ICD Endpoints

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Disclosures

- Dr. Kowey has provided consultation to a number of device and drug manufacturing companies including Medtronic, Sanofi, Gilead, and Allergan (Forest).
- Dr. Kowey uses drugs off label to prevent frequent ICD events because there are no drugs labelled for this indication.

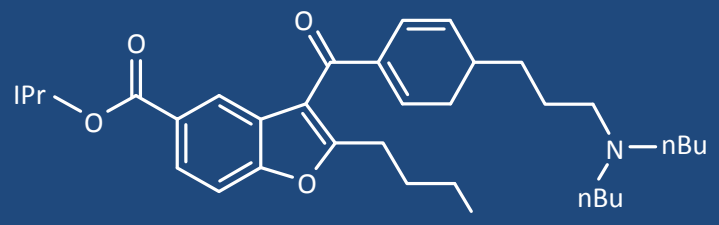
P.J. O'Rourke

"If you think health care is expensive now, wait until you see what it costs when it is free!"

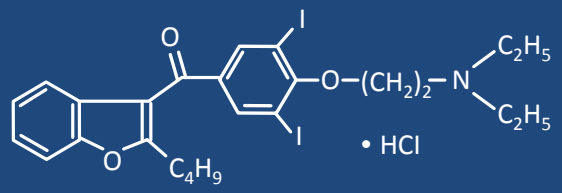
The Conundrum

- Drugs are used frequently, and at variable rates across centers, for the prevention of VT/VF events in patients with ICDs (adjunctive therapy).
- Ablation is a pretty good technique
- Though they have putative value, demonstrating clincial benefit in randomized trials is difficult and perhaps becoming more so.
- Search continues for alternative methods to demonstrate benefit within the constraints of a reasonably sized and priced clinical trial program
- Devices are smarter and keen programming may reduce the need for adjuvant drug therapy

Celivarone Profile



Celivarone
Noniondinated benzofuran derivative



Amiodarone

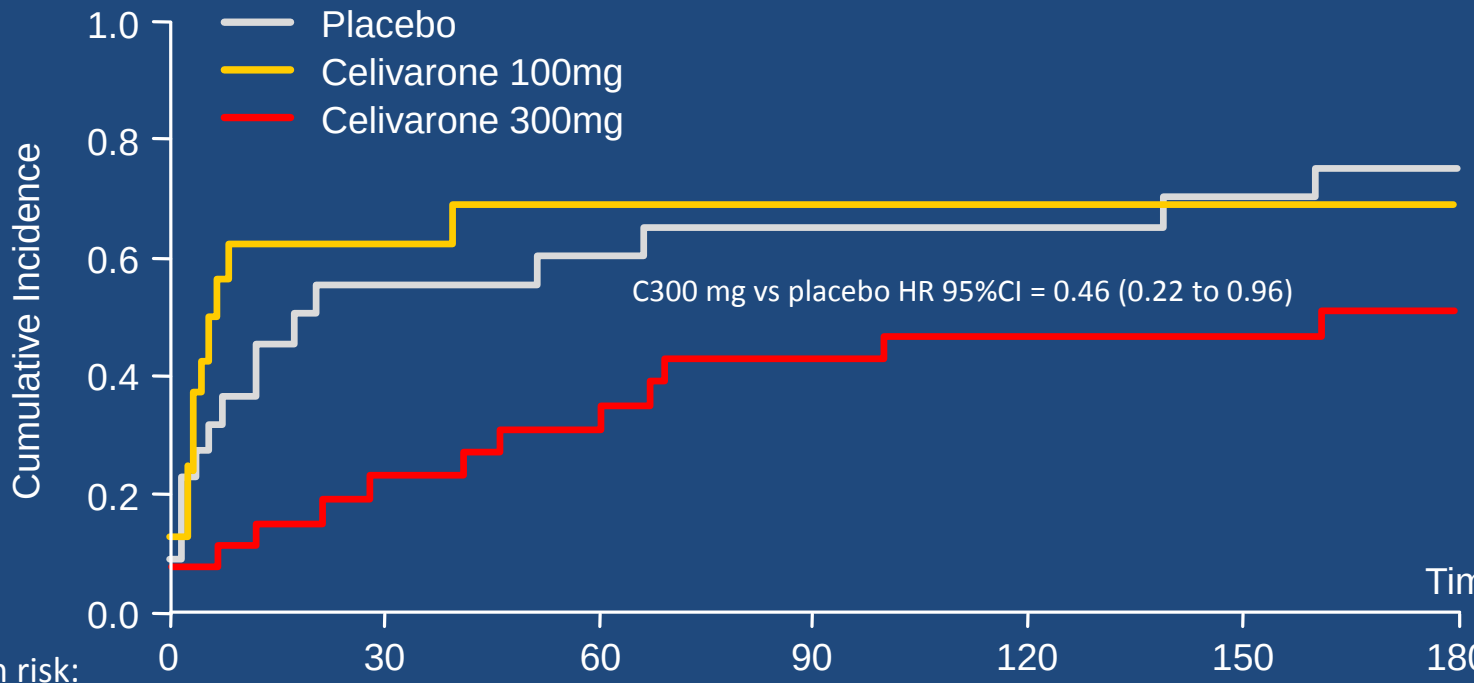
	Celivarone
Mechanism of action (in vitro and preclinical data)	Vaughan Williams Class I to IV Ventricular activity Anti-adrenergic activity
Dosing	Once daily
Drug-drug interactions	Low, based on in vitro CYP profile
Half Life	40-100 hours*
Extra cardiac side effects	Low potential (no iodine, short half life)

ICD-Implantable Cariodverter Defibillator CRT-D- Cardiac Resynchronisation Therapy Defibillator

Gautier et al 2005; J Cardiovasc Pharmacol; Vol 45, No. 2, Feb ; Gautier et al 2004. . J Cardiovasc Pharmacol; Vol 44, No. 2, Aug *Data on file-Clinical Investigator brochure

Rationale for ALPHEE

- ICARIOS post-hoc analysis in patients with last appropriate ICD therapy ≤ 30 days



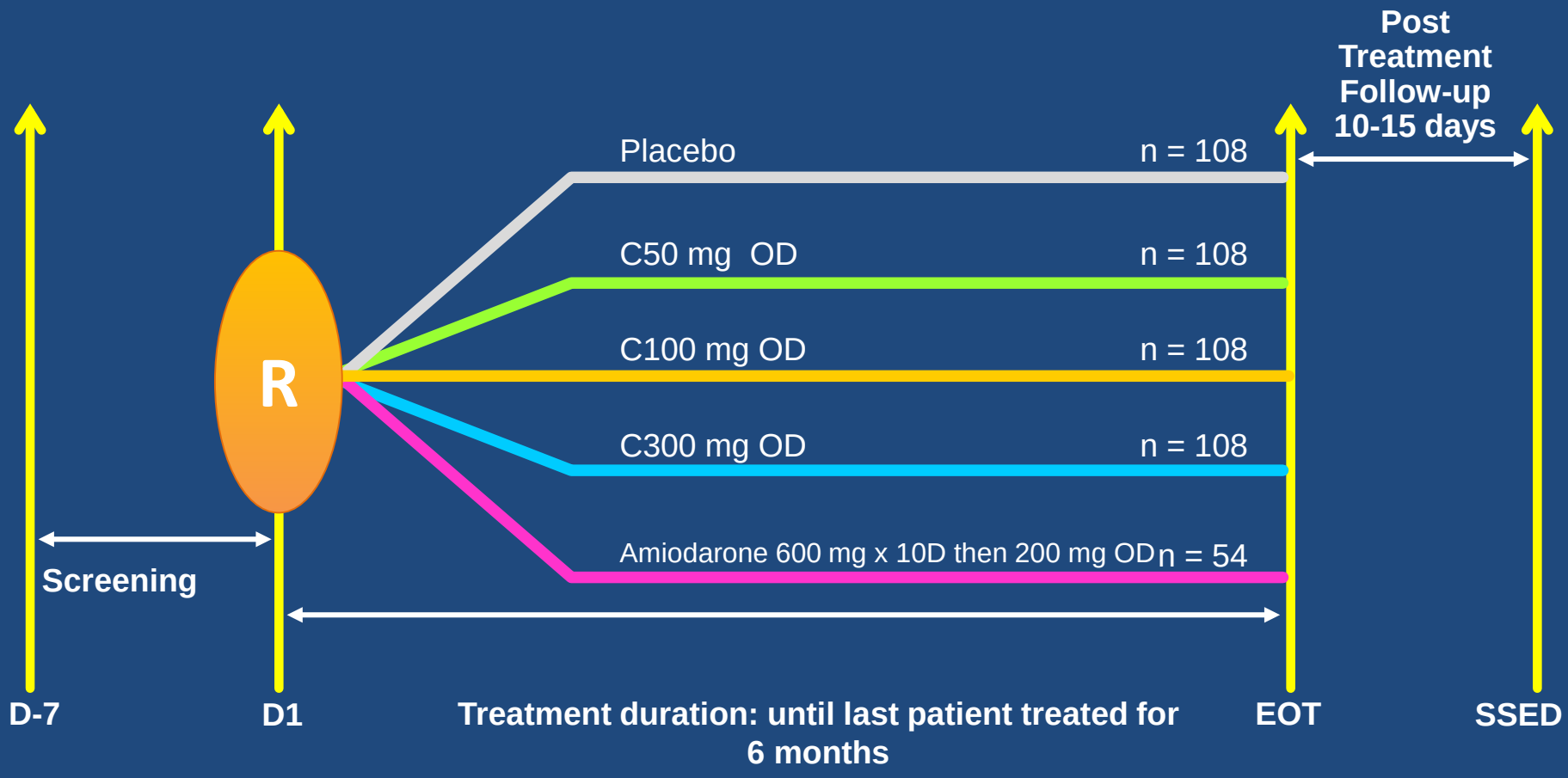
Nb exposed on risk:

Placebo	**22**	**9**	**8**	**7**	**7**	**6**	**5**
Celivarone 100mg	**15**	**5**	**5**	**5**	**5**	**5**	**5**
Celivarone 300mg	**26**	**20**	**18**	**14**	**13**	**13**	**10**

Bertrand Russell

"One of the signs of an approaching nervous breakdown is the belief that one's work is terribly important."

Study Design



D: day
R: Randomization
EOT: End Of Treatment Visit
SSED: Scheduled Study End Date (190 days [up to +14 days] after the randomization of the last patient)

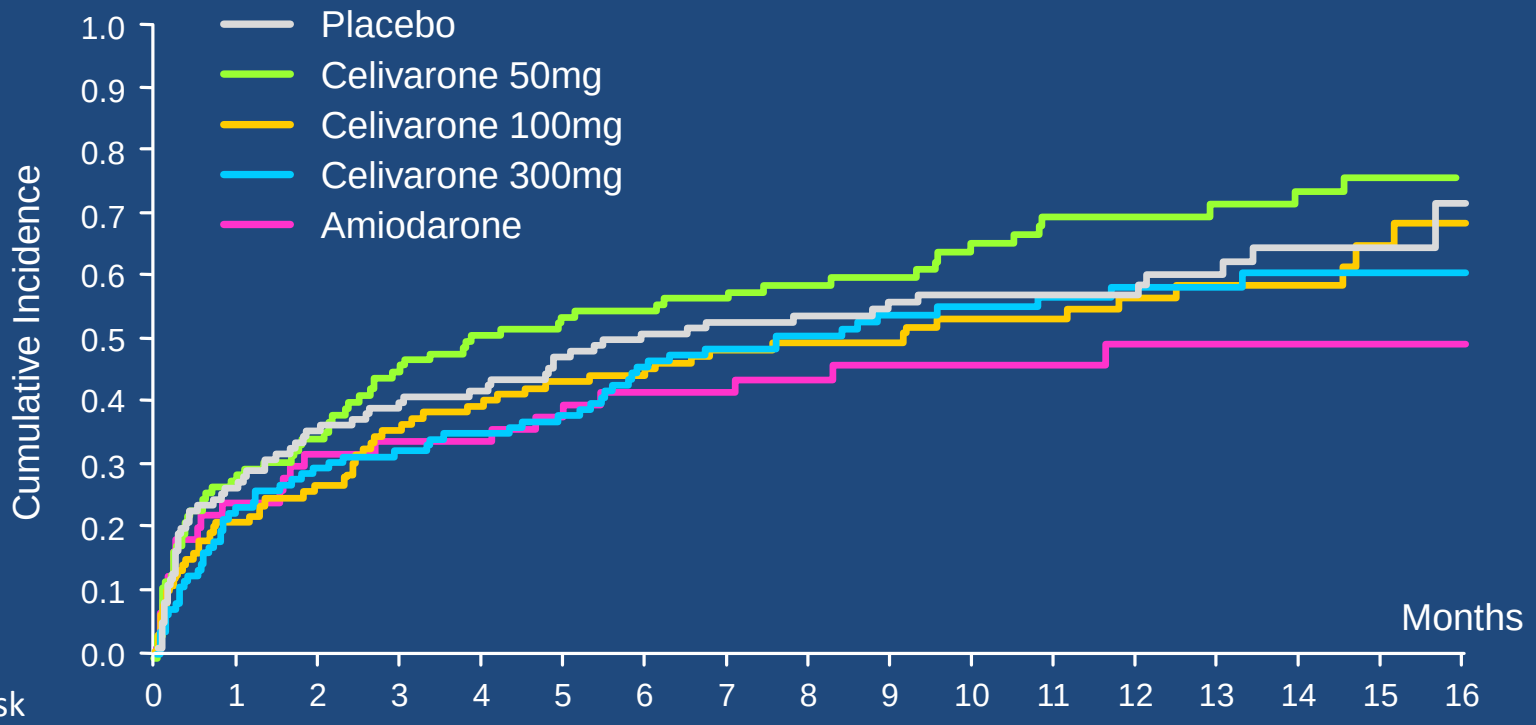
Efficacy Variables

- Primary efficacy variable:
  - VT/VF triggered ICD interventions or sudden death.
    - VT/VF leading to any ICD interventions (ATP or ICD shock) adjudicated by a Central Adjudication Committee (up to 10 episodes/patient)
- Secondary efficacy variable:
  - ICD shocks or death

Sample Size Calculation

- 60% event rate at 6 months expected on placebo (based on ICARIOS and computer simulations)
- 44% RRR in at least one celivarone group vs Placebo
- Global alpha risk = 5% (3 comparisons)
- ≥ *108 pts per group for 85% power*

Primary Endpoint
1st VT/VF Triggering ICD Intervention or Sudden Cardiac Death



Number at Risk

Placebo	**109**	**66**	**54**	**40**	**27**	**9**
Celivarone 50mg	**109**	**58**	**48**	**31**	**19**	**10**
Celivarone 100mg	**102**	**66**	**56**	**40**	**24**	**10**
Celivarone 300mg	**113**	**75**	**57**	**41**	**27**	**8**
Amiodarone	**53**	**34**	**30**	**22**	**15**	**8**

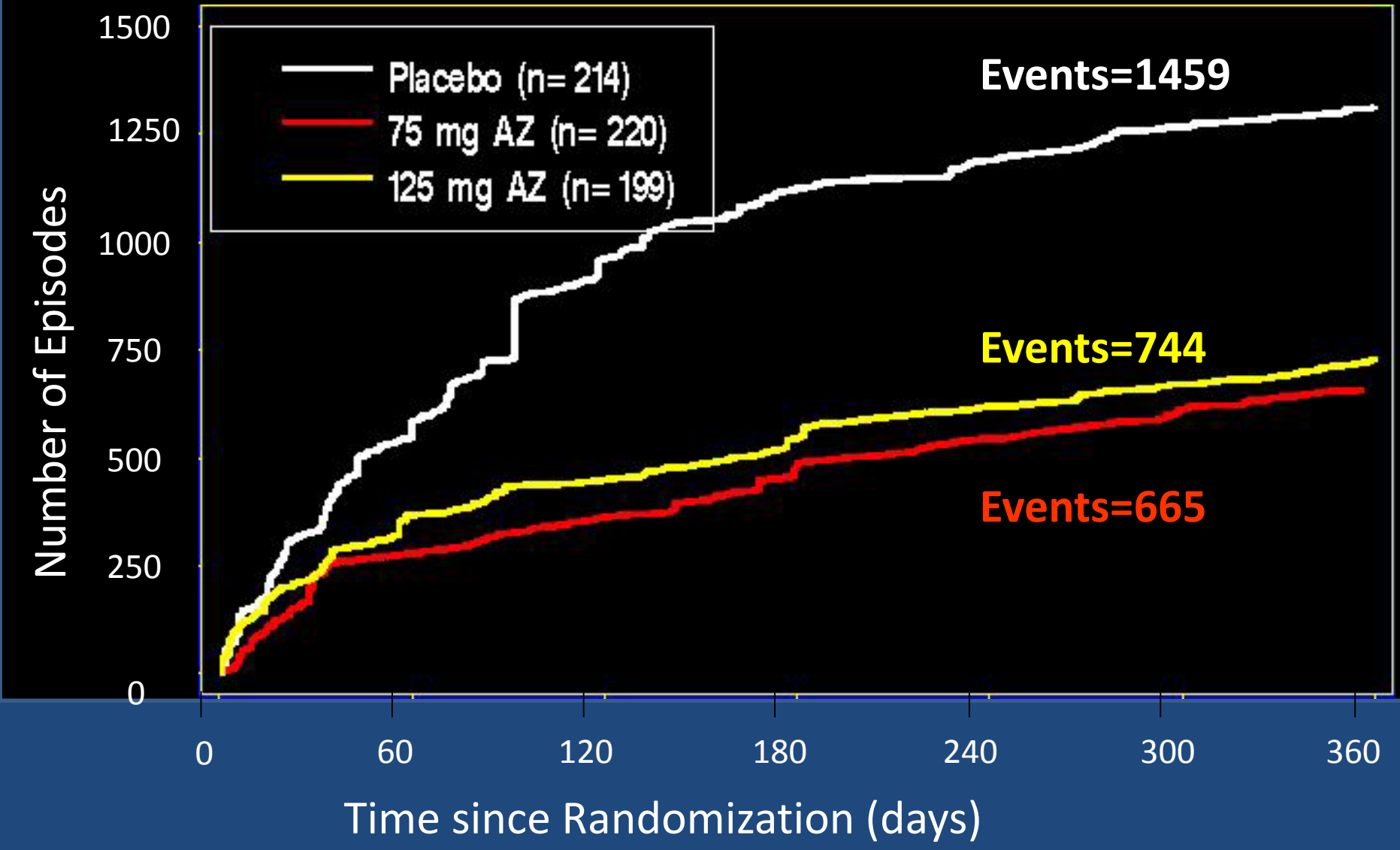
Winston Churchill

"Success is the ability to go from one failure to another with no loss of enthusiasm."

AZIMILIDE DIHYDROCHLORIDE

- Blocks both the rapid (I_{Kr}) and the slow (I_{Ks}) channels
- Produces concentration-dependent QTc prolongation with TDP about 1%
- Long half-life of 114 hours with minimal drug interactions
- Borderline efficacy in preventing PAF
- No increase in mortality post-MI/LVD in ALIVE
- Effective in reducing ICD therapies
  - submitted to FDA for this indication
- Rare agranulocytosis

CUMULATIVE EPISODES OF ALL-CAUSE SHOCKS PLUS SYMPTOMATIC ATP



ADVERSE EVENTS FOR ALL RANDOMIZED

	Placebo n = 214	AZ 75 mg n = 220	AZ 125 mg n = 199
Withdrawn for any reason	**86 (40%)**	**78 (36%)**	**69 (35%)**
Adverse Event (AE)	*46 (22%)*	*43 (20%)*	*42 (21%)*
Patient request	*14 (7%)*	*12 (6%)*	*8 (4%)*
Investigators discretion	*15 (7%)*	*9 (4%)*	*10 (5%)*
QTc prolongation	*0 (0%)*	*3 (1%)*	*2 (1%)*
Other	*11 (5%)*	*11 (5%)*	*7 (4%)*
Patients with AEs	169 (79%)	174 (79%)	153 (77%)
Patients with SAEs	88 (41%)	75 (34%)	91 (46%)
Patients with TdP	**1 (0.5%)**	**2 (1%)**	**3 (2%)**
Patients with neutropenia	**0 (0%)**	**1 (0.5%)**	**0 (0%)**
Death	**7 (3%)**	**6 (3%)**	**7 (4%)**

SHIELD-2

Event-driven, randomized, multi-center, double-blind, placebo-controlled, parallel-group study of the safety and efficacy of a once-daily oral dose of 75 mg of azimilide on the incidence of CV hospitalizations, CV emergency department visits, or death in patients with ICDs and VT/VF.

SHELD-2: Endpoints

Primary

•Time-to first unplanned adjudicated cardiovascular (CV) hospitalisation, CV emergency department (ED) visit or CV death.

Secondary

•Time-to first all-cause adjudicated shock

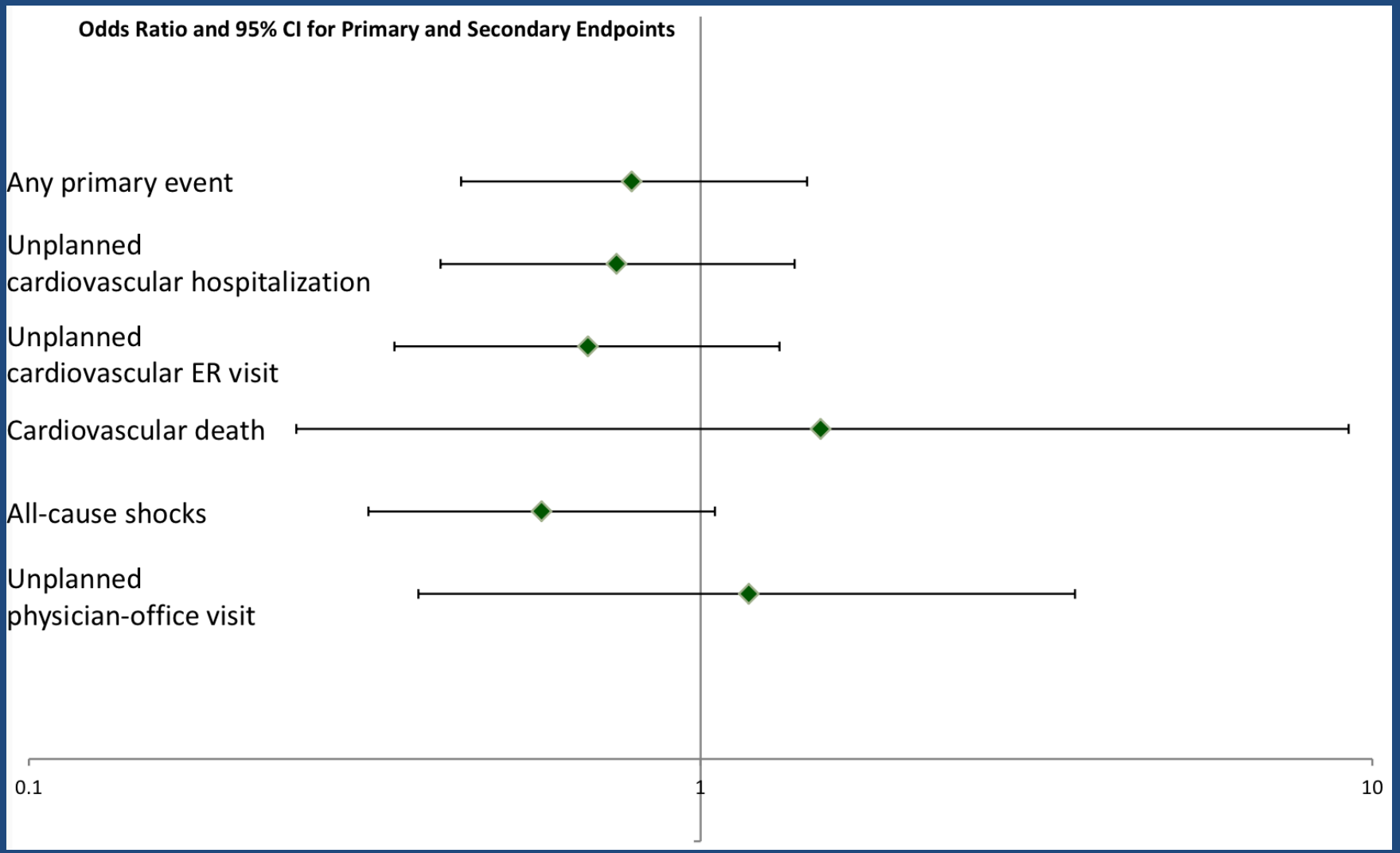
•Time-to first adjudicated outpatient appointment resulting in a change to ICD programming or to medication, as a result of the ICD findings.

Price Cobb

"Some days you're a bug, some days you're a windshield."

SHIELD-2 Results

N=240. 120 randomised to azimilide. 120 randomised to placebo.



RAID

The study aims to determine whether Ranolazine administration will decrease the likelihood of a composite arrhythmia endpoint consisting of ventricular tachycardia or ventricular fibrillation (VT/VF) requiring ICD shocks or death (whichever comes first) in high-risk patients with ICD/CRT-D implanted for primary or secondary prevention of sudden death.

SO WHERE DO WE STAND?

- There are no FDA approved therapies and drugs are not used for primary prevention.
- Most commonly used adjuvant drugs are amiodarone and sotalol, neither of which ever sought regulatory approval.
- Alternative drugs are dofetilide and dronedarone with worse than poor data to support their use.
- Celivarone failed and the azimilide confirmatory trial was stopped for financial reasons.
- Physicians may resort to drug combinations that have been poorly studied but have theoretical advantages.
- Ranolazine has some very interesting POC data and RAID is recruiting. A more selective Ina blocker is in the wings.
- Economic and health care utilization endpoints may be useful but will require careful consideration to make the results interpretable

Robert Frost

“The brain is a wonderful organ. It starts working the moment you get up in the morning and does not stop until you get into the office.”

DEATH ON THE POLE:
A Philip Sarkis Mystery