Characterizing time to conversion to sinus rhythm under digoxin and placebo in acute atrial fibrillation

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Background and Objective

The underlying trial was a randomized, double-blind comparison of intravenously administered digoxin and placebo in patients with acute atrial fibrillation (DAAF). The primary end point was conversion to sinus rhythm within 16 h after randomization, while effect on heart rate (HR) was a secondary end point. The primary publication [1] concluded: "There was no clear correlation between serum concentration of digoxin and changes in ECG or HR". A later analysis [2] reported on the population pharmacokinetics (PK) of digoxin and a HR model. Here, the aim was to evaluate if any predictor of conversion to sinus rhythm can be found using a Time-to-event (TTE) analysis.

Methods

- Sparse PK (1-2) and HR (5) samples per subject were provided by the DAAF study. The time of conversion to sinus rhythm was reported within the 16h observation time.
- The data was analysed using the Laplace method in NONMEM VI.
- The F_Flag functionality was used to simultaneously predict the continuous data (PK and HR observations) and estimate probabilities for the categorical data.
- The PPP&D[3] method was used for the combined PKPD and TTE analysis, since the PK and HR analyses were performed previously. The final model was also rerun fitting the HR and the conversion data simultaneously.
- The assessment of statistical significance of additional parameters was based on the difference between the OFV at the 5% significance level. The predicted performance of the TTE analysis was assessed using Kaplan-Meier VPC graphics and a comparison to parameter estimates from a bootstrap analysis.

Results and Discussion

Table I. *Patients and Study Data*

	Digoxin group	Placebo group
Number of patients	105	122
Sex	Male (n=55) Female (n=50)	Male (n=68) Female (n=54)
Age (yr)	63 (21-85) 71 (42-89)	60 (21-85) 71 (42-88)
Patients with conversion (t<16 h)	49	56
Time to conversion	5.2h (0.08 – 15.9h)	5.8h (0 – 15.3h)

- Digoxin was administered intravenously in 1-3 doses up to a total of 0.015-0.02mg/kg. 105 patients received one dose; a 2nd dose was administered to 88 and a 3rd dose to 63 patients.
- The mean duration of AF before the start of observation was reported as 23.2 h (1.5 – 174.5h) previously[1], however was not available for each individual for this analysis.

- The TTE analysis showed that the main influence on having conversion was 'time' followed by 'age' and 'sex'.
- Time was included as exponential, step or spline functions in the model. The final model included time as a step function with an estimated break point at 4.2h.
- Application of a Weibull survival distribution instead of an exponential did not significantly improve the final model.
- The chance of having a conversion declined exponentially with age. The hazard of having conversion was estimated to be 4.9%.h^{-1} for the typical (65 yr) male and 9.7%.h^{-1} for females. After 4.2h the chance of having a conversion was reduced by 52% for males and 60% for females.

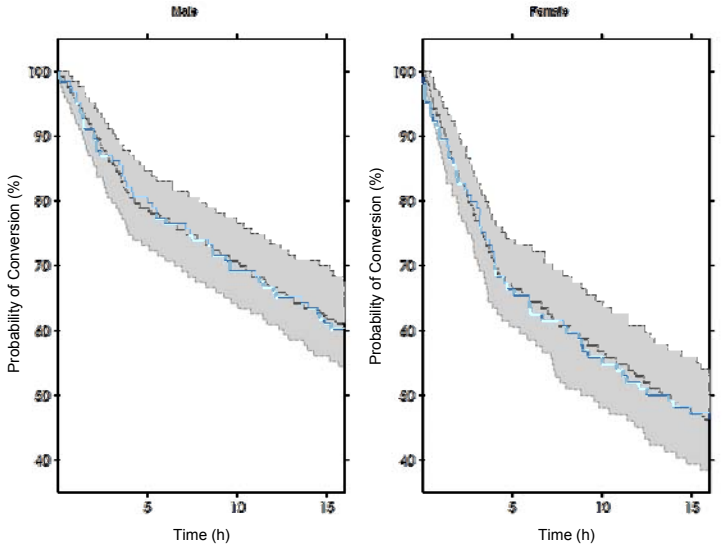

Figure 1. *Visual Predictive Check (VPC) - Kaplan-Meier Plot of the probability of conversion (%) versus time for males and females. The blue shaded area represents the 90% prediction interval (black dashed lines: 5th, 50th, 95th percentile) and the blue line the raw data.*

- The predicted probability of conversion (%) from the final model overlaying the study observations in a Kaplan-Meier VPC showed a good predictive performance of the model for the 16 h observation period (Figure 1).
- Inclusion of HR in the TTE model was inferior to time. Even though HR decreases with time, predominately in the digoxin group [2] , including HR or the change of HR from baseline had no explanatory value in addition to the time effect.
- Similarly, models including digoxin concentrations were not significant. Differentiating Digoxin and Placebo did not improve the model in any way.
- The simultaneous fit of HR and TTE data provided very similar estimates to the PPP&D method as well as the bootstrap analysis (Table 2) .

Table II. *Summary of parameter estimates of the final model using the PPP&D method, the simultaneous fit of HR and conversion data and the bootstrap analysis. (grey parameters were fixed during the analysis)*

	units	Final Model PPP&D	Final Model SIM HR& TTE	Bootstrap (n=200) median (90% CI)
OFV		6248.9	6244.6	6227.1 (6032.7 - 6434.4)
Basline Heart Rate (HR)	bpm	117	118	117
Digoxin effect on HR (slope)	l/nM	-0.103	-0.104	-0.103
Time effect on HR (placebo)	l/h	-0.00175	-0.00160	-0.00175
RUV HR	%	9	9	9
Hazard (Male <BP)		0.145	0.130	0.145 (0.95 - 0.44)
Hazard (Femal <BP)		0.286	0.258	0.286 (0.21 -1.2)
Hazard (Male >BP)		0.0686	0.064	0.0759 (0.04 -0.23)
Hazard (Female >BP)		0.114	0.104	0.12 (0.07 - 0.43)
AGE effect on Harzard		0.0167	0.015	0.0167 (0.01 - 0.04)
Breakpoint (BP)	h	4.2	4.2	4.1 (2.2 - 5.1)
IIV Time effect on HR	%	122.8	127.2	122.7
IIV Basline HR	%	17.7	17.6	17.7

$P(conv)=Hazard*e^{-AGE*\theta(AGE)}$

Conclusion

The model estimated a 30-40% higher chance for females to convert compared to males. No difference on the time to conversion could be found between the digoxin and the placebo group.
The chance of having a conversion was higher for the first 4.2h after start of observation.

References

1. Hornestam B, Held P, Edvardsson N. Digitalis in Acute Atrial Fibrillation (DAAF) Trial Group. Clinical cardiology 1999; 22: 96-102.
2. Hornestam B, Jerling M, Karlsson MO, Held P. Eur J Clin Pharmacol 2003; 58: 747-55.
3. Wade JR, Karlsson MO. PAGE1999: Abstr 139 [www.page-meeting.org/?abstract=39].