CiPA- Regulatory considerations/ Next steps

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Challenges/ Regulatory considerations

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1. “Construct” of the CiPA package
   - What and How different from S7B/ E-14 (?)

2. Cross-Validation - of the package including proposed cutoffs
   - Experience with different data sets..

3. Implementation of methodology..
   - Industry engagement and uptake for routine

4. Labelling & HCP Communication
   - Labelling
   - Enhance understanding

CiPA as a "package"

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- What it does it include and are all components mandatory ?
  - i.e., in silico, myocyte and clinical ECG

Exam Cram Care Package™ Health Nut Care Package™

Need a decision tree

- Where applicable--- Discovery, Screening or further development?
- Sufficiently adaptive for internal as well as regulatory decision making
- Provides some flexibility of approach but largely standardised
- Ideally should avoid repetition of experiments e.g.,

When might CiPA assessment be useful?

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- The biggest opportunity in early phase development lies in identifying risk from compounds that have poor channel selectivity (hERG) but have an important therapeutic potential.
  - hERG positive (narrow safety margin)
  - have effects on other channels – that may or may not be beneficial in all therapeutic contexts.
  - Prolong QTc in in vivo animal studies

- Second- in defining risk of arrhythmia and providing a more comprehensive grading –and managing risk communication to health care professionals.

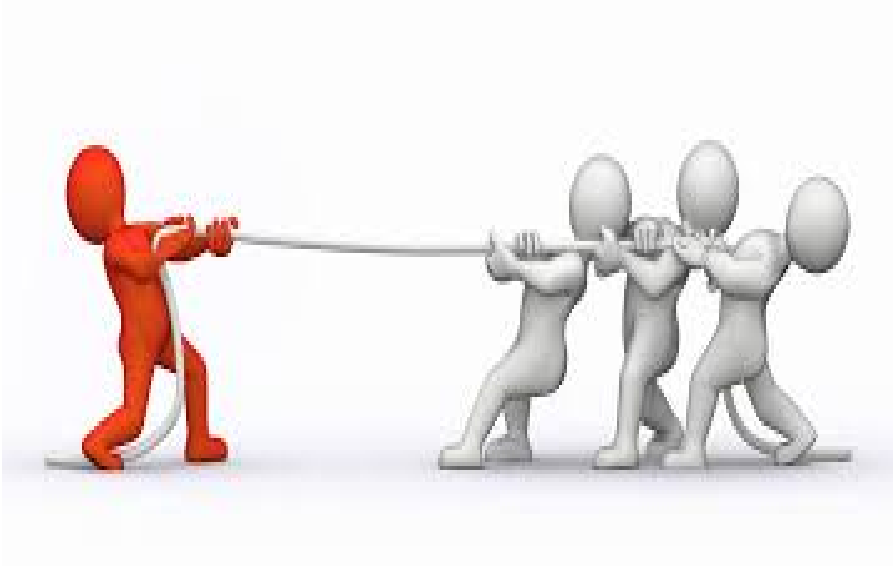
Sponsor uptake

Uptake by sponsors of CiPA and its advantages

Need prospective data to evaluate utility.

SPS survey 2017

- 56 % very familiar with S7B
- ~40% NOT familiar with E-14
- 61% incorporate Ion channel elements of currently
- 31% use stem cell approaches
- 21% (only) use in silico modelling parameters



Need to overcome some of the barriers

Some thoughts on Validation

- Robust testing method that is transferable to external laboratories/ personnel
- Standardise protocols across different laboratories

- Experiments should conform to GLP standards for Regulatory purposes
- **Have we studied enough compounds (variety) to gain comfort and confidence?**

Some validation methods (e.g.,ROC curves) could be very sensitive to errors in gold standard classifications

CiPA: In Silico / ion channel model

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- Opportunity for standardized protocols that can be adopted early in development
- Facilitates comparison of drug properties generating risk metrics and Perhaps aid regulators to compare drug potencies and therefore anticipate effects early
- Better translation of effects to human model.

But;

- The quality of ion channel data is critical.
- **Experience from a wider sponsor group and sets of databases** is needed.
- Need better understanding of effect of risk classification on other and subsequent studies.

CiPA: Myocyte component

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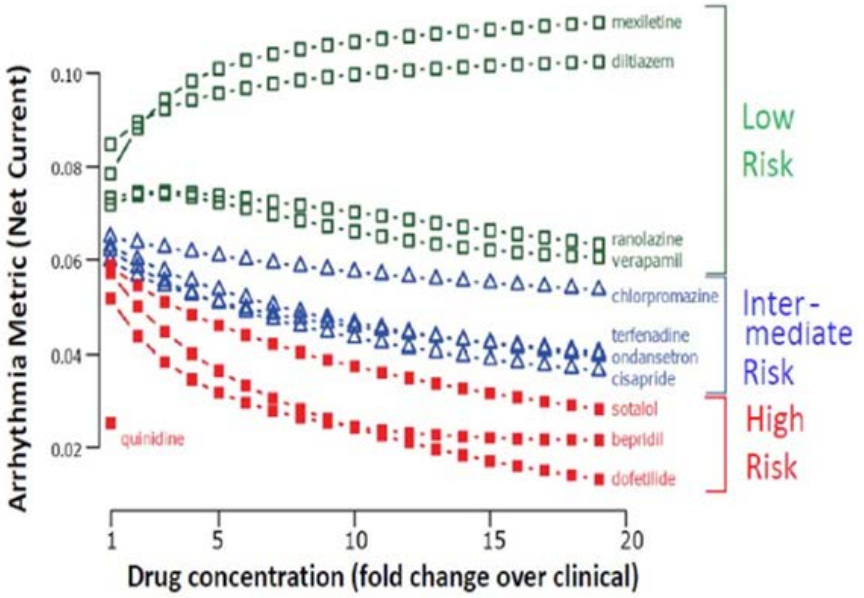
- Offers advantage of routine testing of compounds with a ready supply of established cells using standardized parameters/ methods.
- May obviate need for animal testing, selection of animal model and interspecies differences.
- Higher throughput than animal tissues based approaches.

However;

- Channel expression differences across cell lines,
- May underestimate effect on certain channels (limited reproducibility
- False negative findings that may arise from limited experience of certain technologies.

Difficult areas

- Risk classification- low / intermediate / high risk
  - Cut off values for risk stratification e.g., proximity of Low and intermediate risk (verapamil & chlorpromazine)
  - Discordance and false negatives (e.g., Beperidil in myocyte /IPS-CM assays)
  - Limited predictivity for some channel effects in certain CiPA experiments (e.g.- late Na & hIPSc-CM)
  - Difficulties with classification of Diltiazem
- For prospective evaluations, these do present an issue for sponsors and regulators



Clinical Phase & new BMs-- where to?

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- J-T peak or QTc
  - Reproducibility & interpretation
    We need experience from different data sets to determine feasibility, reproducibility & applicability across wide range of compounds e.g. Dolasetron
  - Where does this fit with CR approaches?

Challenge is to obtain clarity of relative merits of ECG biomarkers **& the advantages**!

Can we develop the other parts of CiPA to limit the need for clinical phase ECGs?

True Challenge of a MIC blocker?

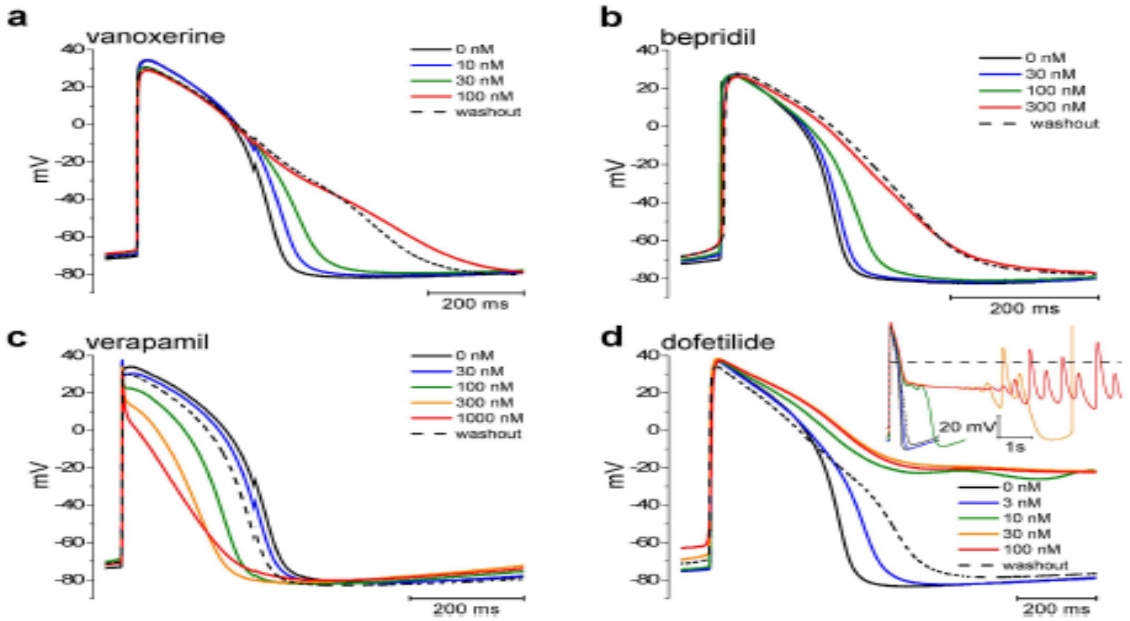


Figure 3. Effect of vanoxerine, bepridil, dofetilide and verapamil on spontaneously beating SC-CMAPs. Spontaneous frequency was ~1 Hz. Note the reduction in action potential amplitude in vanoxerine, bepridil and verapamil and the depolarization of the maximum diastolic potential membrane potential in dofetilide.

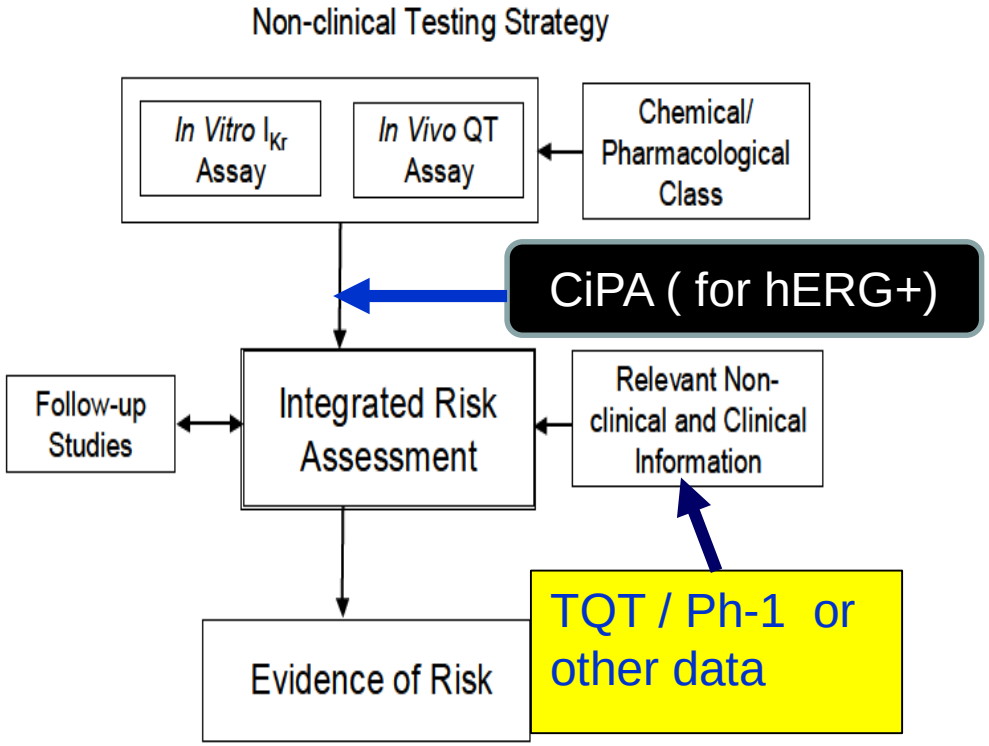
No reported TQT study.

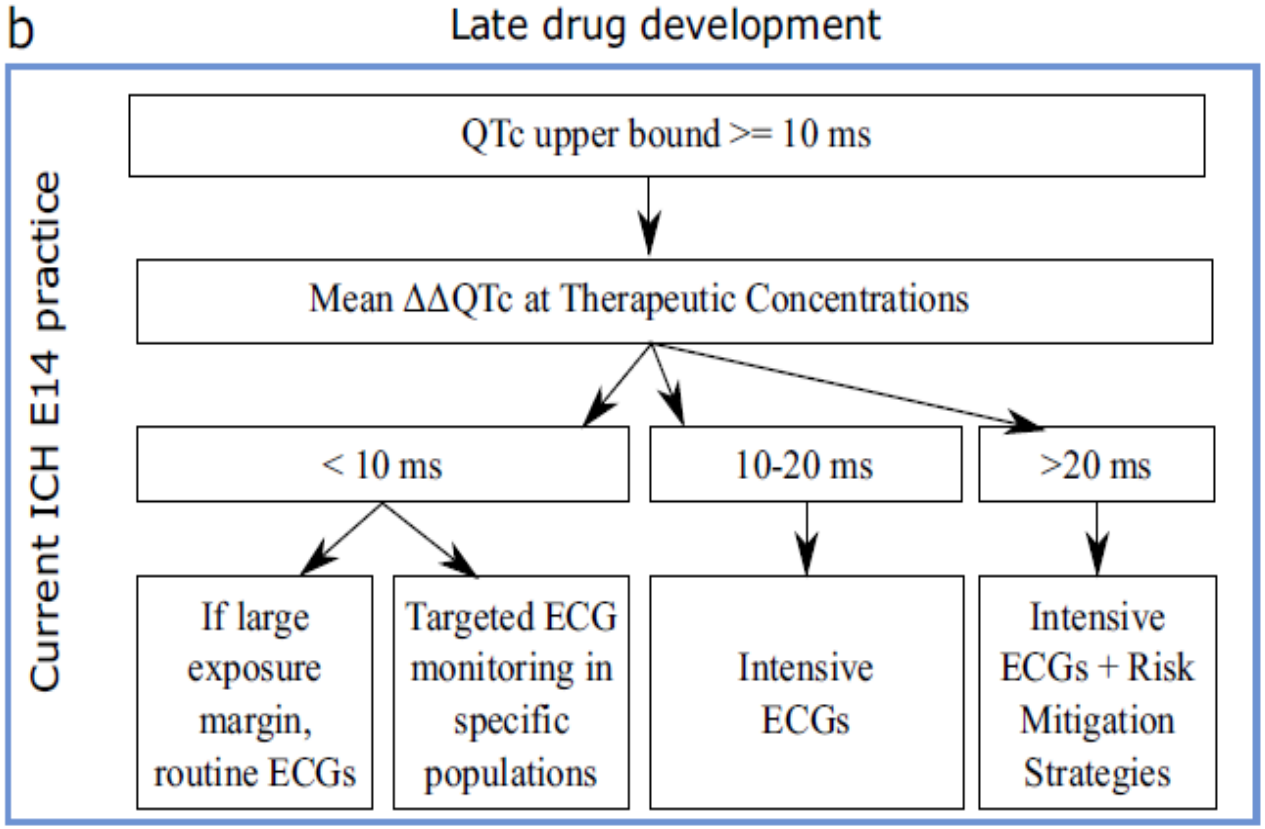
RESTORE`````````````` SR; Heart Rhythm2016;13:1777–1783

CONCLUSION Vanoxerine is an oral, mixed ion channel blocker with I_{Kr}, I_{Na}, and L-type calcium channel activity. While oral therapy with 400 mg of vanoxerine appears effective for the termination of recent onset AF/AFL, its use was associated with a significant risk of ventricular proarrhythmia in patients with SHD.

How does CiPA identify such issues prospectively?

Decision trees





We should look for an integrated decision tree!

Next Steps;

1. Encourage (more) sponsors to share experiences
2. Cross validation (?!)
3. Relative positioning – including advantages
   - Integration with S7B/E14
4. Internal deliberations (Regulatory groups)
5. Presentation of data to ICH Discussion group (started)
6. Discussion at ICH IWG.
   - Update S7B/ E-14 or new multidisciplinary guidance?

Thank you for listening.

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