

**Double Blind Placebo Controlled Dose Ranging Study
Of The Efficacy And Safety Of Celivarone 50, 100 Or
300 Mg OD With Amiodarone As Calibrator For The
Prevention Of ICD Interventions Or Death**

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Concomitant Use of Antiarrhythmic Drug Therapy in ICD Patients

Three main indications:

- ↓ VA in patients receiving frequent shocks
 - 1^o reason for adding AAD in 64%
- ↓ “Inappropriate” shocks
 - 29 % of ICD patients (ST, AF, NSVT)
- ↓ Rate of VT for better hemodynamics and more amenable to ATP or low energy cardioversion

Limited role of AADs in SCD:

- Class I drugs should not be used- ↑risk of SCD and all cause mortality
- B-blockers prevent SCD in CAD and CHF
- Class III drugs treat & prevent VT/VF- variable effect on SCD & all-cause mortality
- Amiodarone - ↓ or ↔risk SCD

Development of new effective AAD desirable

Steinberg JS, et al, Am Heart J. 2001;142(3):520.

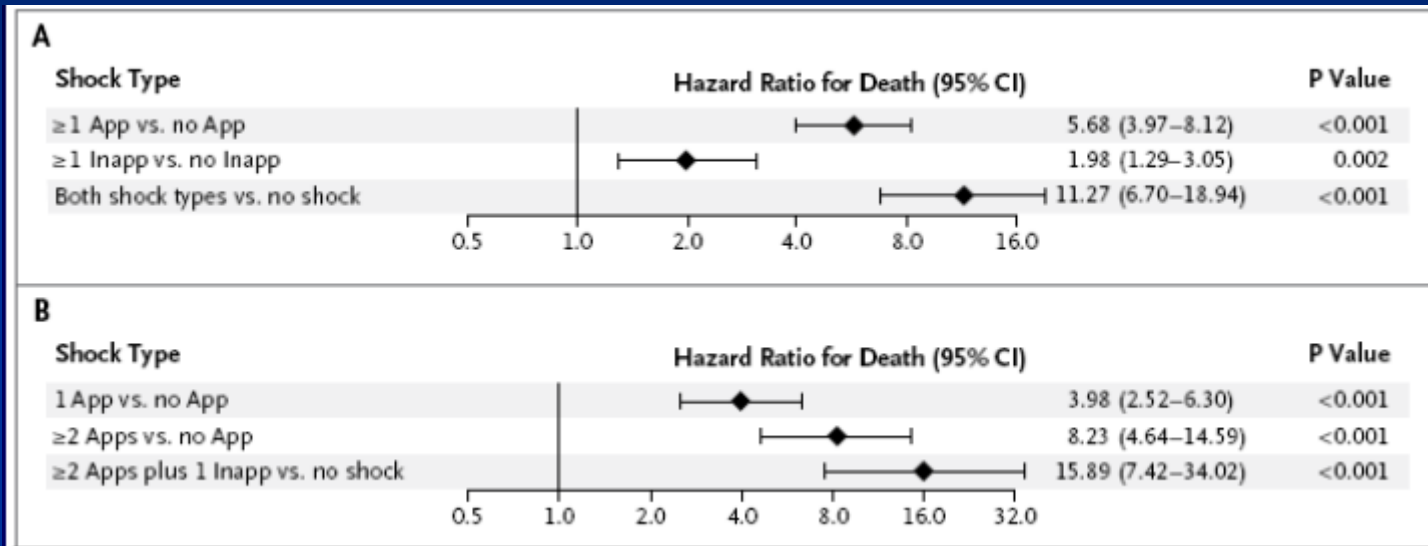
Nanthakumar K, et al. Am Heart J. 2000;139(5):797.

Das MK, Zipes D. J Cardiovasc Pharmacol . 2010;55(5):438-49.

ICD Shocks and Prognosis

SCD-HeFT (ICD group)

N=811 (269 pts received shocks:128 only appr, 87 only inappr, 54 both)



Adjusted for
baseline prognostic
factors
Death due to
Progressive
HF- 42.9%

Possible explanations:

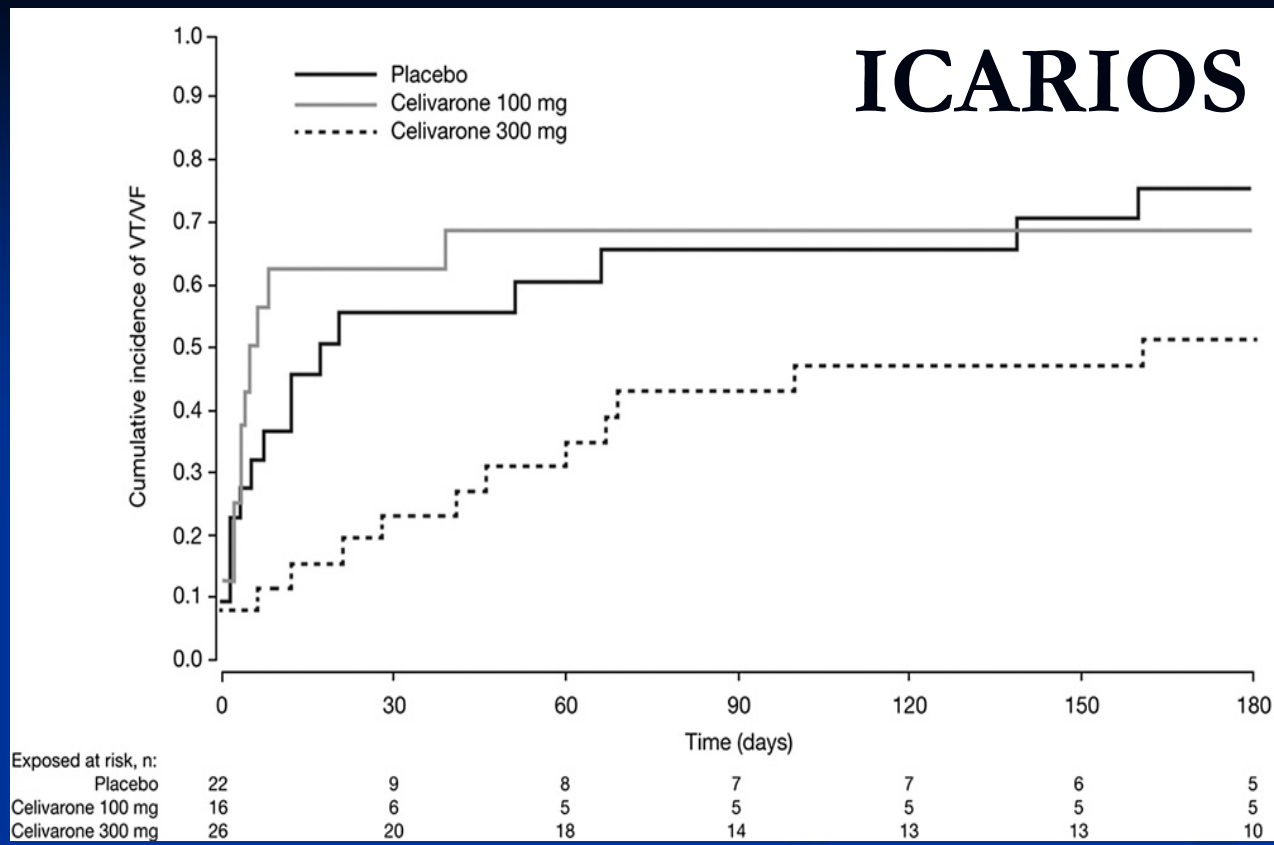
- VT/VF- harbinger of end stage HF
- VT/VF- marker of progressive HD
- Independent impact of shocks (cell damage, negative inotropic effect, activation of signaling pathways)
- Other- post traumatic stress

Adjunctive AADs in Patients with ICDs: Systematic Review

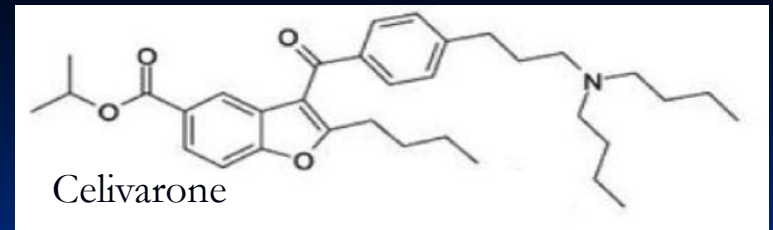
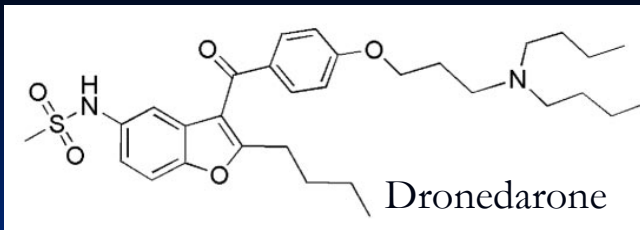
- 8 randomized trials - 1889 patients
- Trial results were divided:
 - Compared class III drugs (sotalol and amiodarone) to beta blockers
 - Compared class III drugs (sotalol, dofetilide and azimilide) to placebo or no AAD
- Systematic review – primary outcome- reduction in all shocks
- Major findings:
 - Amio+ beta blocker significantly ↓ shocks vs. BB alone (HR 0.27, 95% CI 0.14 to 0.52)
 - Sotalol ↓ shocks vs. placebo (HR 0.55, 95% CI 0.4 to 0.78)
 - Sotalol- trend toward ↓ shocks vs. another BB
 - Azimilide or **dofetilide**- nonsignificant ↓ total shocks vs. placebo
 - Appropriate therapies (shocks + ATP) significantly ↓ by azimilide (HR 0.31, 95% CI 0.29 to 0.34)
- Amiodarone- most effective adjunct for reducing total shocks

Additional Concerns with use of AADs in Patients with ICDs

- Efficacy of AADs in prevention of death in ICDs evaluated in multiple primary and secondary prevention trials
 - AADs cannot be relied on to prevent SCD and in “at risk” pts
 - Hence methodology of ALPHEE appropriate- AADs to be tested and used as adjunctive care; use of amiodarone as a “calibrator”
- AADs can :
 - ↑ DFT
 - Slow VT cycle length below cutoff
 - Potential for proarrhythmia due to prolongation of the QT interval
 - ↑ pacing due to changes in sinus rate/AV conduction
- Overall compliance with discharge medications at 1 year- 54%



- N=153 randomized
- 46% ↓ in number of sustained VA episodes requiring ICD therapy in the 300 mg daily group
- ↓ did not achieve statistical significance (P=0.172)



Dronedarone - noniodinated benzofuran compound

■ ANDROMEDA

- Inclusion: Recent decompensated heart failure
- Increased mortality early in trial (8.1% vs 3.8%; HR2.13)

■ PALLAS

- Inclusion: \geq aged 65 years + \geq 1 of the following- CAD; prior CVA; CHF; EF \leq 40%; PAD; or $>$ 75 years + HTN + DM
- \uparrow Composite- CV death, MI, stroke, embolism (2% vs. 0.9%; HR 2.3)
- \uparrow Composite- Death, unplanned CV hosp (7.5% vs. 5.1%; HR 1.5)

■ Poor drug for adjunct in ICD patients

Celivarone (SSR149744C)- noniodinated benzofuran derivative

■ ICARIOS

- \uparrow HF in celivarone groups vs. placebo (P=NS)

■ ALPHEE

- Death 2° HF or cardiogenic shock 2.7-2.9% on celivarone vs. 1.8-1.9% in placebo and amio groups

■ Unexpectedly high mortality/SD in amiodarone group

■ $<$ 100% BB in all study groups (81% in amio group)