from the report by Li et al. However, the CIPA researchers did not use simple channel block, but employed a channel-trapping model in the case of the hERG channel and the IC50 or Hill coefficients for hERG channel for the 16 validation drugs were not mentioned in their report at all. (Li et al., 2019b). Thus, we had to search other published data (Table 1) to replace those for I\textsubscript{Kr} (hERG) of the 16 validation drugs.

### Table 1

| Compound       | IC50 (µM) | Hill coefficient | Model | Literature | Temperature (°C) | Technique     |
|----------------|----------|------------------|-------|------------|-----------------|--------------|
| Ibutilide      | 2        | t\textsubscript{1} | XO    | (Lin et al., 2008) | 21.5           | Voltage-clamp 2-electrode |
| Azimilide      | 0.61     | 1                | CHO   | (Walker et al., 2000) | 22             | Whole-cell PC |
| Disopyramide   | 7.23     | 0.89             | CHO   | (Paul et al., 2001) | 36             | Whole-cell PC |
| Domperidone    | 0.057    | 0.99             | HEK   | (Olaszewski and Zünkler, 2005) | 21            | Whole-cell PC |
| Droperidol     | 0.0322   | 1.39             | HEK   | (Drozdz et al., 1999) | 22.5          | Whole-cell PC |
| Pimozide       | 0.001    | 1.1              | HEK   | (Kirsch et al., 2004) | 35            | Whole-cell PC |
| Astemizole     | 0.0013   | 0.95             | HEK   | (Tarantino et al., 2006) | 35            | Whole-cell PC |
| Clozapine      | 2.5      | 0.82             | HEK   | (Lee et al., 2006) | 35             | Whole-cell PC |
| Clarithromycin | 750      | 1.7              | CHO   | (Abbott et al., 1999) | Whole-cell PC |
| Risperidone    | 0.167    | 1                | CHO   | (Kongsamut et al., 2002) | 23            | Whole-cell PC |
| Metoprolol     | 145      | 1.1              | HEK   | (Kawakami et al., 2006) | 23            | Whole-cell PC |
| Tamoxifen      | 1.2      | 1.4              | HEK   | (Chae et al., 2015) | 23             | Whole-cell PC |
| Nifedipine     | >50      | 1                | HEK   | (Zhang et al., 1999) | 23             | Whole-cell PC |
| Nitrendipine   | 10       |                  | HEK   | (Fledern et al., 2003) | Whole-cell PC |
| Loratadine     | 173      | 0.76             | HEK   | (Crumb, 2000) | 36 ± 1         | Whole-cell PC |
| Vandetanib     | 1.15     | 0.76             | HEK   | (Lee et al., 2018) | 37 ± 0.5       | Whole-cell PC |

CHO, Chinese hamster ovary cells; HEK, human embryonic kidney (HEK293) cells; Whole-cell PC, Whole-cell voltage-clamp recordings.
Calculation of Percentage Block and \( \text{Bnet}_{5\times C_{\text{max}}} \)

The percentage block (\%block) against a repolarization or depolarization ion-channel inputted into the \( \text{Bnet}_{5\times C_{\text{max}}} \) model was calculated using the mean maximal concentration observed (\( C_{\text{max}} \)) corrected for plasma protein binding (thus, unbound concentration) (Mistry, 2018).

\[
\text{%block} = \frac{100 \times (5 \times C_{\text{max}})^{H_{\text{II}}} + IC_{50}^{H_{\text{II}}}}{(5 \times C_{\text{max}})^{H_{\text{II}}}}
\]

\( \text{Bnet}_{5\times C_{\text{max}}} \) was defined as the net difference in \%block of the four most influential channels on the AP shape (\%block of hERG channel - sum of \%blocks of the other channels) at \( 5 \times C_{\text{max}} \) (Supplementary Table 1).

\[
\text{Bnet}_{5\times C_{\text{max}}} = \frac{1}{n} \sum_{i=0}^{n} R_i - \sum_{j=0}^{m} D_j
\]

where \( R_i \) and \( D_j \) represent the \%block against repolarization (\( I_{\text{Kr}} \)) and depolarization (\( I_{\text{NaL}}, I_{\text{CaL}}, \) and \( I_{\text{Na}} \)) ion-channels, respectively for a specific drug.

There are three major differences between the original Bnet (Mistry, 2018) and \( \text{Bnet}_{5\times C_{\text{max}}} \). First, compared to the original Bnet proposed by Mistry, \%block in our study (\( \text{Bnet}_{5\times C_{\text{max}}} \)) took Hill coefficient into consideration. Second, the original Bnet proposed by Mistry did not include \( I_{\text{Na}} \), we included it because the four channels have been selected to calculate TMS by CiPA researchers. Third, the original Bnet used values at \( 1 \times C_{\text{max}} \) but \( \text{Bnet}_{5\times C_{\text{max}}} \) used values at \( 5 \times C_{\text{max}} \).

Calculation of Dynamic Bnet

We compared TMS and \( \text{Bnet}_{5\times C_{\text{max}}} \) with “dynamic Bnet” (Mistry, 2019a), which reflects hERG dynamics as TMS used. We utilized the publicly available data set that Mistry provided (Mistry, 2019b) and in the data set, hERG dynamics was included into Bnet by replacing the static hERG block with the dynamic hERG blocking using IC50 and maximal inhibition at the \( 1 \times C_{\text{max}} \).

Torsade Metric Score

The TMS, mean of \( q_{\text{Net}} \) values at \( 1 \times, 2 \times, 3 \times, \) or \( 4 \times C_{\text{max}} \) derived from the CiPAORdv1.0 model was digitized from a report by Li et al. (2019b). As mentioned in the previous section, only the TMS values from manually measured data were collected for comparison.

Ranking Performance Measures

Statistical analysis was performed using R Statistical Software version 3.6.0 (R Core Team, 2019). The ROC AUC (receiver operating characteristic curve area under the curve) (Zou et al., 2007) for TMS and \( \text{Bnet}_{5\times C_{\text{max}}} \) was calculated based on the known risk classifier. A logistic regression analysis using maximum likelihood estimation of the metric and the torsadogenic risk categories was performed by the rms R package (Harrell, 2019).

RESULTS

Risk Misspecification by TMS and \( \text{Bnet}_{5\times C_{\text{max}}} \) in the Validation Drug Data Set

The TMS and \( \text{Bnet}_{5\times C_{\text{max}}} \) of all 12 training drugs tested with Crumb’s data (Crumb et al., 2016) were accordant to the risk categories (low vs. intermediate/high) (Figure 1). In the case of the 16 validation drugs, there were a few mismatches in categories both in the TMS (Figure 1A) and \( \text{Bnet}_{5\times C_{\text{max}}} \) methods (Figure 1B): tamoxifen and metoprolol (low-risk drugs) were located in the intermediate-risk cluster in the TMS and clarithromycin, domperidone, and risperidone (intermediate-risk drugs) were located in the low-risk cluster in the \( \text{Bnet}_{5\times C_{\text{max}}} \). Dynamic Bnet using hERG dynamics decreased

![FIGURE 1](image-url)
the misspecification but a drug of the validation data set, risperidone, still was misclassified (Figure 1C).

**Strong Correlation Between TMS and Bnet$_{5\times C_{max}}$ in the Training Drug Data Set**

Bnet$_{5\times C_{max}}$ has shown performance similar to that of TMS as they are correlated with each other ($r^2 = 0.663$) (Figure 2). The correlation between Bnet$_{5\times C_{max}}$ and TMS was stronger in the training drugs ($r^2 = 0.867$) than in the validation drugs ($r^2 = 0.597$), suggesting that the training drugs may possess better *in vitro* (patch-clamp study) data quality.

**Performance Comparison: TMS and Bnet$_{5\times C_{max}}$**

Both TMS and Bnet$_{5\times C_{max}}$ seemed to discriminate low proarrhythmic risk drugs from intermediate/high-risk drugs quite well because the TMS and Bnet$_{5\times C_{max}}$ values of low-risk drugs were significantly different ($t$-test, $p < 0.005$, and $p < 0.001$, respectively) from those of intermediate- and high-risk drugs (Supplementary Figure 1). The ranking performance measure for TMS and Bnet$_{5\times C_{max}}$ was evaluated using ROC AUC (low vs. intermediate/high risk), and the values were 0.956 and 0.959, respectively (Table 2, Supplementary Figure 2).

The ROC AUC (Low/Intermediate Vs. High Risk) and $\chi^2$ Statistic Derived From Univariable Logistic Regression Analysis of TMS Were Higher Than Those of Bnet$_{5\times C_{max}}$, Suggesting That TMS Outperforms Bnet$_{5\times C_{max}}$ in Discriminating Intermediate- and High-Risk Drugs (Table 2).

**DISCUSSION**

This is the first study to examine the performance of Bnet$_{5\times C_{max}}$, a simple metric calculated as the gap in blocking four representative ion channels by 28 CiPA drugs. We showed that Bnet$_{5\times C_{max}}$ provided predictability comparable to the large-scale mechanistic model.

The therapeutic $C_{max}$ value directly affects the TMS and the Bnet metric. The TMS is calculated by averaging qNet values at $1\times$, $2\times$, $3\times$, or $4\times C_{max}$ and Bnet$_{5\times C_{max}}$ is calculated based on %block at $5\times C_{max}$. We have first screened Bnet for $1\times$, $5\times$, and $10\times C_{max}$ and the Bnet$_{5\times C_{max}}$ showing the best performance was further used in our study (Supplementary Table 2).

Although the TMS and Bnet$_{5\times C_{max}}$ of all 12 training drugs tested with Crumb’s data (Crumb et al., 2016) were in the exact order, the data based on the 16 validation drugs showed a few incorrect predictions both in TMS and Bnet$_{5\times C_{max}}$. This misprediction seems to have been caused by the patch-clamp experiments on the validation drugs not as qualified as in the 12 training drugs.

The reliability of patch-clamp experiment data is known to be highly variable by laboratories and skillfulness of the experimenter. Thus, measurement of IC50 and Hill coefficients using the patch-clamp method performed by well-trained personnel appears critical for the appropriate assessment of both TMS and Bnet, regardless of using the silico method. The CIPAs attempt to estimate TMS with combined *in vitro* and *in silico* approaches is worthwhile in that the variability in multiple channel blocking is rigorously validated. Nonetheless, the performance of TMS is also dependent on the quality of patch-clamp experiment data for the ion channels that are input into the *in silico* simulation step.

The major limitation of Bnet is the inability to discriminate drugs with atypical binding kinetics (Li et al., 2019a). Because the hERG trapping observed in some drugs is not measured by the conventional ion channel blocking assay, CIPA has used the

| Performance metric | TMS | Bnet$_{5\times C_{max}}$ | Dynamic Bnet |
|--------------------|-----|-------------------------|--------------|
| ROC AUC (low vs. intermediate/high risk) | 0.956 | 0.959 | 0.994 |
| ROC AUC (low/intermediate vs. high risk) | 0.990 | 0.844 | 0.925 |
| $R^2$ | – | 0.662 | 0.878 |
| $\chi^2$ statistic† | 41.73 | 23.70 | 33.55 |

*Coefficient of determination with torsade metric score and Bnet$_{5\times C_{max}}$ or dynamic Bnet.

†Univariable logistic regression analysis to assess the correlation between the metric and the torsadogenic risk categories.

**FIGURE 2** Correlation between Bnet$_{5\times C_{max}}$ and median TMS (torsade metric score, the average of qNet at $1\sim4 \times C_{max}$) of (A) 12 training drugs, (B) 16 validation drugs, and (C) all 28 CiPA drugs. $C_{max}$, peak plasma concentration.
dynamic-hERG binding model for the data obtained using the Milnes protocol (Li et al., 2017). When the conventional IC50 is used to calculate Bnet for drugs that are significantly trapped in the hERG channel (e.g., dofetilide, bepridil, and terfenadine exemplified by Li et al. (2017)), their Bnet would be underestimated. However, the three drugs have shown Bnet values high enough to fall in the “intermediate/high” cluster in our study (Figure 1).

Recently, Mistry calculated “dynamic Bnet” (Mistry, 2019a) using hERG dynamic IC50 which may partly reflect binding kinetics and showed the higher correlation of dynamic Bnet with TMS of the 28 CiPA drugs ($r^2 = 0.86$) than the conventional Bnet at Cmax ($r^2 = 0.66$) presented in Figure 2 in this report. The ROC AUC values of low- versus intermediate/high-risk for TMS, $Bnet_{5\timesCmax}$, and dynamic Bnet were 0.956, 0.959, and 0.994, respectively. Although dynamic Bnet showed the best performance, it also requires the additional $in silico$ approach and the time and resources spent to acquire the metric in the discovery or preclinical stage may still be substantial. The $Bnet_{5\timesCmax}$ can be a straightforward, accessible, and simple screening tool to discern the low-risk drugs.

The highest prediction performance of low/intermediate-risk versus high-risk drugs was observed in the TMS (ROC AUC $= 0.99$, Table 2). However, in the actual early development process, drug candidates with an intermediate risk often cannot survive to the next development step, and we believe that this limitation of poor discerning between intermediate and high risks may not affect go/no-go decision at the early stage in almost of therapeutic areas except for antiarrhythmics.

The $Bnet_{5\timesCmax}$ metric may be used as a simple screening biomarker in drug discovery and early development. We demonstrated that the $Bnet_{5\timesCmax}$ (or Bnet at concentrations regarded high enough when no Cmax data are available) provides initial information whether a candidate is at low proarrhythmic risk or not. For a candidate worthy of further development even with intermediate/high risk according to the $Bnet_{5\timesCmax}$ metric, $in silico$ approaches proposed by CiPA or dynamic Bnet may be helpful.

AUTHOR’S NOTE

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DATA AVAILABILITY STATEMENT

Publicly available datasets were analyzed in this study. This data can be found here: https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1002/cpt.1184 and https://github.com/HiteshBMistry/Re-analysis-of-CiPA/blob/master/dynamic_qnet-versus_dynamic_bnet.csv.

AUTHOR CONTRIBUTIONS

SuH, K-SK, H-AL, and D-SY contributed to the acquisition of data and provided experimental data guidance. SuH, SeH, and D-SY contributed to designing the work and carried out simulations. SuH, SeH, and D-SY contributed to the analysis and interpretation of the data and writing of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2019.01419/full#supplementary-material

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Conflict of Interest: The authors declare that the research was conducted in the
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