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Background

- Drug regulatory agencies require a detailed ECG evaluation on all systemically administered drugs, including a "thorough QT study" (TQTS) to evaluate drug effects on cardiac repolarization.
- The TQTS includes subject groups receiving different doses of study drug, as well as placebo and positive control groups. As a result, a TQTS requires accurate and precise interval duration measurements (IDM) performed on as many as 30,000 ECGs.
- Continuous 12-lead ECG Holter recordings simplify the process of obtaining large numbers of ECGs. With Holters, a technician visually selects three 10-sec ECGs from the recording near each designated study time point for each subject. However, this method of visual ECG extraction is labor-intensive and prone to error and variability.
- Computer automation of the ECG selection process offers to opportunity to select with accuracy and consistency recorded segments with stable heart rates and low noise content
- Here, we evaluate a new computerized algorithm for ECG extraction from Holter recordings. The algorithm is designed to assess both noise content and stability of IDMs to assure that the highest-quality and most stable ECGs are consistently selected.

Methods

- **Study Design.**
 - Randomized, placebo-controlled crossover design; all subjects had a placebo day and another day on moxifloxacin 400 mg po
 - Enrolled 72 subjects, 4 subjects withdrew; thus; presented data is from 68 subjects (41 males, 27 females, mean age 42.6 yrs)
 - Continuous 12-lead Holters were obtained on both study days
- **Manual ECG selection**
 - For each subject at each treatment period (TPD), three 10-sec ECGs were selected by visual inspection of the Holter data
 - Interval duration measurements (IDMs) were made using the QTInno™ fully automated ECG analysis program, on either (1) three consecutive complexes in each ECG having the lowest standard deviation for QTcF (referred to herein as **Man-3C**); or (2) on all complete complexes in the ECG (**Man-AC**)
- **Automated ECG selection**

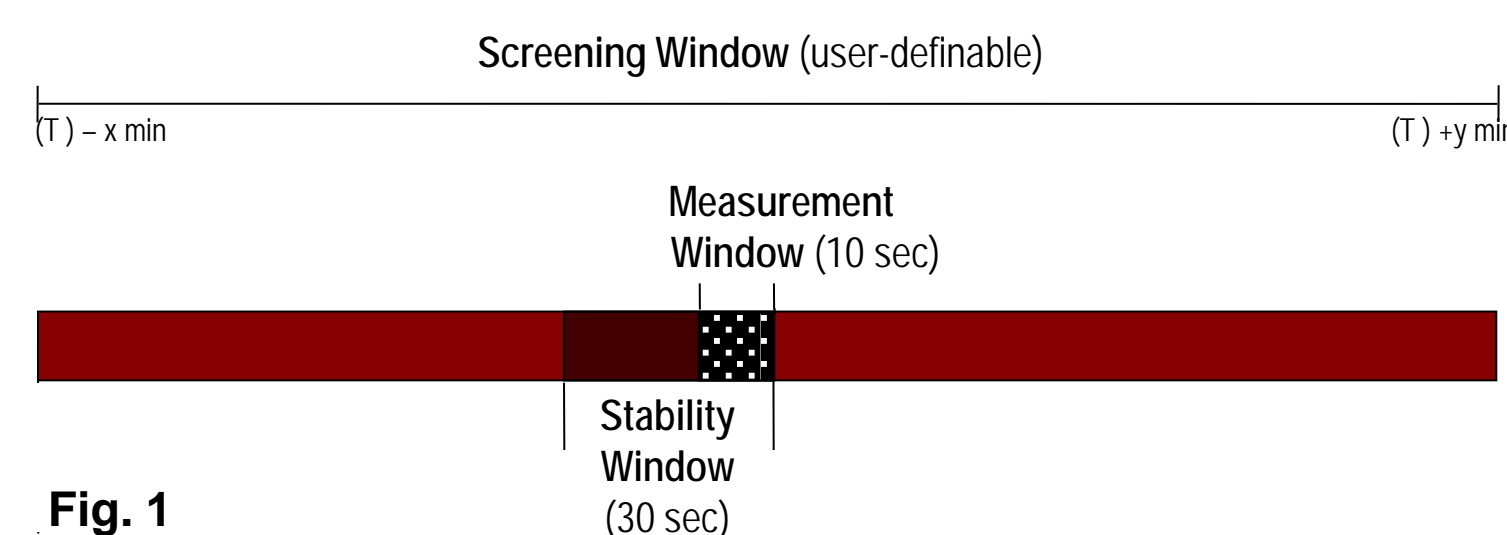


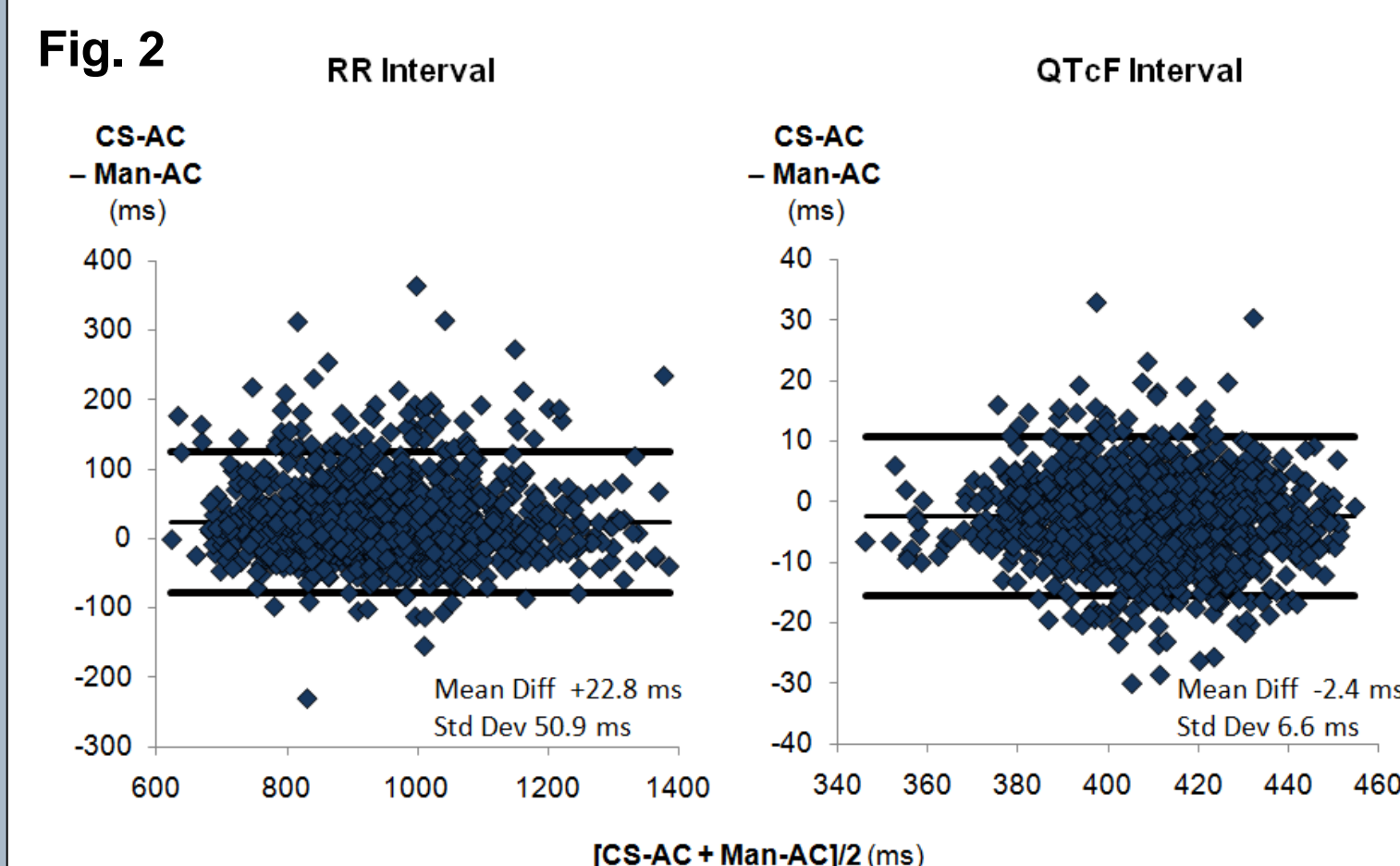
Fig. 1

- **Screening Window.** A Screening Window is set by the user at any value between -10 and +5 min relative to the study time point. In this study, the Screening Window was set at -7 min to +3 min.

Methods (continued)

- **Stability Window** is a sliding 30-sec window that is moved in an iterative process, starting at the earliest time in the Screening Window, and moving rightward by 1 sec increments until all 30-sec Stability Windows in the Screening Window have been scored. The 3 non-overlapping Stability Windows with the highest CS score are selected for IDM determination.
- **Measurement Window** is the final 10 sec of the selected Stability Windows, where all IDMs are made by the QTInno automated algorithm
- **Automated Selection of Complexes for IDM determination**
 - There were 2 different automated protocols for IDMs:
 - Three consecutive complexes read in each ECG, the **CS-3C** (Computer Selection – 3 Consecutive Complexes) method; or
 - All complexes read in each selected ECG, the **CS-AC** (Computer Selection – All Complexes) method

Results

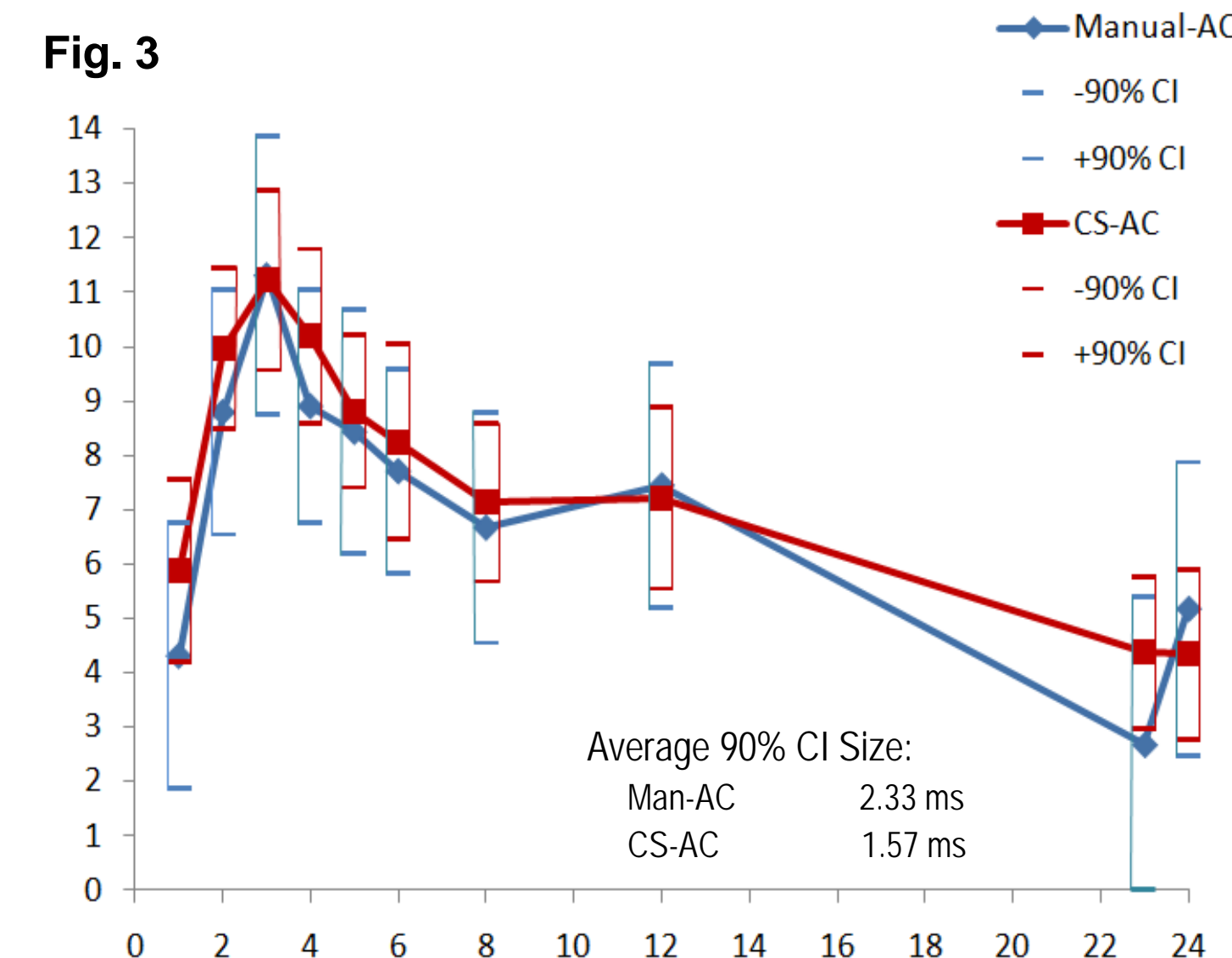


- From Bland-Altman comparison of CS-AC and Man-AC for RR intervals (Fig. 2), the mean difference was 22.8 ms, showing that computerized ECG selection results in lower heart rates than manual
- The average difference for QTcF between ECG selection methods was considerably smaller (-2.6 ms), and was reduced to <0.6 ms in Bland-Altman comparisons of dQTcF and ddQTcF (data not shown)
- When baseline-corrected RR intervals (dRR) were compared by Bland-Altman analysis, the mean difference between CS-AC and Man-AC results was reduced to 2.4 ms (data not shown)

Figure 3 (next column). ddQTcF curves by hour for manual (Manual-AC) and computerized (CS-AC) ECG selection methods.

- All methods produced a typical rise-and-fall pattern expected for ddQTcF after moxifloxacin administration, with a peak of 11.2-11.6 ms at 3 hours post-drug (Man-3C and CS-3C not shown)
- Adequate assay sensitivity was established for all methods, with the lower 90% CI excluding 5 ms at 7 of 10 time points
- Although the mean hourly values for ddQTcF were very similar between methods, computer selection resulted in a >30% reduction in the size of 90% CIs relative to manual selection

Results (continued)



		QT	QTcF	RR	PR	QRS
Man-3C	Average SD	9.31	8.53	61.98	5.61	3.09
	90% CI	0.30	0.23	1.96	0.22	0.13
CS-3C	Average SD	5.81*	3.94*	34.94*	3.32*	1.77*
	90% CI	0.14	0.05	0.97	0.10	0.07
Man-AC	Average SD	8.65	7.53	58.30	5.57	3.06
	90% CI	0.30	0.24	1.94	0.22	0.13
CS-AC	Average SD	6.89**	5.36**	41.60**	3.95**	2.10**
	90% CI	0.14	0.05	1.00	0.12	0.07

Table 1. Within-Subject Average Standard Deviation (SD) by ECG selection method. A mean and standard deviation were calculated for each triplicate ECG; these SDs were averaged across all subjects and time points ("Average SD"). 90% confidence intervals ("90% CI") for Average SDs are also shown.

* $p < 0.001$ for the difference in means for CS-3C vs. Man-3C (two-tailed t-test)
** $p < 0.001$ for the difference in means for CS-AC vs. Man-AC

Method	dQTcF		dRR	
	Between-subject (ms)	Within-subject (ms)	Between-subject (ms)	Within-subject (ms)
Manual-3C	6.0	7.4	48.2	61.2
CS-3C	4.7	5.1	42.8	60.4
Manual-AC	6.0	6.9	48.5	54.9
CS-AC	4.5	5.0	45.2	54.7

Table 2. Between and Within-Subject Covariances for dQTcF and dRR) shown by ECG selection method

- Computer selection of ECGs reduced both between- and within-subject dQTcF covariances by 22-28% relative to manual selection

Results (continued)

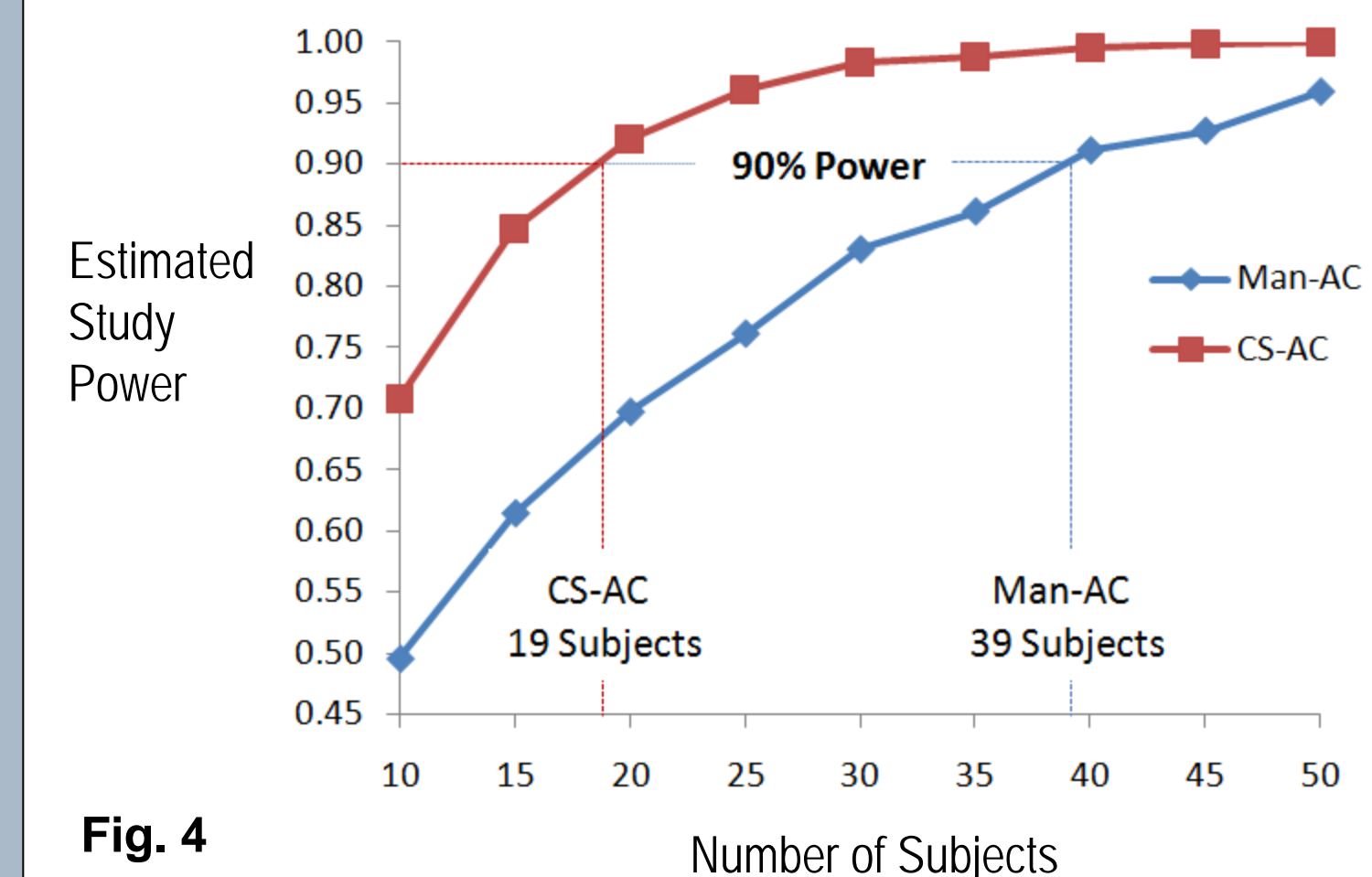


Fig. 4

Study Power	Estimated Number of Subjects Needed			
	Man-3C	CS-3C	Man-AC	CS-AC
80%	25	13	28	13
90%	35	20	39	19

- Fig. 4 and Table 3 present the results of bootstrap power estimates
- For bootstrap analysis, hourly ddQTcF estimates are calculated for 5000 randomly selected subsets of fewer subjects than the original total. The proportion of simulations where at least one 90% lower CI excludes 5 ms is the estimate of study power for the chosen number of subjects
 - For example, when 5000 simulations were run with 10 randomly selected subjects, the 90% CI excluded 5 ms in 49.5% of simulations for Man-AC, and in 70% for CS-AC
- Results show that computer selection of ECGs substantially increases study power over manual selection, or allows the study to be done at the same power with about half as many subjects

Conclusions

- Both visual and computer-based ECG selection methods returned similar hourly point estimates for ddQTcF, and both methods showed a typical progression for hourly change in ddQTcF
- The major difference between the two approaches was seen in variability metrics – standard deviations, 90% confidence interval size, and mixed-model covariances. In all of these parameters, computer ECG selection showed a substantial advantage over manual selection
- As a result of the reduced measurement variability, computer ECG selection produced substantially higher estimated study power
- Higher study power reduces the risk of a failed or incorrect TQTS, and enables the study to be done more reliably, with fewer subjects, and at less cost