Transdermal Testosterone Administration Attenuates Drug-Induced Lengthening of Early and Late Repolarization in Older Men

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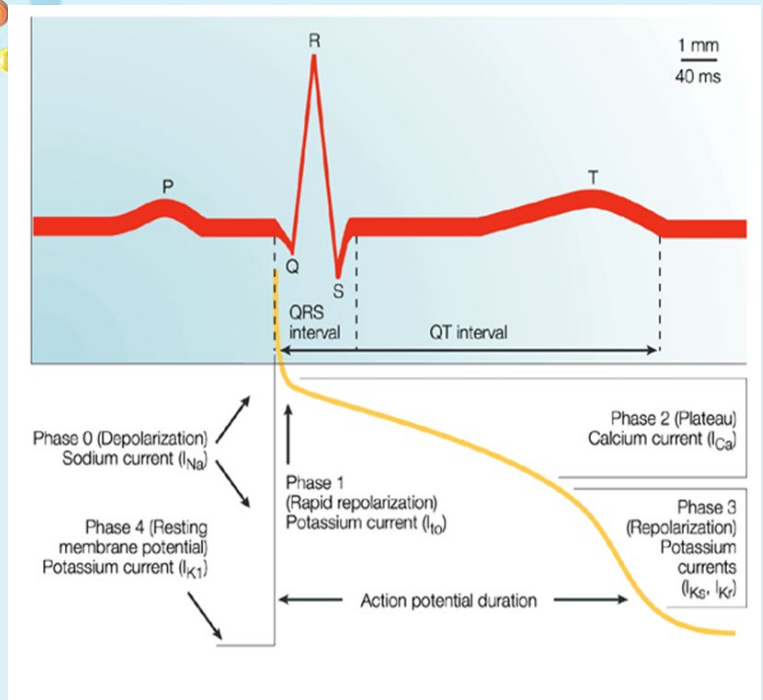
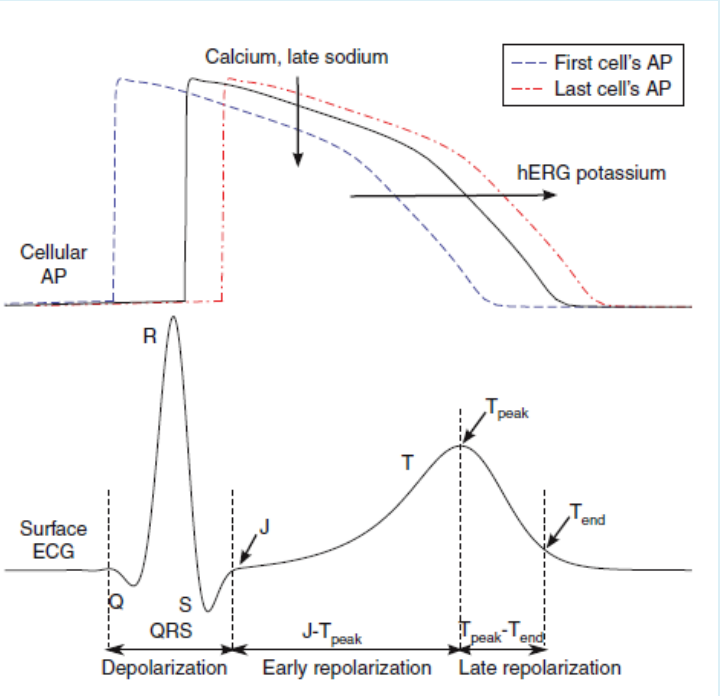
QT, J-Tpeak and Tpeak-Tend Intervals



QT Interval: ECG representation of ventricular depolarization and repolarization



J-Tpeak and Tpeak-Tend: ECG representation of early vs late ventricular repolarization

Nat Rev Drug Discov. 2003;2:439-47; Clin Pharmacol Ther 2014;96:549-558

Sex Differences in Ventricular Repolarization

FROM MOLECULE TO PATIENT

Female sex is a risk factor for drug-induced QT prolongation, however **29-46% of reported cases of TdP have occurred in men**

Older age is a risk factor for drug-induced QT prolongation due to **declining testosterone** concentrations in men

Administration of **transdermal testosterone attenuates** drug-induced QT lengthening in **men ≥65 years**

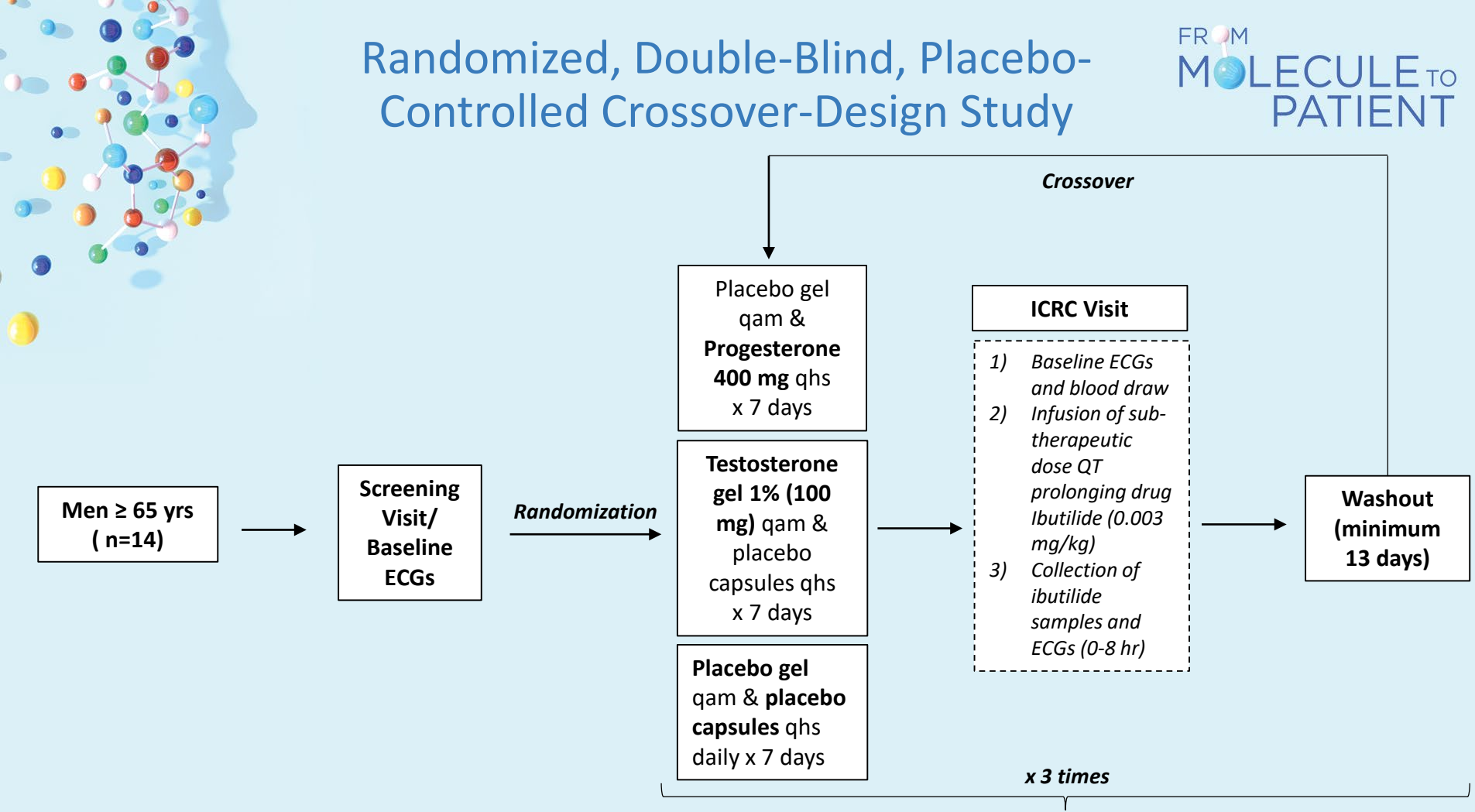
Oral progesterone attenuates drug-induced QT interval lengthening in **young women during the menses phase**

- **GAP IN KNOWLEDGE**: The effects of progesterone and testosterone on early and late ventricular repolarization associated with attenuation of drug-induced QT-interval lengthening are still unknown
- **HYPOTHESIS:** Transdermal testosterone and oral progesterone attenuate drug-induced lengthening of both the J-Tpeak$_c$ interval (early repolarization) and Tpeak-Tend interval (late repolarization) in older men

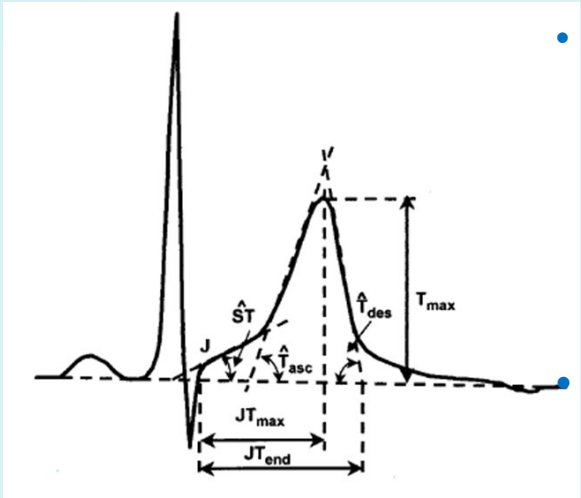
JACC Clin Electrophysiol. 2016;2:765-774, JAMA. 1993;270:2590-2597, J Am Coll Cardiol. 2006;48:471-477, Circulation 2018;138:A15197

Randomized, Double-Blind, Placebo-Controlled Crossover-Design Study

FROM MOLECULE TO PATIENT

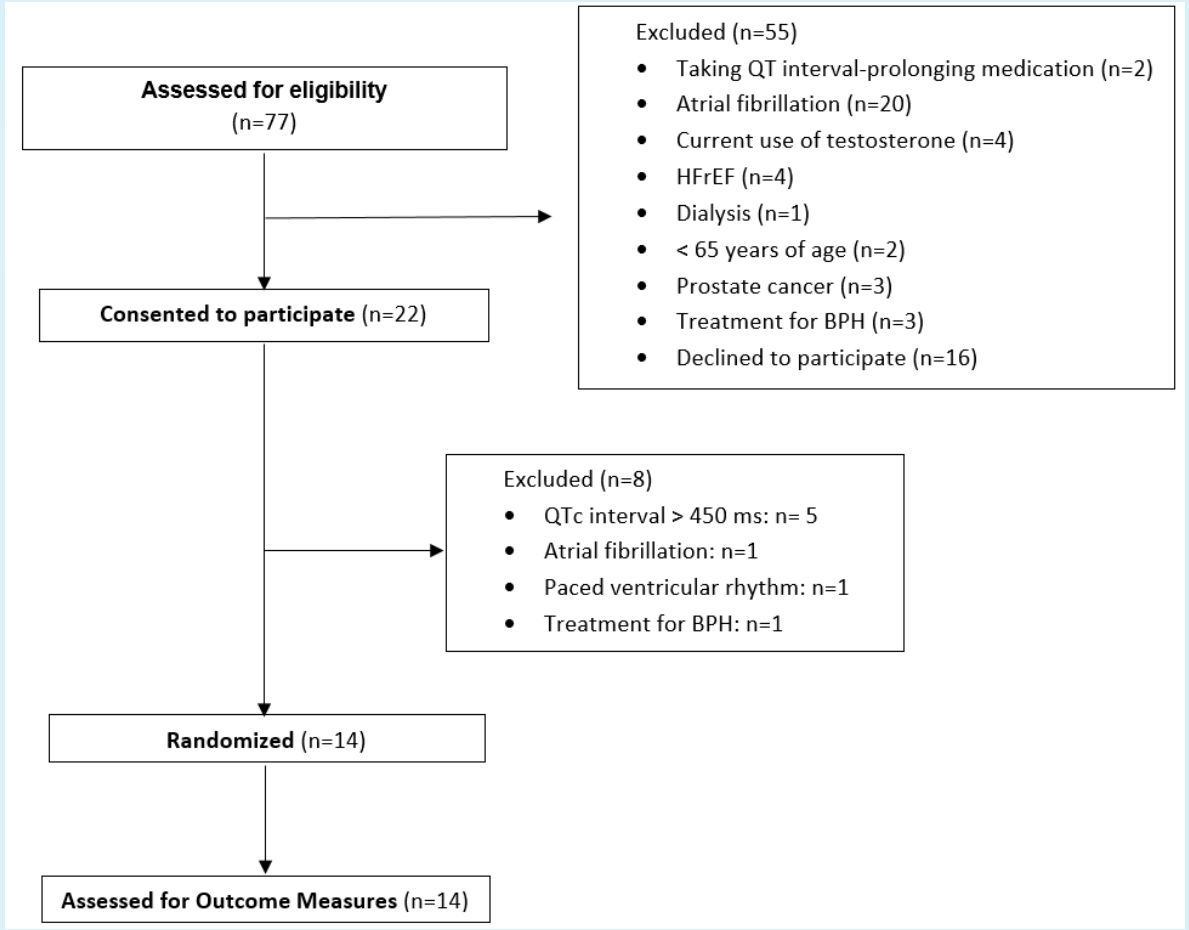


Study Methods



- **ECG intervals were determined manually from lead II**
  - Computerized electronic caliper (EP Calipers 1.6)
  - Investigator (E.T.M.) blinded to the subjects' assigned groups
- **ECG interval heart rate corrections**
  - J-Tpeak$_c$ = J-Tpeak /(RR)$^{0.58}$
- **Primary Outcome Measures**
  - Baseline J-Tpeak$_c$ and Tpeak-Tend intervals
  - Maximum J-Tpeak$_c$ and Tpeak-Tend intervals
  - Area under the effect (J-Tpeak$_c$ and Tpeak-Tend intervals)-time curves for 1.17 and 8.17 hours during and after ibutilide infusion (AUEC$_{0\text{-}1.17}$ and AUEC$_{0\text{-}8.17}$)
- **Statistical analyses (SPSS Inc, Chicago, IL)**
  - Repeated-measures ANOVA with Bonferroni *post-hoc* test
  - Data are presented as means, SD in table and SEM in figures

Subject Recruitment



Serum Hormone and Ibutilide Concentrations During Testosterone, Progesterone and Placebo Phases

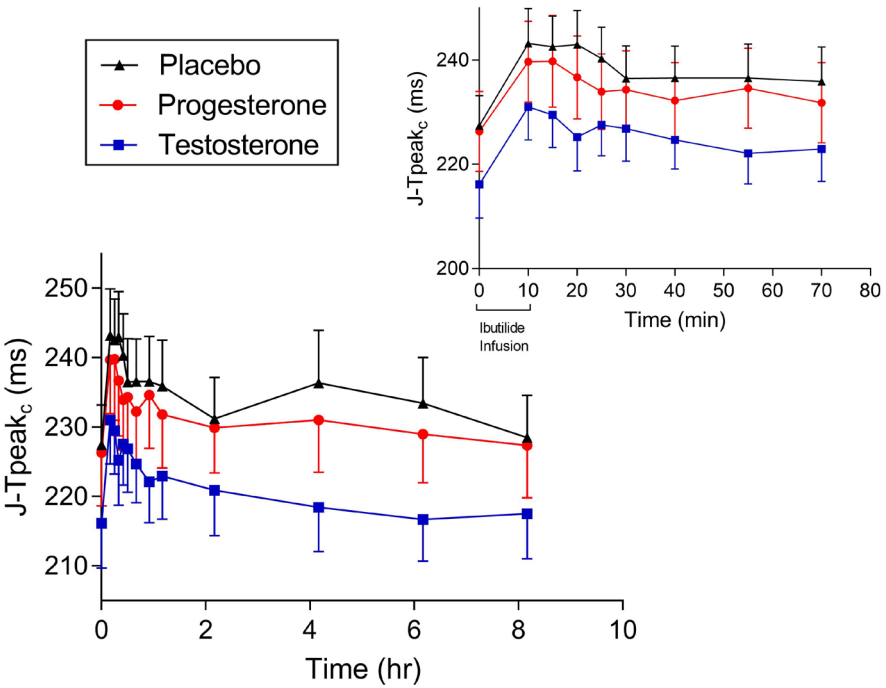
FROM MOLECULE TO PATIENT

	Testosterone	Progesterone	Placebo	p
Serum testosterone concentration (ng/dL)	904 ± 789*	261 ± 44	267 ± 77	<0.001
Serum progesterone concentration (ng/mL)	0.5 ± 0.2	20.9 ± 11.5§	0.4 ± 0.2	<0.001
Serum peak ibutilide concentration at end of infusion (ng/mL)	1236 ± 762	1144 ± 587	1121 ± 600	0.35

Bonferroni-adjusted P-value < 0.05

*Testosterone vs Placebo, §Progesterone vs Placebo

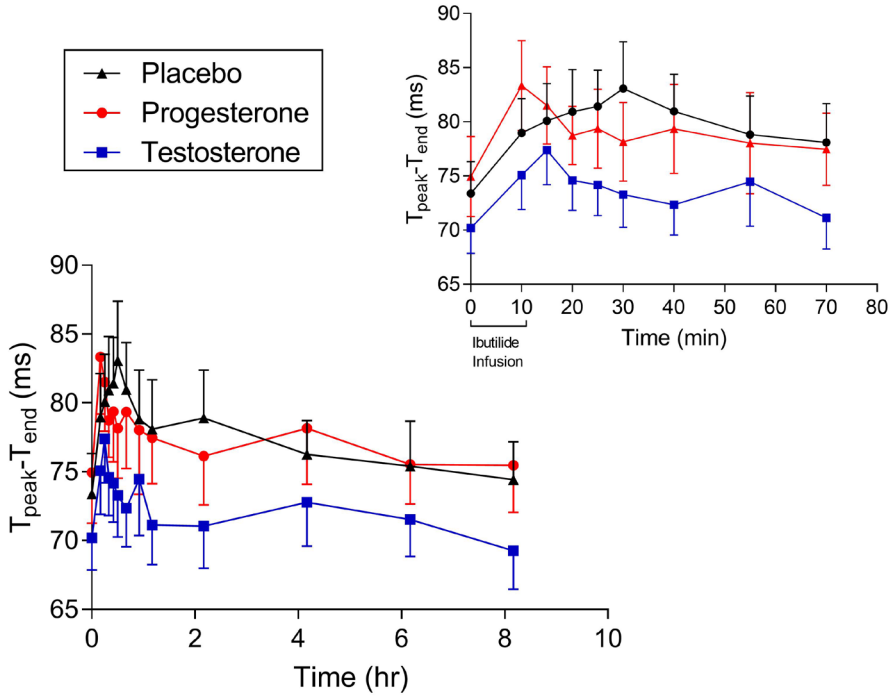
Results – Early Repolarization



	Testosterone	Progesterone	Placebo	p
Baseline J-Tpeak$_c$ (ms)	216 ± 23*	226 ± 28	227 ± 21	0.004
Maximum J-Tpeak$_c$ (ms)	233 ± 22*	246 ± 29	249 ± 24	<0.001
Maximum % change in J-Tpeak$_c$ from baseline (%)	8.2 ± 4.8	9.3 ± 5.1	8.6 ± 4.1	0.70
AUEC$_{0\text{-}1.17hr}$ J-Tpeak$_c$ (ms·hr)	262 ± 25*	273 ± 32	277 ± 26	<0.001
AUEC$_{0\text{-}8.17hr}$ J-Tpeak$_c$ (ms·hr)	1797 ± 176*	1881 ± 207	1915 ± 191	<0.001

Bonferroni-adjusted P-value < 0.05: * Testosterone vs. Placebo

Results – Late Repolarization



	Testosterone	Progesterone	Placebo	p
Baseline Tpeak-Tend (ms)	70 ± 8	75 ± 13	73 ± 11	0.16
Maximum Tpeak-Tend (ms)	80 ± 12*	89 ± 18	87 ± 15	0.008
Maximum % Change Tpeak-Tend from Baseline (%)	14.5 ± 10.1	18.2 ± 9.1	18.0 ± 11.4	0.52
$AUEC_{0\text{-}1.17hr}$ Tpeak-Tend (ms·hr)	86 ± 13*	92 ± 15	93 ± 14	0.001
$AUEC_{0\text{-}8.17hr}$ Tpeak-Tend (ms·hr)	583 ± 79*	628 ± 95	626 ± 85	0.008

Bonferroni-adjusted P-value < 0.05: * Testosterone vs. Placebo

Conclusion & Clinical Implications

- Transdermal testosterone attenuates drug-induced lengthening of both early and late ventricular repolarization
- Oral progesterone does not attenuate drug-induced lengthening of early or late ventricular repolarization

- Transdermal testosterone may be effective for attenuating QT interval lengthening associated with drugs that prolong early repolarization, late repolarization, or both