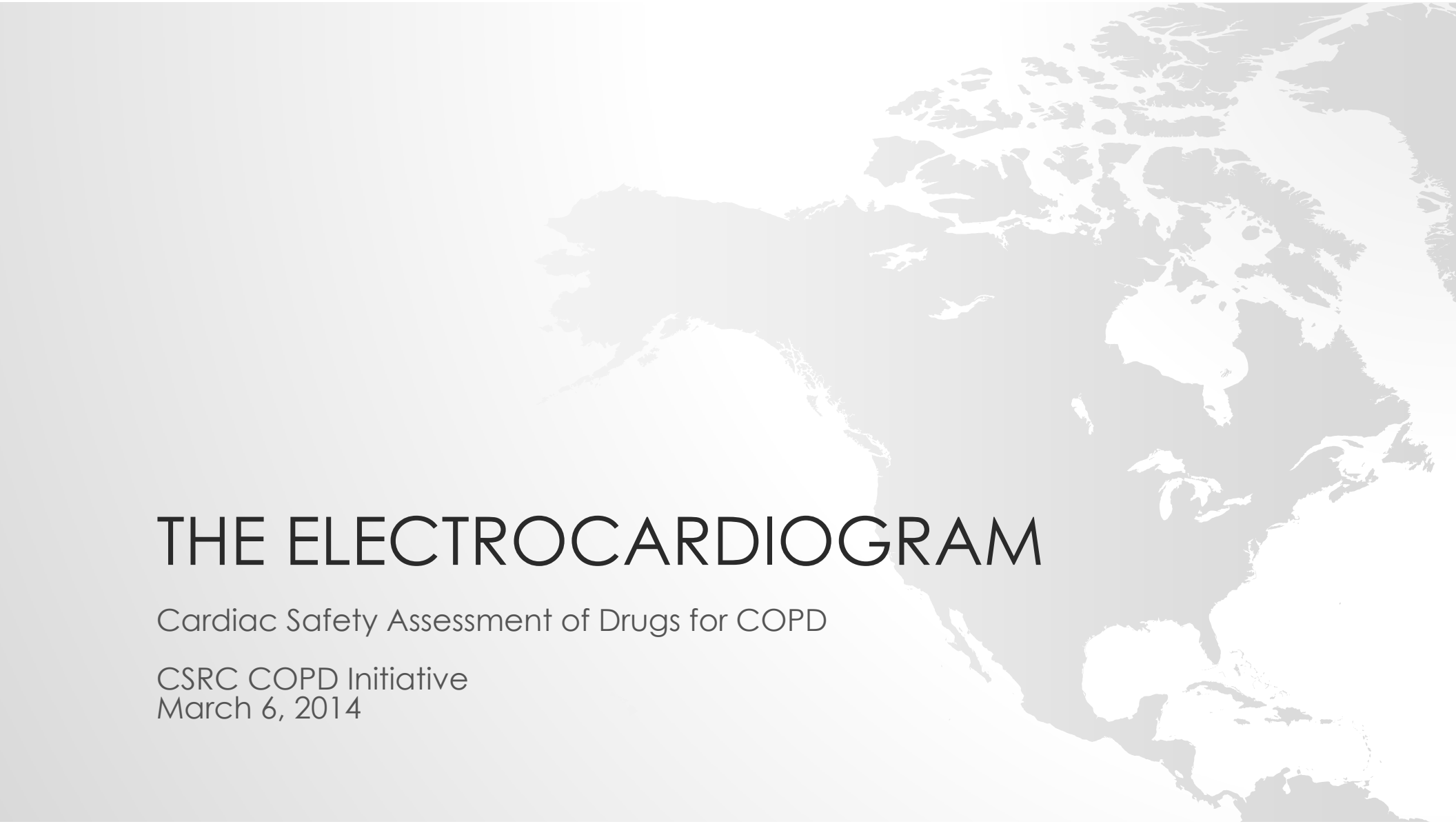
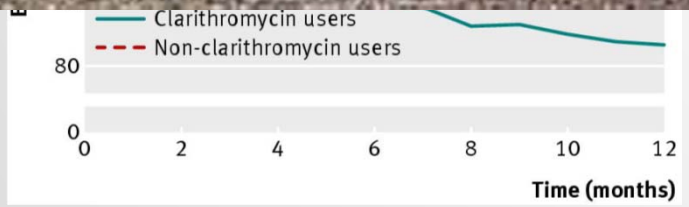


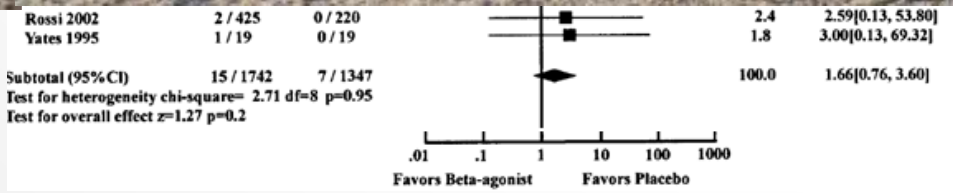
THE ELECTROCARDIOGRAM

Cardiac Safety Assessment of Drugs for COPD

CSRC COPD Initiative
March 6, 2014

ARRHYTHMIAS AND SUDDEN DEATH IN COPD





GENERAL ECG EFFECTS OF DRUGS FOR COPD

Drug	Rhythm	T Wave	QTc	PR	QRS
Short Acting β-2 Agonist	+	+	+	+	-
Long Acting β-2 Agonist	+	+	+	+	-
Antimuscarinic	+	+	+ (-)	+	-
PDE Inhibitor	+	-	-	-	-
PDE4 Inhibitor	-	-	-	-	-
Antibiotic	+	+	+	-	-
Steroid	-	-	-	-	-

Red = potential safety issue

SPECIFIC ECG EFFECTS

Drug	Rhythm‡	T Wave	QTc
Short Acting β-2 Agonist	VEA?	Flattening*, inversion*	↑*
Long Acting β-2 Agonist	VEA?	Flattening*, inversion*	↑*
Antimuscarinic		Flattening†	↑†
Antibiotic	TdP◊	Flattening◊, inversion◊	↑◊

‡ Sinus tachycardia, related to multiple mechanisms, is an off-target effect shared by all listed drugs
? Ventricular ectopic activity, possibly related to increase calcium transient, or to direct cAMP-mediated effect or to *
* Related to drug-induced $\downarrow K^+$
† Related to vagal withdrawal
◊ Torsades de pointes VT related primarily to I_{Kr} block

PROPOSED SAFETY SIGNALS

CAUTION

Change	Signal
↑ QTcF	> 60 msec, and QTcF > 480 msec
Sinus rate	> 20 BPM and HR > 100
Ventricular ectopic activity	New or increased frequency
T Wave	New or augmented generalized flattening > 25% or deep inversion involving one new lead, or both

WITHDRAWAL

Change	Signal
↑ QTcF	> 60 msec and/or QTcF > 500 msec
Sinus rate	> 30 BPM and HR >120 BPM
Ventricular ectopic activity	New and frequent or tripled frequency, any long run
T Wave	New or augmented generalized flattening > 50% and/or deep inversion involving multiple new leads

ADDITIONAL NOTES

- QT prolonging antibiotics should be used infrequently and cautiously in patients receiving β-2 agonists or antimuscarinics.
- Since COPD alone, and its treatment, may predispose to QT prolongation, an ECG should be acquired prior to enrollment of a patient in a trial, or to a change in treatment that could adversely affect repolarization.
- In patients with risk factors for adverse repolarization or heart rate increase, the individual drugs contained in combination products can be started serially. This could be done both in clinical trials and clinical care.
- Short rhythm recordings (2 to 5 minutes) should be added to the routine ECG when β-2 agonists, antimuscarinics or macrolide antibiotics are used in COPD trials and clinical care.

MORE NOTES

- Holter monitoring is far more effective than periodic ECGs in detecting arrhythmias, but it is expensive, inconvenient and very inefficient in detecting drug-related arrhythmia exacerbation.
- Proarrhythmia detection by short rhythm recordings under controlled conditions has not been assessed, but may be less prone to variability than HM.

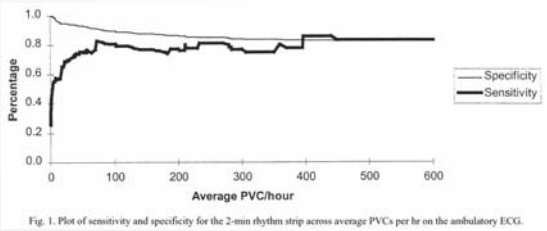


Fig. 1. Plot of sensitivity and specificity for the 2-min rhythm strip across average PVCs per hr on the ambulatory ECG.

Evenson, J Clin Epidemiol, 2000

- Rate correction of QT after an increase in HR is highly problematic. On pure arithmetical grounds, QTcF is less likely to distort QTc at higher rates due to its cubic exponential, and it has been shown to yield less residual HR dependence than QTcB.

SUMMARY SLIDE: HR/ECG/ARRHYTHMIAS/BP/ISCHEMIC EVENTS

Weight of Evidence LABA/SAMA/LAMA/ICS and combinations are associated with ….	LABA, SABA and macrolide antibiotics associated with VEA
What (if anything) was required to evaluate perceived "risk"	Serial ECG and rhythm recordings
Presence of a Likely MOA for Risk LABA/SAMA/LAMA/ICS	LABA and SABA: Probably due to increased calcium transient Macrolides: I_{Kr} block
Is perceived risk: Generalizable to Other Drugs with Same Efficacy MOA?	Yes
Lessons Learned	Arrhythmia risk may be underappreciated