

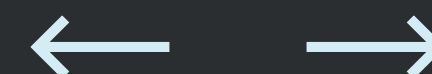


2024

# Ivabradine and the Risks of Torsades: a Case-Based Analysis

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# Research Question and Background

Investigating relationship between Ivabradine and Torsades de Pointes (TdP) via Literature Review and Causality Assessment

Torsades de Pointes: cellular and electrophysiology and its risk factors

- Slower action potential repolarisation -> Torsade des Pointes

Ivabradine: uses, pharmacology, and side effects

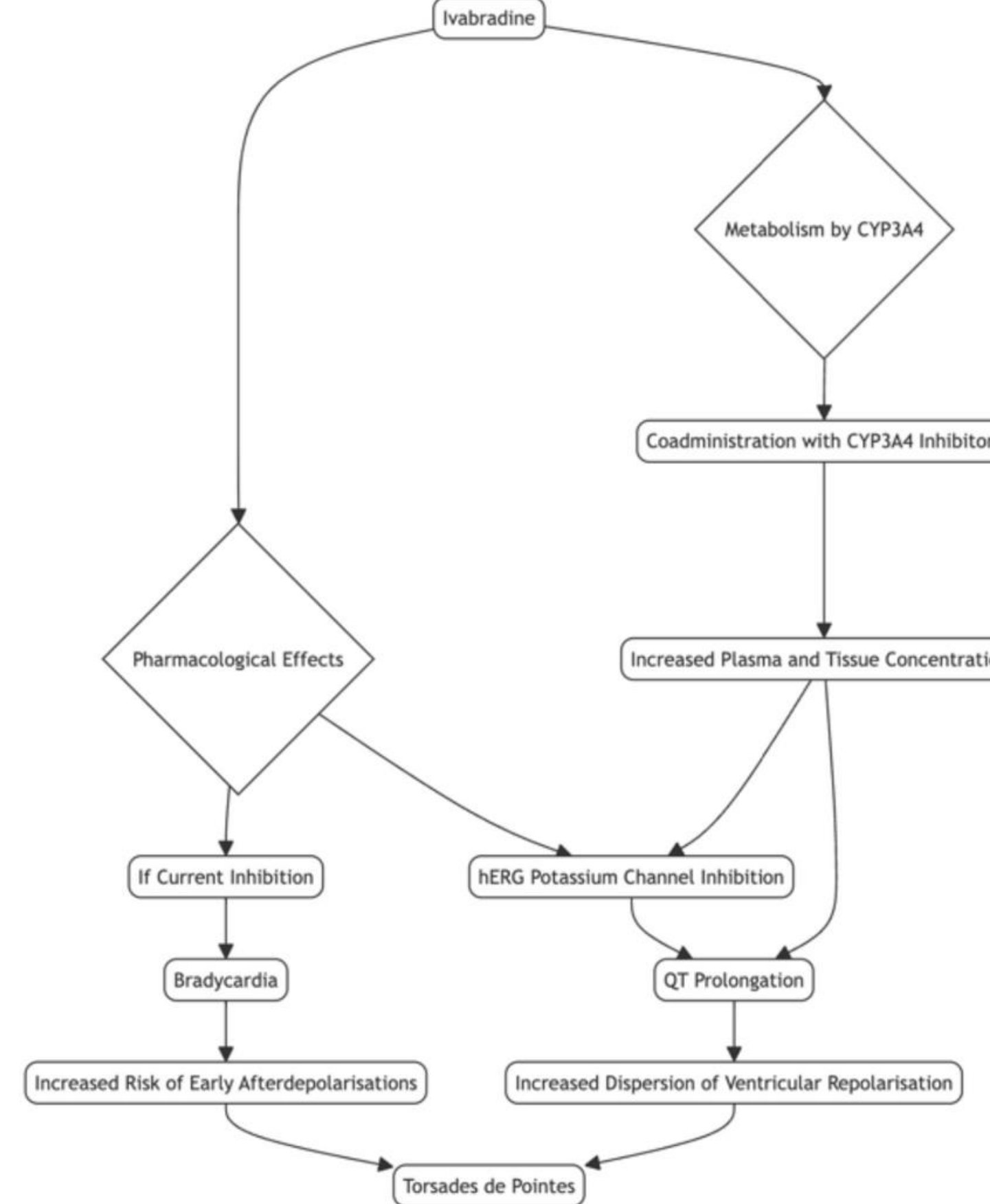


# Ivabradine and the risk of TdP

- Inhibits 'funny' current in the sinoatrial node, slowing heart rate.

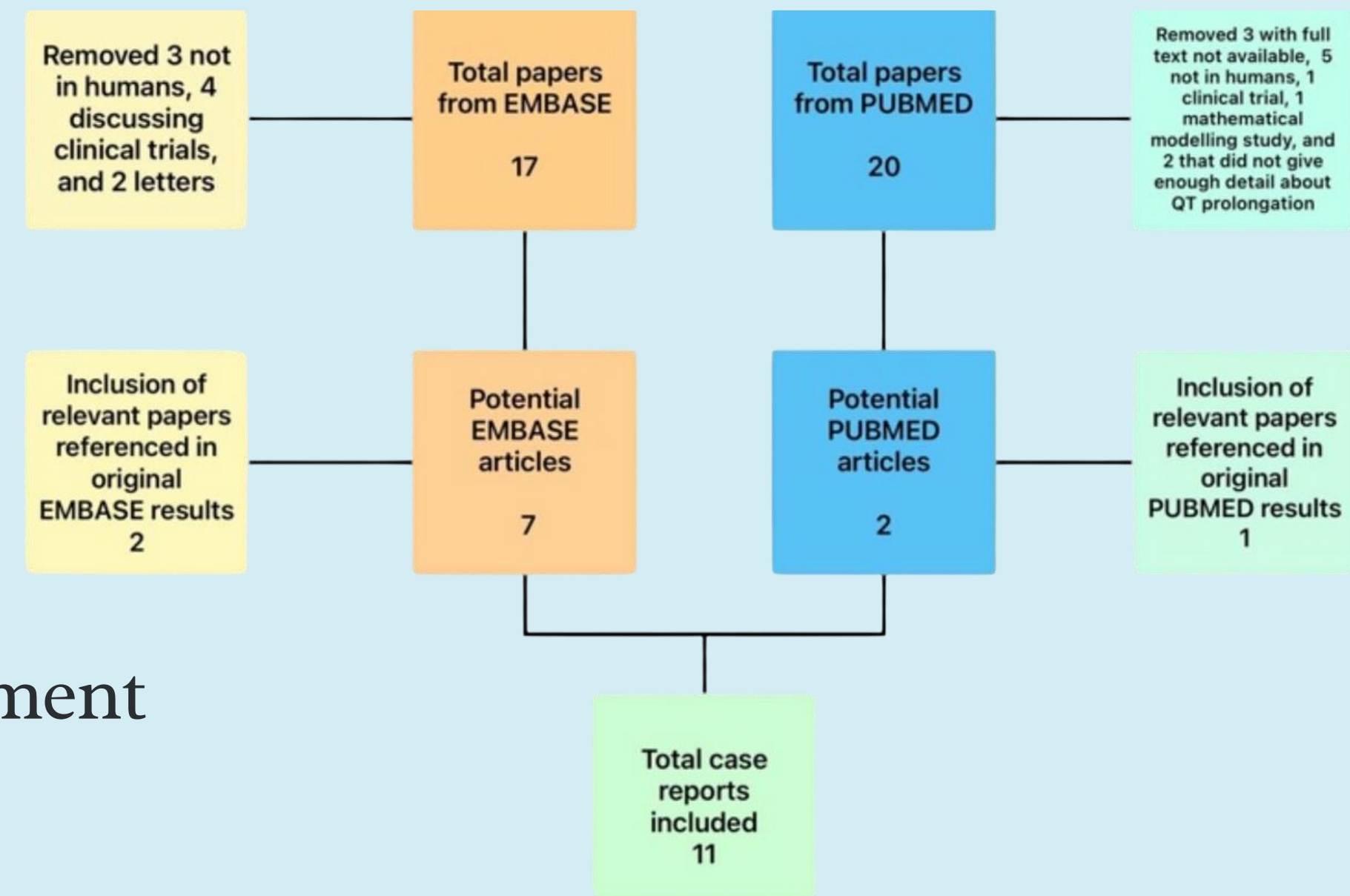
Reasons for choice:

- Bradycardia also increases risk
- HERG off-target effects
- Patient population



## — Literature Evaluation

- PUBMED and EMBASE search using MeSH terms
  - › Human only, full text available, references searched
- Databases, cohort studies, and clinical trials
  - › 3 clinical trials, 1 cohort study, and 2 international databases analysed



## — Data Analysis and Causality Assessment

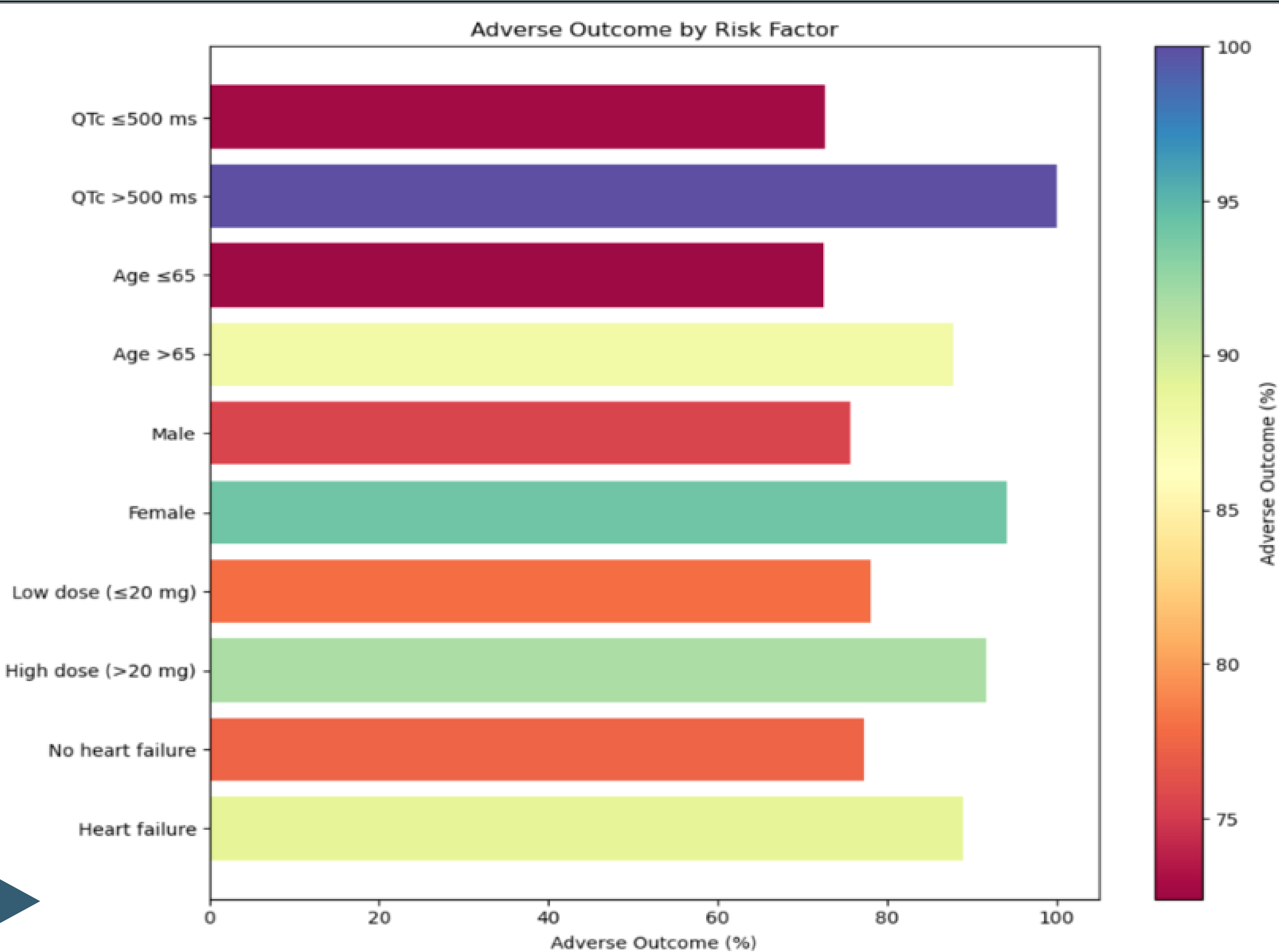
- Naranjo Assessment
- WHO-UMC Scoring
- Tisdale Classification
- Risk factor correlation statistics

# Methods

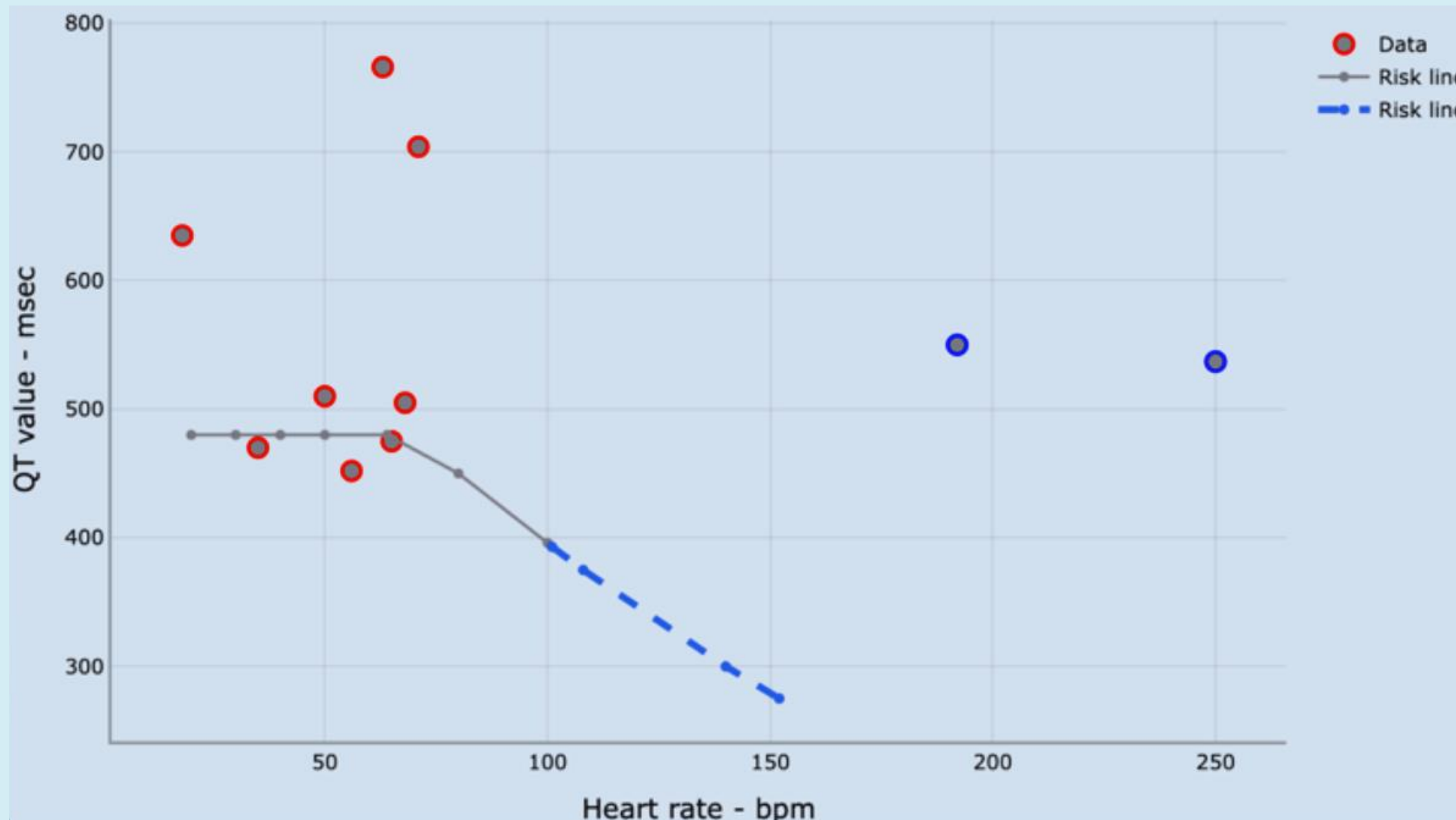


# Results Overview

- 11 case reports, 12 individual patients
- Mean age of the patients was 49.73 years (range: 19-83 years)
- 54.5% were female
- most common indication was heart failure with reduced ejection fraction
- All patients experienced at least one QTc prolongation
- 8 patients (67%) developed TdP, which typically occurred within the first 48 hours of ivabradine initiation or dose adjustment.
- All had ≥1 additional risk factor



# Results from Case Reports



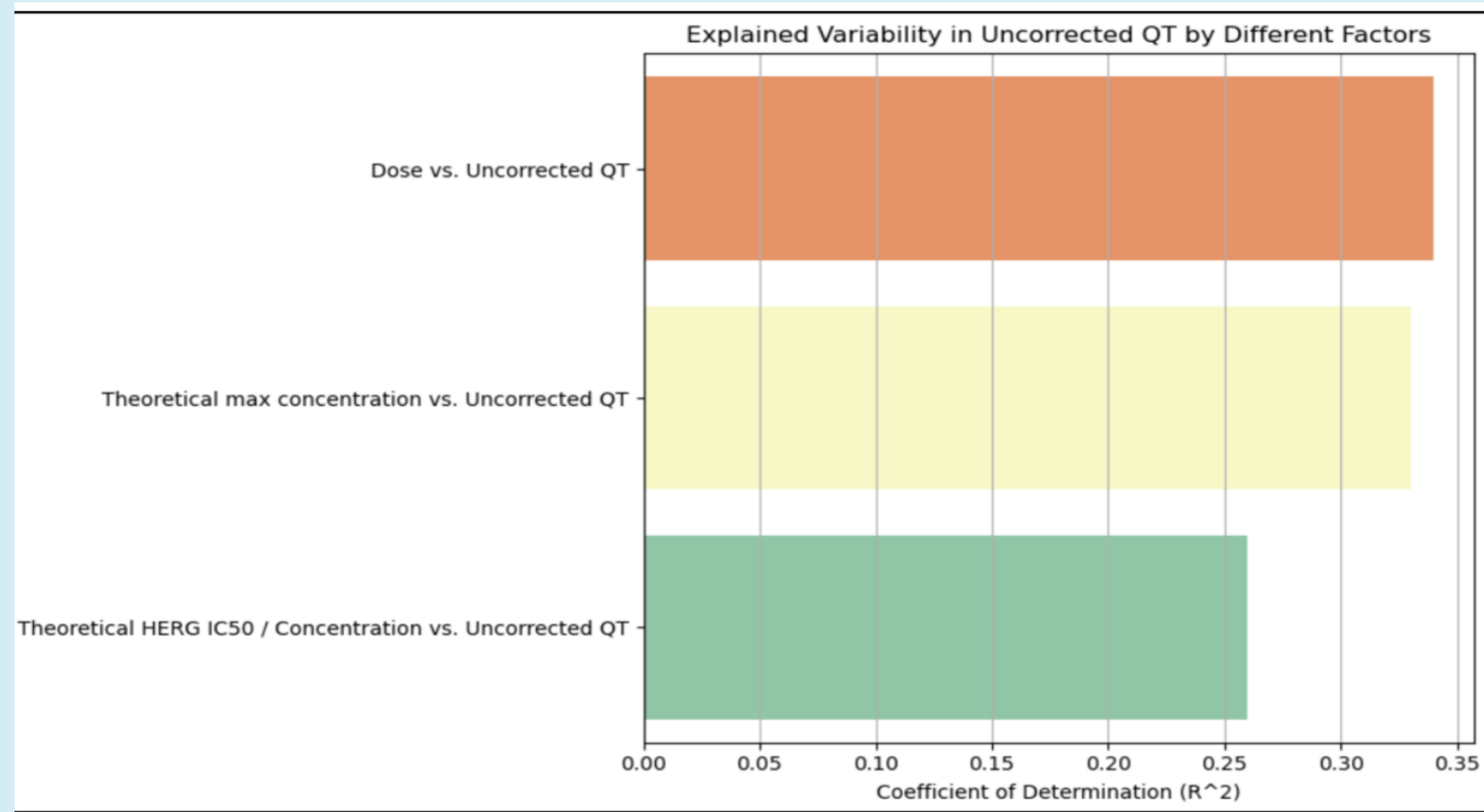
Naranjo	WHO-UMC	Tisdale
7	Probable/Likely	9
2	Probable/Likely	11
5	Probable/Likely	9
5	Probable/Likely	10
5	Probable/Likely	11
6	Probable/Likely	11
3	Possible	12
5	Probable/Likely	11
2	Probable/Likely	10
5	Probable/Likely	12
2	Probable/Likely	10
2	Probable/Likely	10

- QT interval prolongation confirmed using a QT nomogram, Bazett's formula used to estimate uncorrected QT interval when unavailable
- Points above risk line indicate a significant risk of TdP

# Case Reports, continued

Explained variability in uncorrected QT due to risk factors, using Pearson correlation coefficients of determination

Dose and theoretical max concentration had moderate positive correlations with uncorrected QT ( $R^2 = 0.34$  and  $0.33$ ), theoretical HERG IC<sub>50</sub> / concentration had a weaker negative correlation ( $R^2 = 0.26$ ,  $r = -0.51$ )







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# Case Series, Clinical Studies, and the importance of Quality Data

O1 Concomitant use of ivabradine and cyp3a4 inhibitors in critical cardiac patients

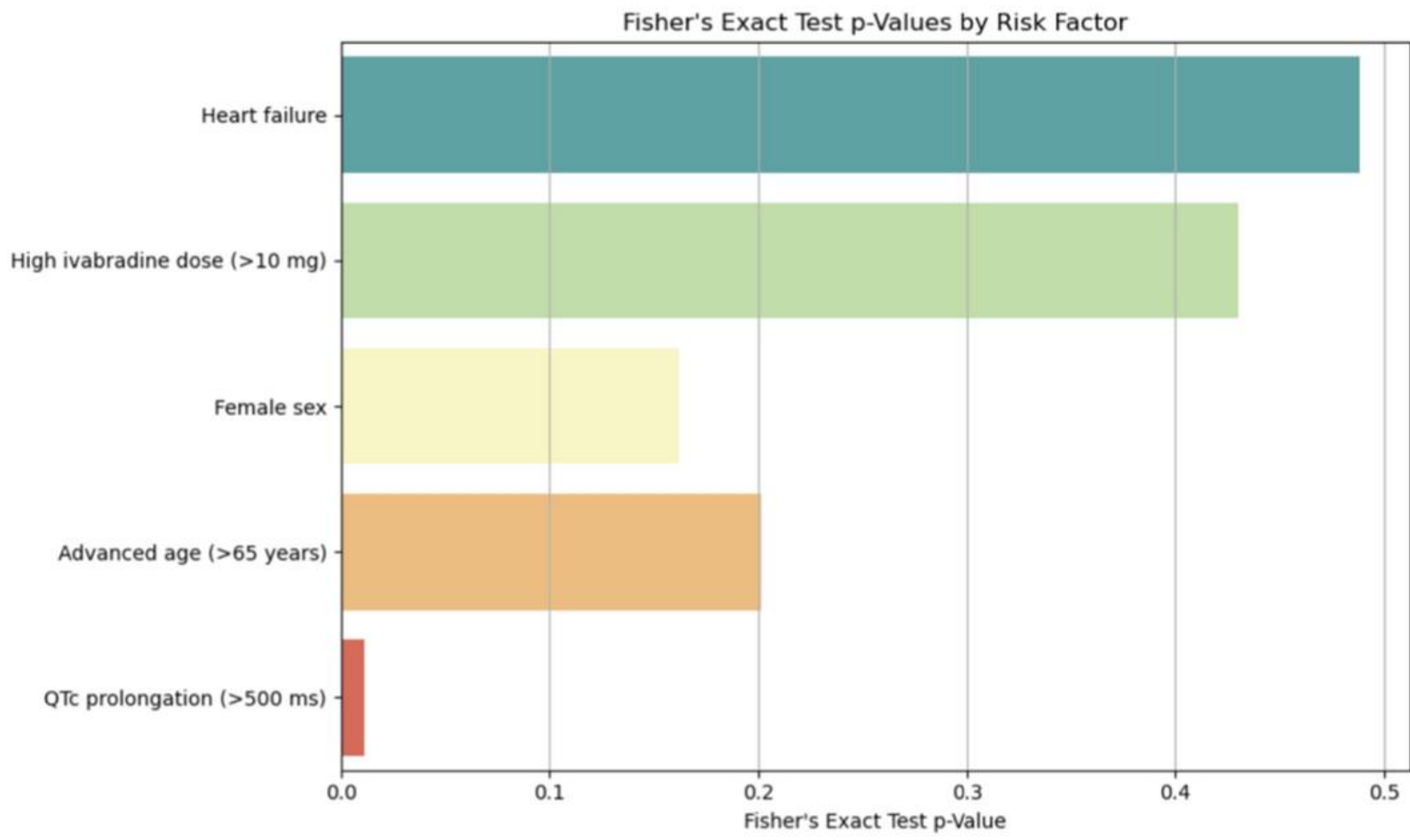
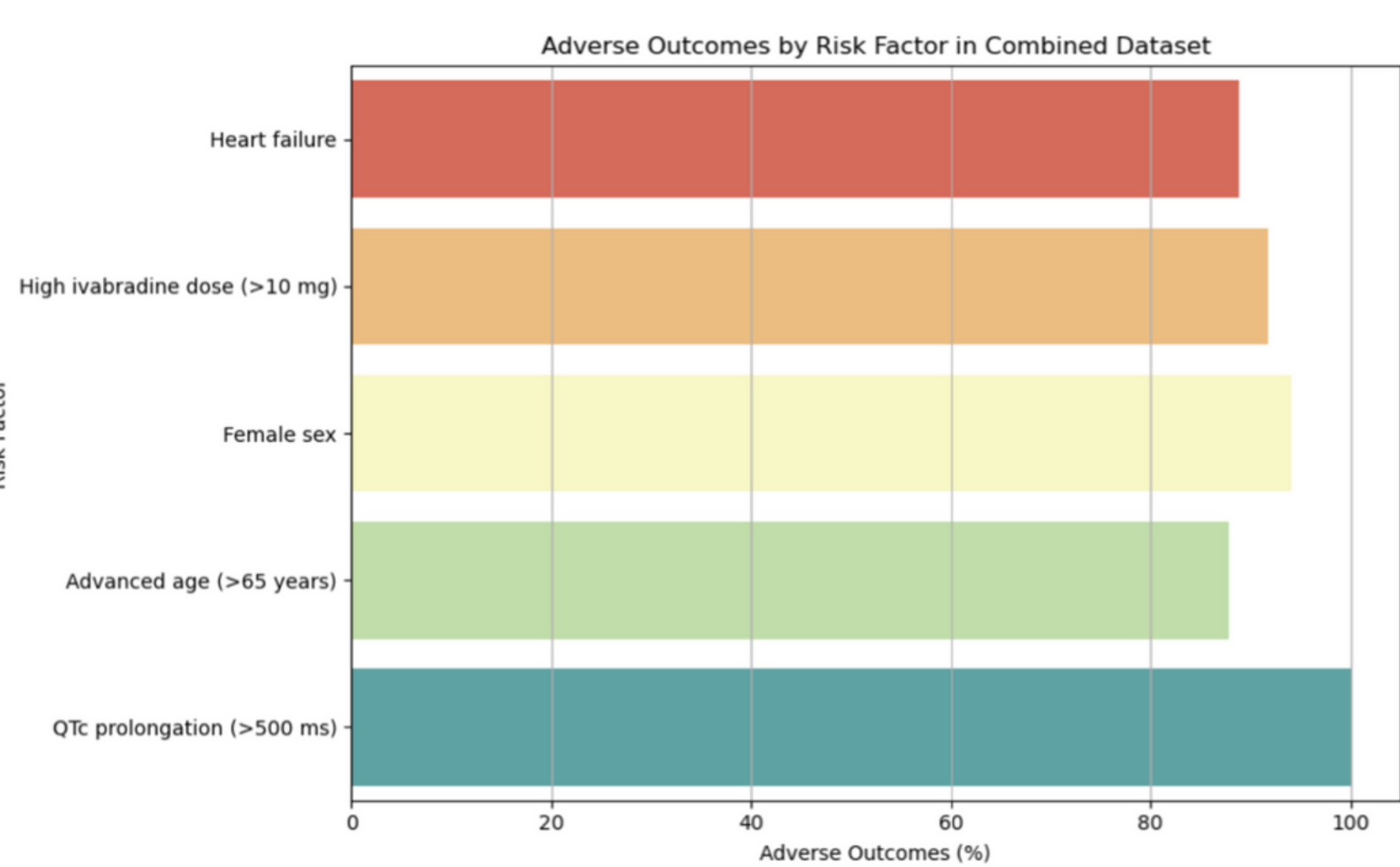
O2 SHIFT, SIGNIFY, and BEAUTIFUL

O3 EUDRAVIGILANCE and FAERS

EudraVigilance: 68 reports of TdP, 32 reports of QT prolongation. 36% female, and 18 fatalities. Mean age was 64.3 years, many had pre-existing risk factors

Food and Drug Administration Federal Adverse Event Reporting System: 79 cases of QT prolongation and Torsades, similar male: female ratio, and mean age was 56.8.

# Databases, continued



## — Heart Failure

Increased risk of TdP via  
altered ion channel  
expression, structural  
remodelling, and  
neurohumoral activation

## — Data Accessibility

Lack of complete  
(several case reports)  
and poor quality  
(FAERS and  
Eudravigilance) data

## — Limitations

Small number of  
identified cases  
Causality assessment  
tools  
Data availability and  
analyses  
Solutions?

# Discussion

# Conclusion:

Probable causal association between ivabradine and QTc prolongation/TdP risk identified, particularly in patients with other risk factors

- Careful patient selection, regular monitoring, and consideration of drug interactions are essential to ensuring its safe and effective use.
- Further research, e.g., post-marketing surveillance and prospective studies, is needed to better characterise this risk
- Focus on refining ivabradine's safety profile, potential modifications to improve selectivity and minimise off-target effects also needed.
- Development of guidelines and risk stratification tools for clinician use in identifying patients who may benefit most while minimising risk of adverse events



# Thank You

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