



# Relationships to Disclose

- During the course of my career I have been a consultant or advisor to, investigator for, or served on the speaker's bureau of multiple pharmaceutical and medical device companies.
- Currently, I am PI on Medtronic's REVEAL AF trial.
- I have no investments in medical industry companies.
- My presentation has been designed to be free of any actual conflict of interest as regards the above relationships.

And, My Favorite Lobbyist Is .....



# Electrocardiographic Monitoring During Drug Development

- The assessment of electrocardiographic and dysrhythmic effects, if any, are evaluated as part of the development process for all new pharmaceutical agents.
- Observations are made on heart rate, PR, QRS, and QT intervals, and any new dysrhythmias that may develop.
- Most often, the dysrhythmias of concern are new tachyarrhythmias, such as atrial fibrillation and ventricular tachycardia, including TdP or sudden cardiac death.
- However, significant bradyarrhythmias can also be consequent to drug administration.

# Electrocardiographic Monitoring During Drug Development

- The type, duration, and timing of monitoring are important variables in electrocardiographic assessment.
- Consideration with respect to the type and timing of monitoring must be given to the pharmacokinetics of both the parent compound and any active metabolites.
- ECG parameter changes are typically stable by the time steady state is reached; whereas, the development of arrhythmias may be dependent not only upon attainment of steady state but also upon a change of concomitant medications and/or comorbid disorders.
- The type and duration of monitoring are also dependent upon issues of practicality.

# Electrocardiographic Monitoring During Drug Development

- For a drug with a prolonged and uncertain half-life, such as amiodarone, and an almost infinite list of drug interactions (as well as an active metabolite), the timing and duration of adverse dysrhythmias (usually bradyarrhythmias) is different than for short half-life drugs, as would be its monitoring requirements.

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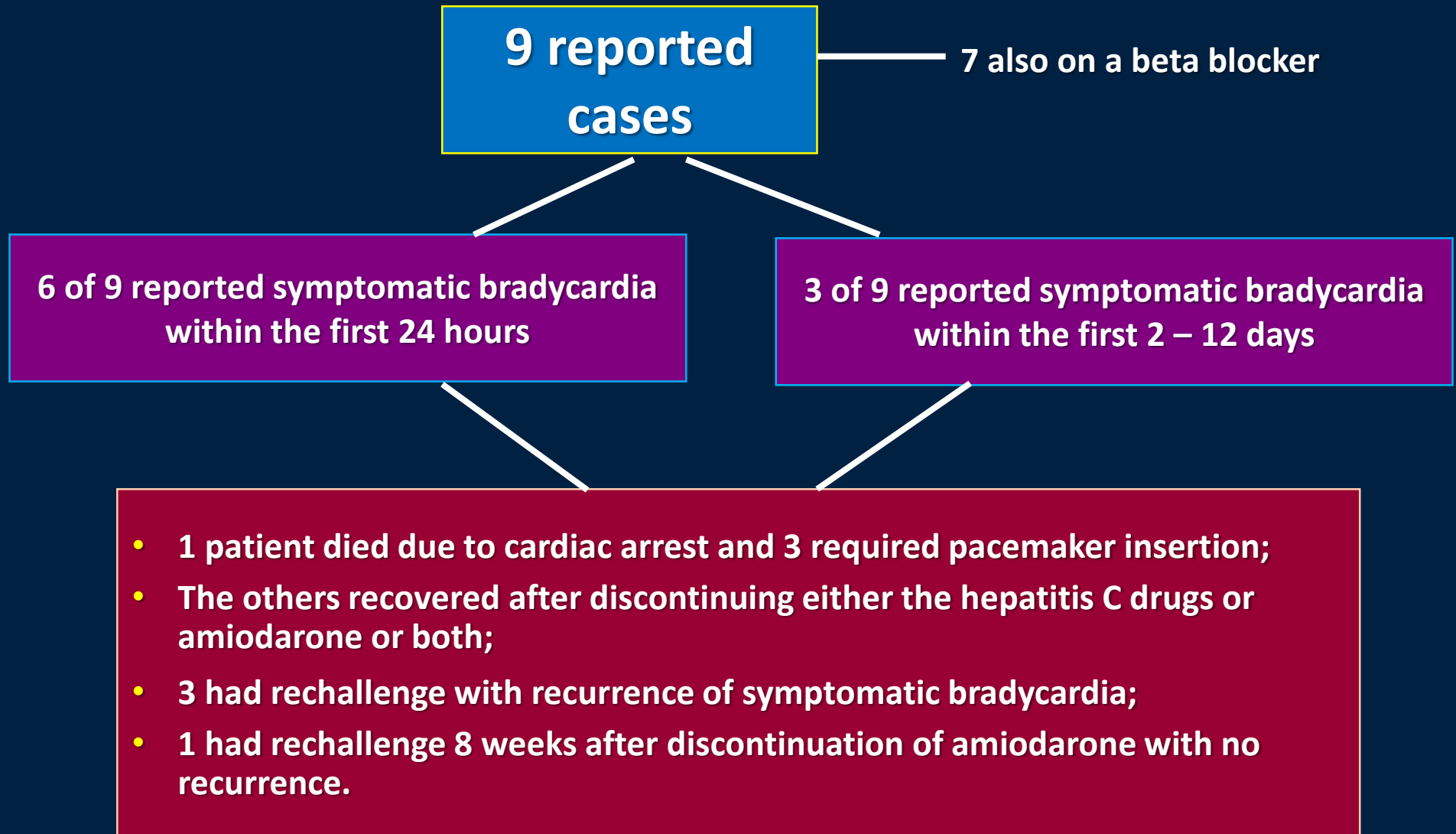


Let's Look at the Harvoni Story, For  
an Example of the Latter

# Harvoni

- Postmarketing cases of serious and life-threatening symptomatic bradycardia, as well as one fatal cardiac arrest and several cases requiring pacemaker insertion, have been reported when either Harvoni (a fixed dose combination of ledipasvir/sofosbuvir) or Sovaldi (sofosbuvir) combined with another hepatitis C antiviral was given to patients taking amiodarone.
- Bradycardia was seen within the first few hours or days of initiation, as well as up to 2 weeks after coadministration.
- Accordingly, cautions have been added to the package inserts of these agents (which in the interest of time I will not specifically review).

# Harvoni / Sovaldi Cases:



# Harvoni

- **The mechanism for this bradycardic effect is uncertain.**
  - All patients had underlying cardiac disease, concomitant beta blocker therapy, and/or advanced liver disease.
  - Presumably, the new drug altered the  $I_f$  current, already prone to dysfunction due to the underlying disease or concomitant medication, and/or conduction out of the sinus node.
- **Several characteristics of these cases suggest a causal association:**
  - Short time to symptom onset from starting either Harvoni or Sovaldi combined with a direct-acting antiviral.
  - Resolution of symptoms upon drug discontinuation.
  - Recurrence of symptoms upon rechallenge.

# Harvoni

- Understanding the mechanism underlying the Harvoni-amiodarone story might help prevent a similar outcome with other agents in the future.
- Without this understanding, however, although this story warns us that such a scenario can occur, we do not yet know how it might best be extrapolated to future drug development or which patients might need prophylactic monitoring.

# Solvaldi

- More recently, in a letter to the NEJM, three more cases of bradyarrhythmias associated with sofosbuvir-based regimens were reported – this time, only one in association with amiodarone. Syncope occurred in 2 of the 3 cases.
  - Sinus node dysfunction was the bradyarrhythmia in two patients; 3<sup>rd</sup> degree AV block occurred in the third. All 3 underwent pacemaker implantation.
  - In patient 1, it persisted after discontinuation of propranolol. Pacemaker interrogation showed atrial pacing 26% of the time while on Solvaldi, but only 4% after it was discontinued.
  - In patient 2, it resolved after stopping Solvaldi, simeprevir, and amiodarone but after reintroduction of Solvaldi plus ribavirin 46 days later, it recurred in 6 days.
  - In patient 3, there was no known bradycardia-associated concomitant medication.
  - The authors suggest consideration of risk factors for bradyarrhythmias before starting Solvaldi-containing regimens and monitoring of rhythm during the initiation of therapy....**but by what method and for how long?**

# Sinus Node, AV Node, His-Purkinje Tissue

- Sinus node function, AV node function, and His-Purkinje conduction can all be affected by administered medications; and, SN and AVN function can also be affected by changes in autonomic balance.
- The extent to which their function becomes abnormal is in large part dependent upon any baseline dysfunction present, the dose of the drug given, its direct and indirect actions, any interacting co-administered agents, and sometimes the time at which it is examined.
  - With respect to the latter, a drug that is parasympathomimetic might only produce substantial sinus node or AV node dysfunction at times that physiologic vagotonia is also high – such as during sleep, GI distress, etc.

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- Electrocardiographic monitoring is a the major noninvasive method to assess the effect of a drug on these specialized cardiac tissues.
- However, we need to recognize that, to some extent, the interpretation of monitor recordings requires knowledge of the normal range of function seen in these tissues across (1) the diurnal cycle, (2) activity levels during monitoring, and, (3) the patient's age.



# The AV Node as an Example

- AV Wenckebach and even periods of complete heart block at the AV node can be normal during sleep in young or physiologically trained healthy individuals.
  - This has been demonstrated by monitoring studies in military recruits and in medical students, among others.
- However, AVW and CHB in older individuals, especially during wakeful hours, is pathologic.
- Hence, the interpretation of findings must be made with an understanding of what observations represent physiology within the normal range in the population being examined and which represent pathophysiology that require further study or treatment.

# AV Node Function

- Medications that are parasympathomimetic or are direct depressants of the AV node may produce high-degree AV block – but do so most commonly if there is underlying dysfunction present prior to their administration (such as noted by a prolonged PR interval) or if there is disease-mediated AV node injury concomitant with their administration (such as with an acute inferior infarction).
- Accordingly, if a drug with potential adverse effects on the AV node is given to a patient with either baseline dysfunction or a concomitant potentially interacting condition, I believe that ECG monitoring should be employed from initiation to steady state.

# AV Node Function

- A similar caution should be taken if a patient with manifest His-Purkinje dysfunction, such as bundle branch block, is given a drug with sodium channel blocking properties.
- Understanding a new drug's pharmacology and pharmacokinetics should help determine what risks may be encountered and what type and duration of monitoring should be employed during its development.
- When a scenario such as the Harvoni story is encountered, the most important consideration to address is the mechanism – which will play a major role in determining what monitoring should be employed going forward.

# Steady State Should Affect Monitoring Duration

- Steady state is generally thought to be attained after 5 half-lives.
- However, many drugs have a wide range of half-lives, depending upon the patient's age, hepatic and renal function, genetic factors, concomitant therapies.
- Using flecainide as an example, the  $T_{1/2}$  varies substantially (shown on the next slide) from 6 to 29 hrs.

# Flecainide

- **PHARMACOKINETICS**

- **Absorption:** Nearly complete;  $T_{max}$  = 3 hrs.
- **Distribution:** Plasma protein binding (40%); found in breast milk.
- **Metabolism:** Extensive via CYP2D6 conjugation; meta-O-dealkylated flecainide (major, active urinary metabolite), meta-O-dealkylated lactam of flecainide (major, non-active urinary metabolite).
- **Elimination:** Urine (30% unchanged,  $\leq 3\%$  metabolites), feces (5%);

- **$T_{1/2}$  = 19 hrs (NYHA Class III CHF patients), 20 hrs (PVC patients), 29 hrs (at birth), 11-12 hrs (3 months of age and 12-15 yrs of age), 6 hrs (1 yr of age), 8 hrs (1-12 yrs of age).**

# Steady State Should Affect Monitoring Duration

- When monitoring a patient until steady state is attained (to assess electrocardiographic effects, safety, and possibly efficacy) before increasing the dose or changing treatment -- *especially in the outpatient setting* -- it is best to *use the maximal, not the mean*, half-life when calculating the time to attain steady state and to determine the duration of monitoring to be utilized.
- Accordingly, monitoring flecainide for 24 hrs may suffice if its half-life were short (e.g., 3-5 hrs) but should be almost 6 days if the half-life were 29 hrs.
  - Thus, monitoring might require a Holter (24 hrs) or 1 week of a patch monitor, auto-triggered loop recording, MCOT, or daily ECG tracings.
- This same consideration would be appropriate for agents under development once their pk characteristics are known.
- And then there is amiodarone – with a very long and uncertain half-life where steady state is likely not reached for months.

# The Challenge

- Considering the Harvoni story, where the observation only became apparent long after its approval and clinical use, and only under the specific circumstance of amiodarone co-administration, how is the FDA to know what to do with future drugs pre-release?
- The challenge is not simply what type of monitoring to utilize, but to further understand the mechanism of such interactions so that perhaps they may be more predictable and investigations most appropriately designed and timed during the drug development stage.
- Short of that, recognizing which agents are known to affect SN, AVN, and H-P tissues, and by what mechanism, extrapolation to new agents with similar mechanistic characteristics could determine what monitoring approach might best be used during phase 1-3 trials.

# Monitoring for Bradycardia and Conduction Defects: What Works and When

- ECG:
  - Daily up to or at steady-state, or with symptoms.
- 24-48 hr Holter monitoring:
  - Daily up to or at steady-state or with frequent but intermittent symptoms.
- 14 day patch monitoring:
  - for drugs with longer half-lives.
- 30-day memory loop monitoring:
  - for intermittent but less frequent symptoms.
- MCOT:
  - For drugs with high risk of severe bradyarrhythmias (or tachyarrhythmias) that require a rapid response.
- Implantable monitor:
  - For drugs with very long half-life and high risk – especially if events are rare and unpredictable.



# Final Thoughts

- **What works well today** ---- the options we have for monitoring, and the ability to add warnings to package inserts.
- **What is missing** --- understanding the mechanism by which each agent may cause a bradyarrhythmia or conduction defect --- we know many, but the Harvoni case reminds us we do not know all we need to.
- **Where should we go from here** --- when a significant pharmacologically-induced bradyarrhythmia occurs whose mechanism is uncertain, the FDA should consider requiring additional mechanistic studies be initiated as a requirement for continuing marketing of the drug.