Preclinical ECG Biomarkers of Cardiac Toxicity: Are They Relevant to Pediatric Safety?

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Pediatric Drug-Induced QT Prolongation: Broad Range of Pathological Consequences

- Multiple clinical case reports of QT prolongation in children

Incidence of QTc > 440 ms
- Cisapride: 12-48%
- Doxapram: 15%
- Ziprasidone: 15%

Isolated case reports
- Sevoflurane
- Droperidol
- Atomoxetine
- Quetiapine

Toxicological trends
- Strong correlation between ΔQTc and age
- 8% incidence of QT dispersion
- Lack of $T_{peak} – T_{end}$ dispersion
- Bradycardia, 2:1 AV block

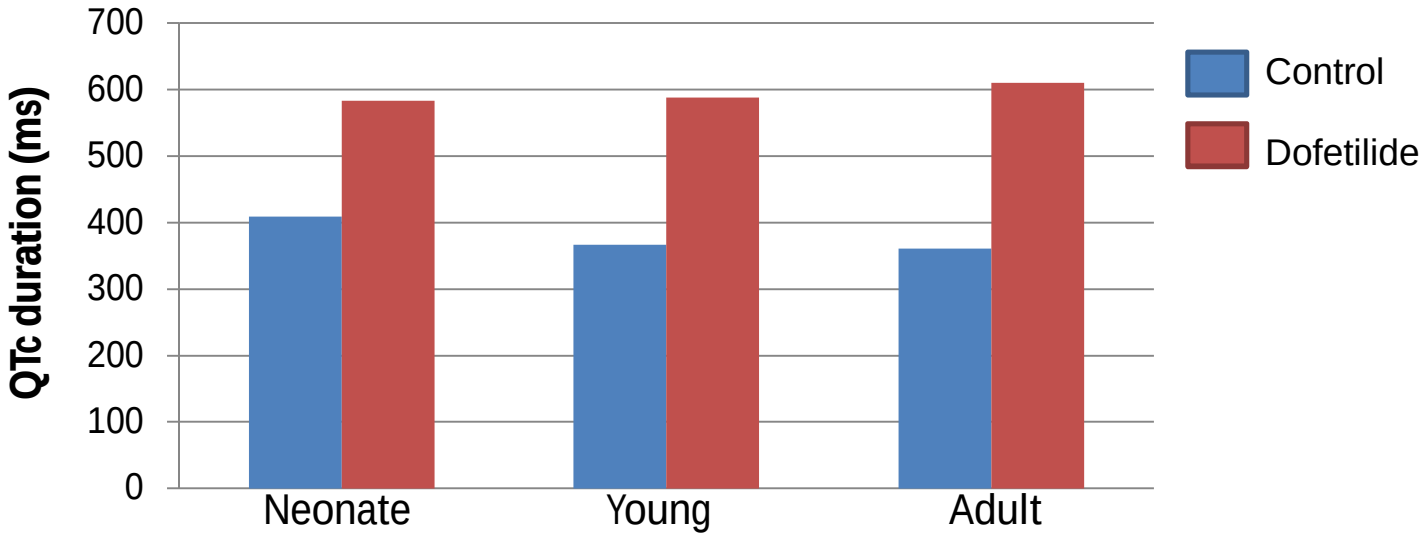
- Very low rate of confirmed TdP (~2 cases reported)

- Multiple factors could drive a low rate of ventricular tachycardia
  - Increased rate of monitoring
  - Medical care could lead to a lower risk of polypharmacy e.g. with CYP450 drugs
  - Medical intervention: dose titration or drug discontinuation

- **Could the development of the heart also play a role in determining risk?**

Consistent QT Effects Seen in Animal Studies; Do the Underlying Mechanisms Vary?

- *In vivo* canine recordings validate clinical findings



- Canine cellular studies highlight the maturation of the heart's electrophysiological profile

Neonate **Adult**

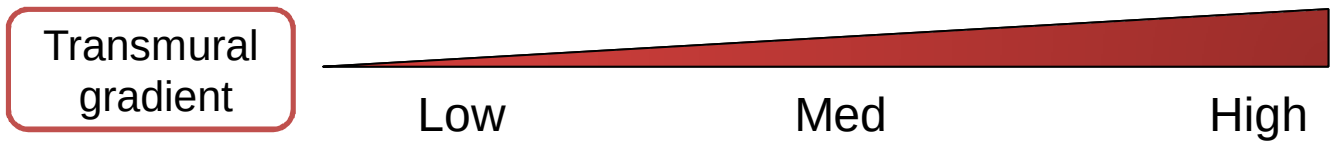
Dof: Dofetilide (I_{Kr})
Azi: Azimilide (I_{Ks})

Adapted from
Obreztchikova M, 2003

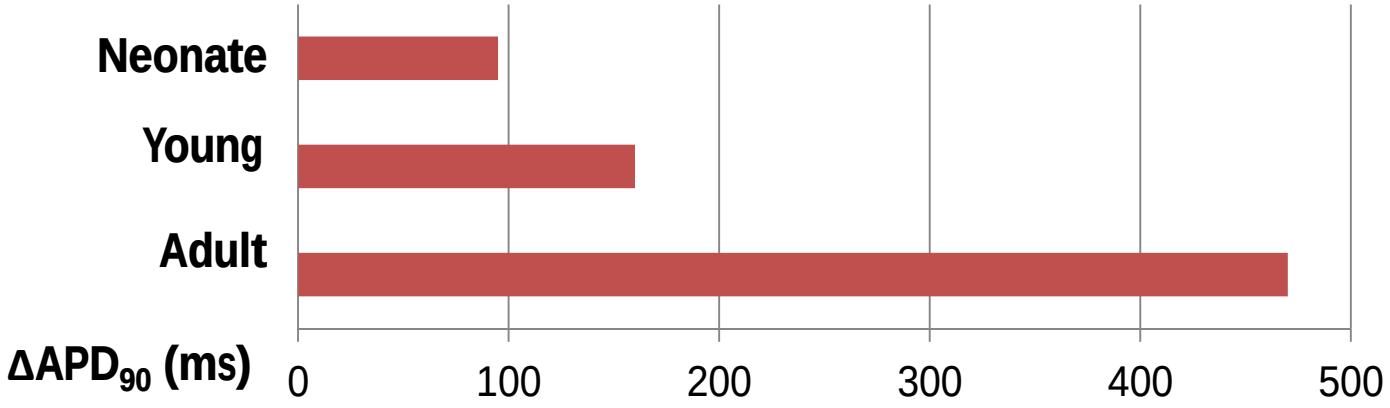
Could the Evolution of Repolarization Gradients Drive a Drug's Torsadogenic Potential?

- Transmural recordings demonstrate that a repolarization gradient develops with age

Neonate **Young** **Adult**



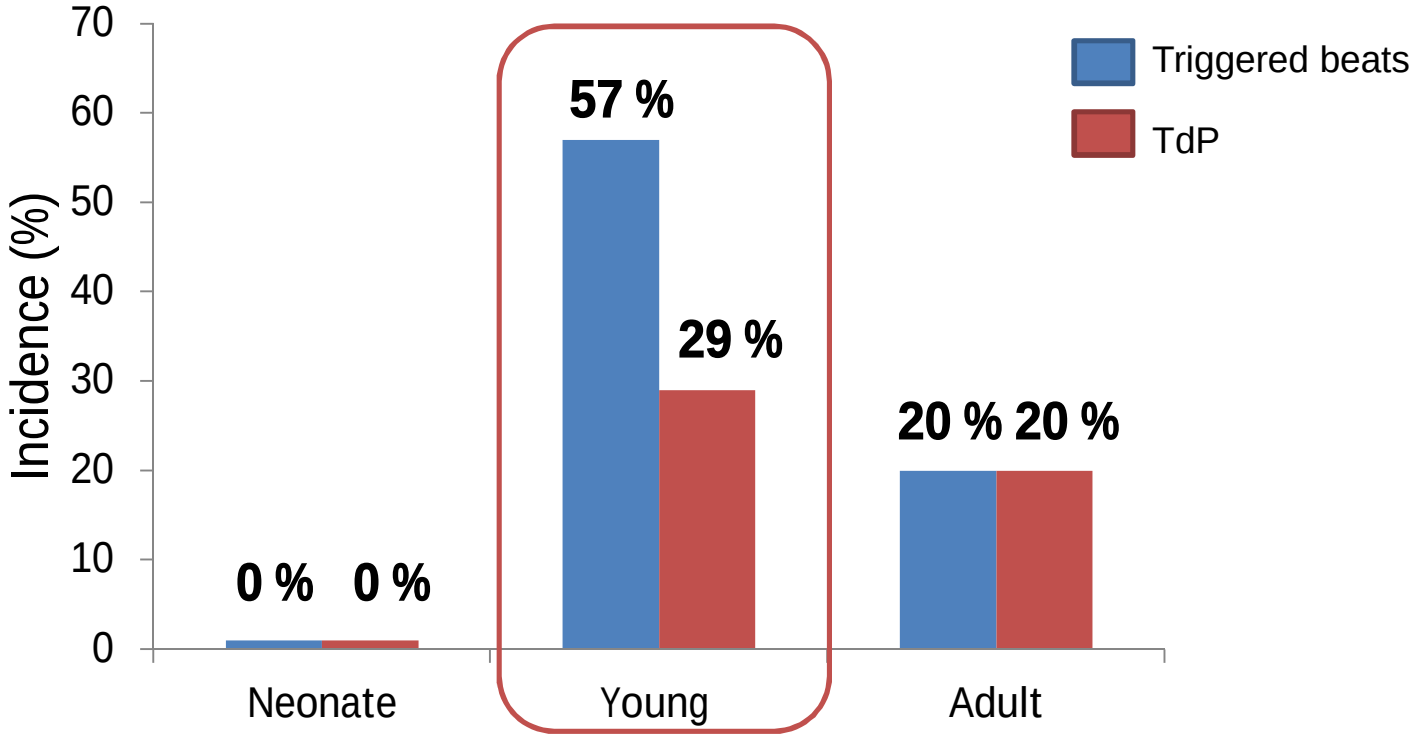
- Dofetilide-induced amplification of TDR is strongly correlated with age



Adapted from Obreztchikova M, 2003

Increased Susceptibility of Young Hearts to Premature Depolarizations Increases Risk of Drug-Induced TdP

- Higher rates of triggered beats in young animals lead to a greater incidence of TdP



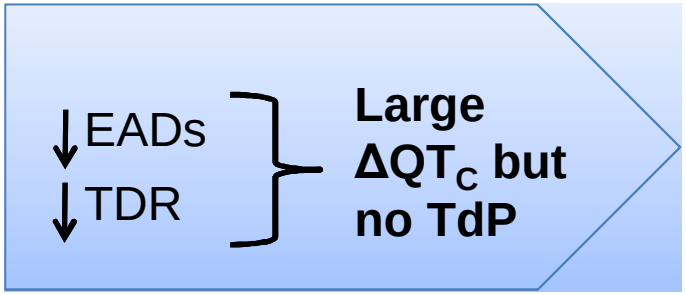
- The maturation of Ca^{2+} handling proteins/regulation of Ca^{2+} channels could confer a higher risk of EADs in young hearts
- Critical developmental overlap of maturing calcium homeostatic processes and a small, but sufficient, TDR could underlie the higher rate of TdP

Adapted from Obreztchikova M, 2003

How do Preclinical Findings Correlate With Clinical Reports?

Preclinical

Neonate



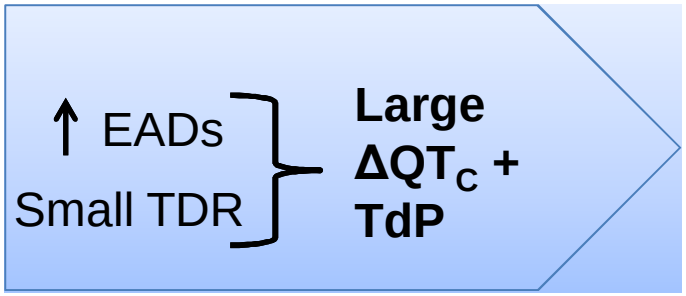
Clinical

- Despite high risk of QT prolongation, drug-induced TdP is very rare
- Multiple reports of bradyarrhythmias
- AV block reported with cisapride, amiodarone, and sotalol

- Neonatal proarrhythmia: potentially strong correlation between preclinical and clinical findings

Preclinical

Young (~90 days)



Clinical

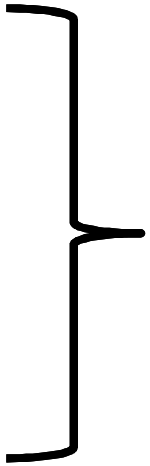
- High risk of QT prolongation
- No reported cases suggesting an increased risk of TdP in this age range

- Discordance between preclinical and clinical findings could point to important species-related differences

Can Zebrafish Serve as a Useful Model for Detecting Pediatric Cardiotoxicity?

- Zebrafish studies reveal potential mechanisms underlying reports of 2:1 AV block
  - QT prolonging drugs significantly reduce heart rate in embryonic fish
  - Breakdance mutants (lacking HERG) recapitulate these findings

Action potentials from isolated hearts



2:1 infranodal AV block despite regular atrial rhythm: prolonged ventricular APD increases refractoriness

Milan D, 2003

What are the Implications of These Findings and Where do we go From Here?

- Findings suggest that arrhythmia risk and phenotype evolves with age

Stage of development	Embryonic	Neonatal	Juvenile	Adult
TDR	–	Low	Med	High
EAD risk	–	Low	High	Low
VT risk	–	Low	Med-High	Low-Med
Arrhythmia	Bradycardia/ asystole	Bradycardia/ AV block	VT/TdP	VT/TdP

Remaining questions

- **Are pediatric patients less susceptible than adults to drug-induced TdP?**
- **What are the consequences of QRS and PR prolongation in pediatric patients?**
- **Can immature hepatic enzymes lead to drug accumulation and further raise the risk of cardiac toxicity?**