# Atrial Antitachycardia Pacing and Managed Ventricular Pacing Reduce the Endpoint Composed by Death, Cardiovascular Hospitalizations and Permanent Atrial Fibrillation Compared to Conventional Dual Chamber Pacing in Bradycardia Patients: Results of the MINERVA Randomized Study

Presenter: Giuseppe Boriani, Univ of Bologna, Policlinico S.Orsola-Malpighi, Bologna, Italy

Authors: Giuseppe Boriani, M.D., Ph.D., Raymond Tukkie, M.D., Lluis Mont, M.D., Helmut Pürerfellner, M.D., Antonis S. Manolis, M.D., Massimo Santini, M.D, Giuseppe Inama, M.D., Paolo Serra, M.D., Silvia Parlanti, M.S., Lorenza Mangoni, M.S., Andrea Grammatico, Ph.D., Luigi Padeletti, M.D., on behalf of the MINERVA Investigators.

Sponsor: Medtronic Inc.

Clinical Registration: clinicaltrials.gov ID NCT00262119

# Background - Clinical Importance

- Over 128,000 people in the US have sinus node dysfunction, which accounts for ≈50% of implantations of pacemakers (AHA 2013 Statistics).
- Atrial fibrillation (AF) is a frequent comorbidity in pacemaker patients and has been associated with compromised hemodynamic function, higher risk of heart failure, stroke, and death.
- Unnecessary RV pacing has long-term deleterious effects that include increased AF risk.
- Enhanced pacing modalities, including strategies to reduce unnecessary RV pacing, have yet to demonstrate benefit in delaying AF disease progression.

# Enhanced Pacing Modalities

- **MVP**
  - **Managed Ventricular Pacing (MVP):** an atrial-based pacing mode that is designed to switch to a dual chamber pacing mode in the presence of AV block and to reduce unnecessary RV pacing.

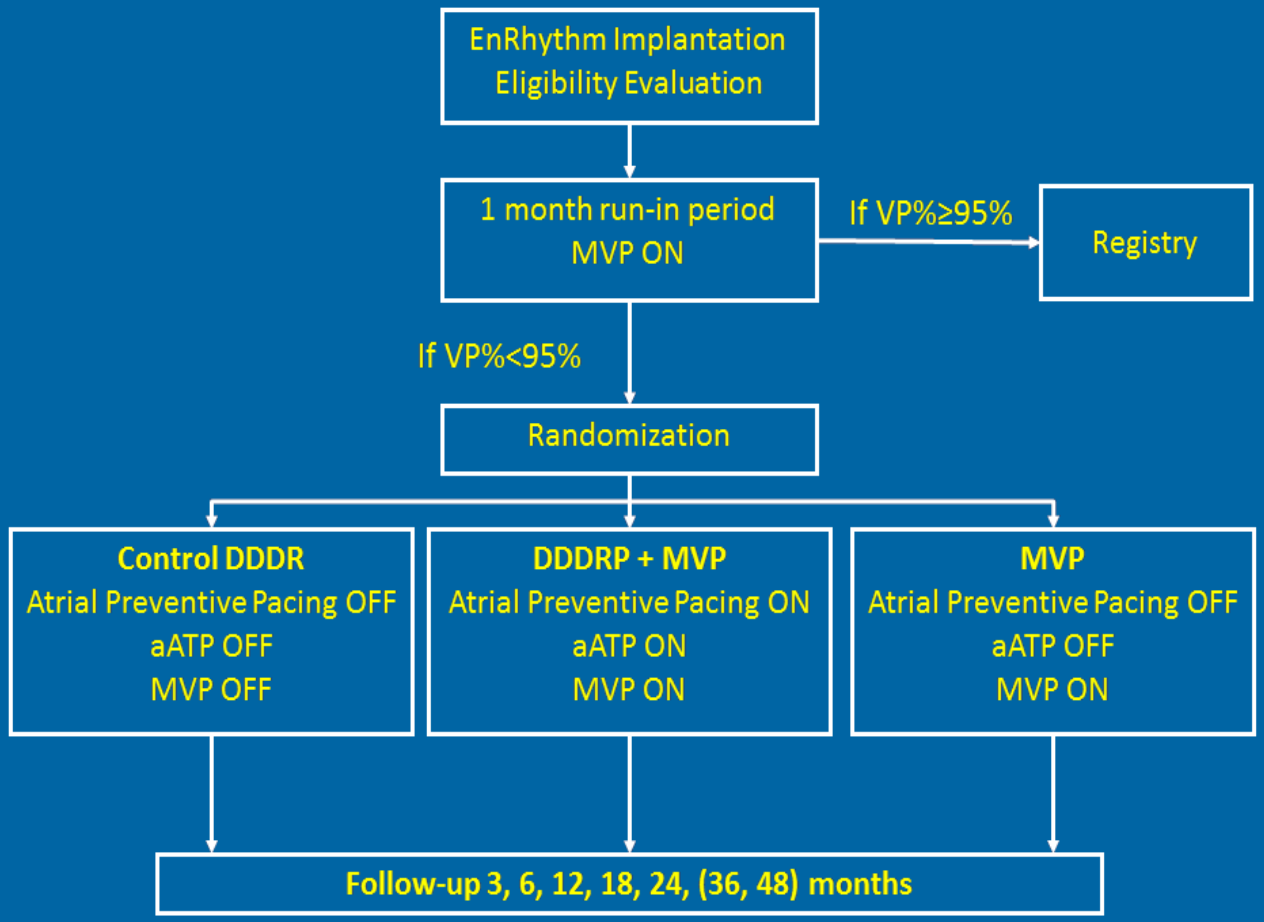
- **DDDRP**
  - **Atrial Prevention Pacing:** three algorithms of **atrial pacing** designed to recognize and respond to potentially proarrhythmic intrinsic events that could trigger an AT/AF episode.
  - **Atrial Antitachycardia Pacing (aATP):** low voltage atrial pacing during regular atrial tachyarrhythmia intended to restore sinus rhythm. Reactive ATP re-arms in the event of changes in cycle length rate or regularity and in the event of long duration episodes.

# Study Aim and Design

**Aim: to evaluate whether DDDRP+MVP or MVP reduces mortality, morbidity, or progression to permanent AF compared with standard dual-chamber pacing.**

Multicenter (63 centers), international, randomized, single blind study with 3 arms enrolling patients with:

- Class I or class II indications for dual-chamber pacing
- Previous atrial tachyarrhythmias
- No history of permanent AF or third-degree AV block



# Primary and Secondary Objectives

**PRIMARY OBJECTIVE:** To assess if DDDRP+MVP is superior to Control DDDR in terms of 2-year incidence of a composite clinical outcome composed by all-cause death*, cardiovascular hospitalizations* or permanent AF [investigator decision not to cardiovert the patient and long duration AF (at least two consecutive follow-up visits with documented AF)]*

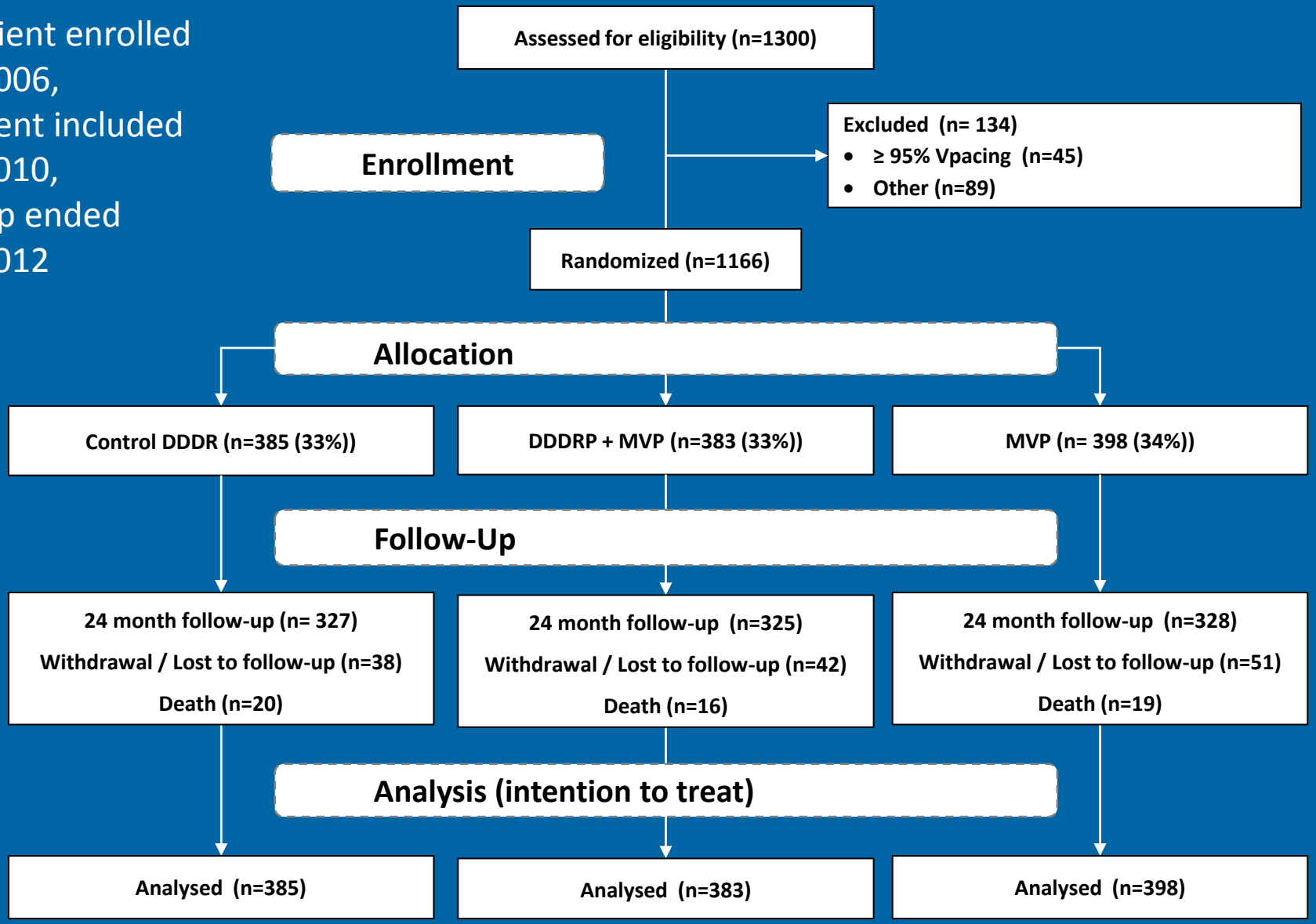
*All events were reported by study investigators according to pre-defined conditions and was then adjudicated by an independent Event Adjudication Committee.

**SECONDARY OBJECTIVES:**

1. Compare primary endpoint in MVP arm vs. Control DDDR arm
2. Compare DDDRP+MVP vs. Control DDDR and MVP vs. Control DDDR in terms of other variables such as incidence of components of the composite endpoint and incidence of persistent AF

# CONSORT Flow Diagram

First patient enrolled in Feb 2006, last patient included in Apr 2010, follow up ended in Apr 2012



# Baseline Patient Characteristics

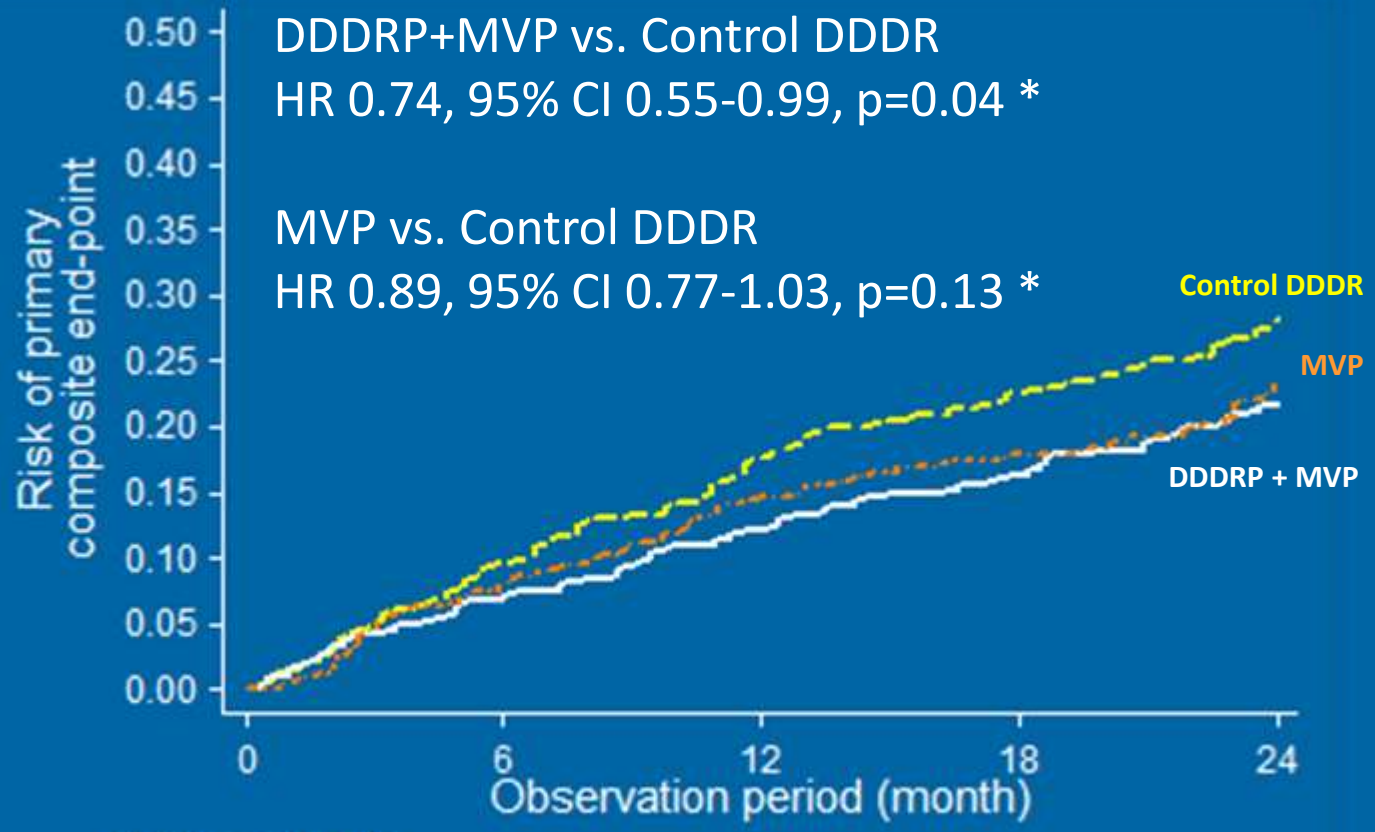
| PARAMETER | STAT | Control DDDR (385 patients) | DDDRP+MVP (383 patients) | MVP (398 patients) |
|---|---|---|---|---|
| Gender (Male) | % | 53 | 45 | 53 |
| Age | Mean (std) | 73 (9) | 74 (9) | 74 (9) |
| History of syncope | % | 26 | 26 | 29 |
| CMP | % | 11 | 11 | 16 |
| Ischemic | % | 26 | 23 | 25 |
| MI | % | 16 | 12 | 14 |
| Hypertension | % | 70 | 73 | 74 |
| HF | % | 9 | 9 | 8 |
| EF (%) | Mean (std) | 56 (9) | 57 (10) | 56 (10) |
| TIA or Stroke | % | 11 | 10 | 9 |
| Diabetes | % | 19 | 15 | 16 |
| Renal disease | % | 6 | 6 | 6 |
| COPD | % | 8 | 9 | 8 |
| AF (vs. AT/AFL) | % | 87 | 83 | 89 |
| PR (ms) | Median (IQ-IIIQ) | 187 (160-205) | 186 (158-200) | 192 (160-210) |
| Implant indication | | | | |
| SND | % | 83 | 82 | 84 |
| I or II degree AV block | % | 7 | 8 | 6 |
| Other | % | 10 | 10 | 10 |
| Medication | | | | |
| Anticoagulants | % | 45 | 44 | 44 |
| AAD class I or III | % | 45 | 43 | 44 |
| Beta-blockers | % | 34 | 29 | 35 |

# Primary Outcome
## (All-Cause Death, CV hospitalizations, or Permanent AF)

Intention-to-treat survival analysis using time to first event

DDDRP+MVP vs. Control DDDR
HR 0.74, 95% CI 0.55-0.99, p=0.04 *

MVP vs. Control DDDR
HR 0.89, 95% CI 0.77-1.03, p=0.13 *




| Number at risk | | | | |
|---|---|---|---|---|
| Control DDDR 385 | 335 | 299 | 275 | 224 |
| DDDRP+MVP 383 | 338 | 311 | 288 | 221 |
| MVP 398 | 350 | 318 | 295 | 228 |

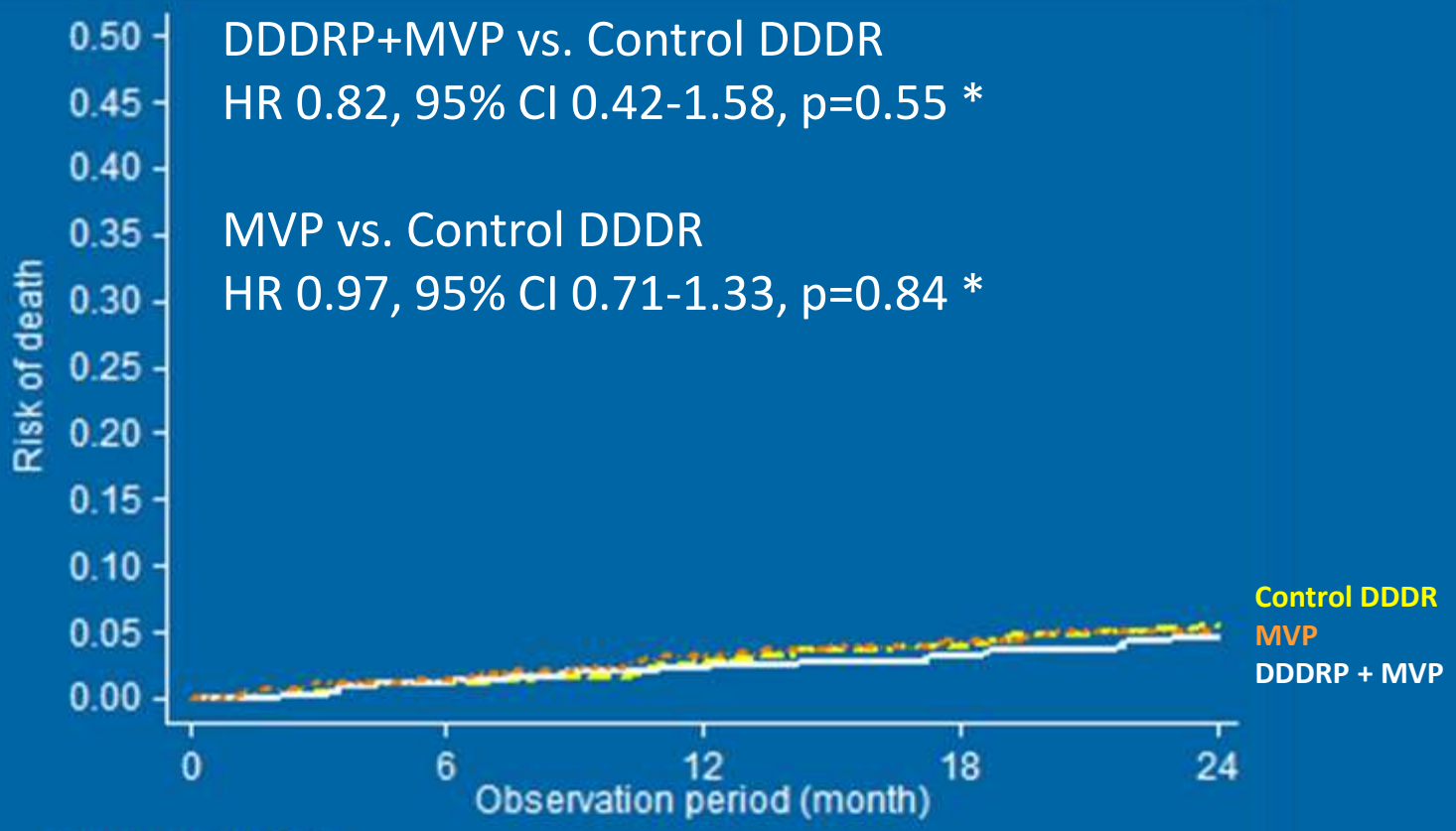
*After adjustment for gender HR 0.73, p=0.04, and HR 0.89, p=0.12, respectively

# All-Cause Death

Intention-to-treat survival analysis using time to first event

DDDRP+MVP vs. Control DDDR
HR 0.82, 95% CI 0.42-1.58, p=0.55 *

MVP vs. Control DDDR
HR 0.97, 95% CI 0.71-1.33, p=0.84 *




| Number at risk | | | | |
|---|---|---|---|---|
| Control DDDR 385 | 366 | 352 | 340 | 288 |
| DDDRP+MVP 383 | 360 | 346 | 334 | 269 |
| MVP 398 | 375 | 360 | 342 | 282 |

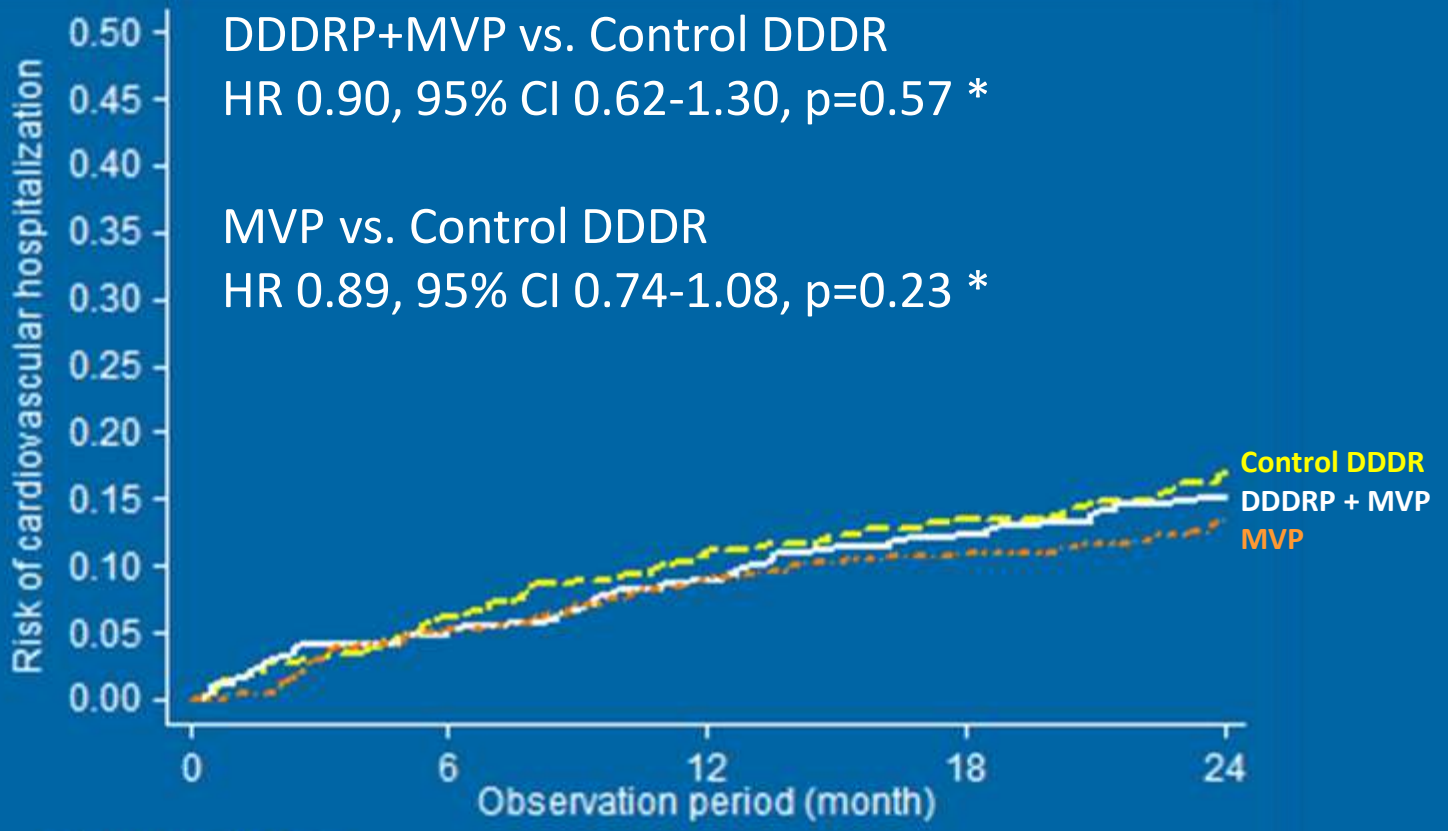
*No change after adjustment for gender

# CV Hospitalizations

Intention-to-treat survival analysis using time to first event

DDDRP+MVP vs. Control DDDR
HR 0.90, 95% CI 0.62-1.30, p=0.57 *

MVP vs. Control DDDR
HR 0.89, 95% CI 0.74-1.08, p=0.23 *




| Number at risk | | | | | |
|---|---|---|---|---|---|
| Control DDDR | 385 | 344 | 314 | 296 | 241 |
| DDDRP+MVP | 383 | 342 | 316 | 293 | 226 |
| MVP | 398 | 355 | 327 | 306 | 244 |

*No change after adjustment for gender

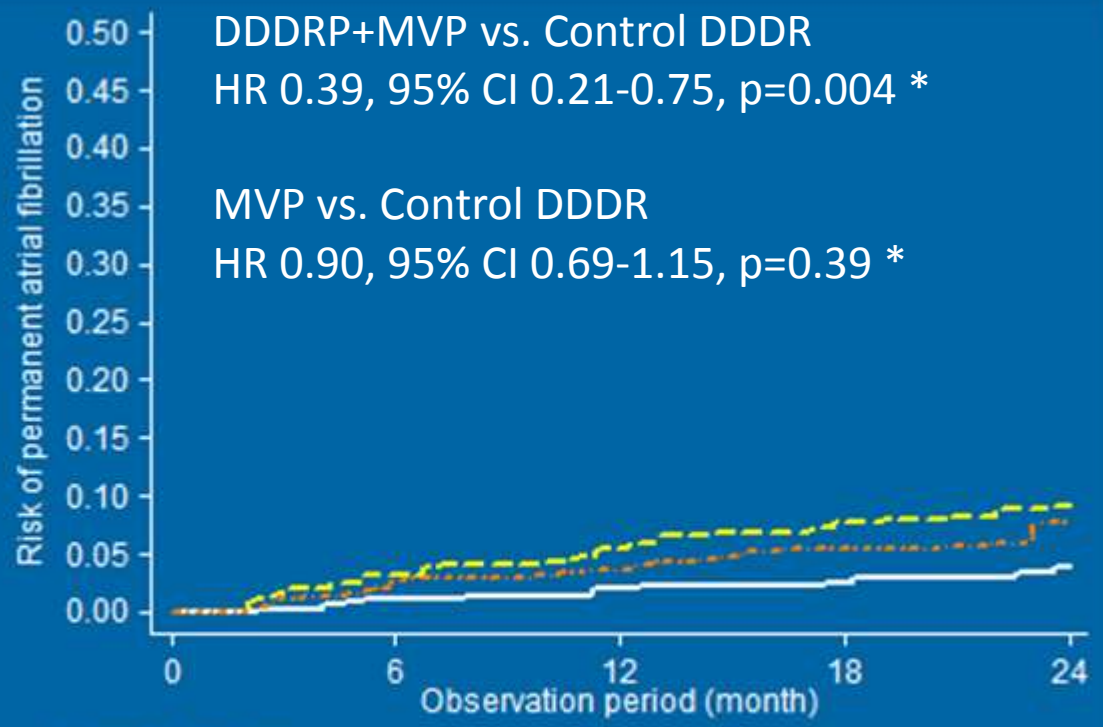
MINERVA AHA 2013

# Permanent AF

## Intention-to-treat survival analysis using time to first event

DDDRP+MVP vs. Control DDDR
HR 0.39, 95% CI 0.21-0.75, p=0.004 *

MVP vs. Control DDDR
HR 0.90, 95% CI 0.69-1.15, p=0.39 *




| Number at risk | | | | |
|---|---|---|---|---|
| Control DDDR 385 | 355 | 336 | 316 | 265 |
| DDDRP+MVP 383 | 356 | 339 | 325 | 260 |
| MVP 398 | 366 | 347 | 325 | 260 |

*No change after adjustment for gender

- Atrial cardioversion occurred less frequently in the DDDRP+MVP vs. Control DDDR (49% relative reduction, p=0.001)
- AF-related hospitalizations and ER visits occurred less frequently in the DDDRP+MVP vs. Control DDDR (52% relative reduction, p<0.0001)

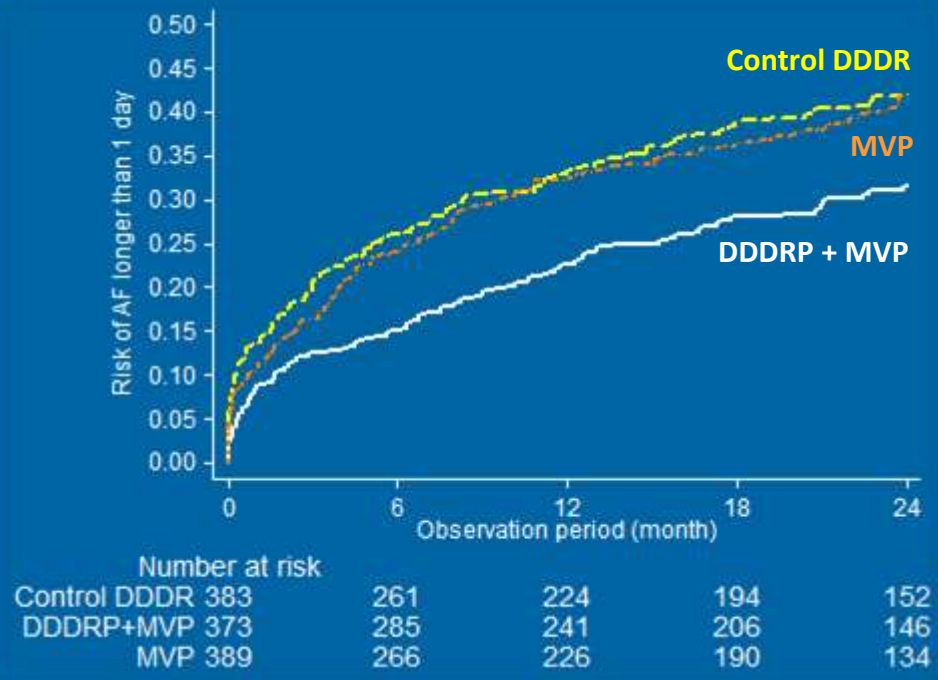
# Incidence of AF

Intention-to-treat survival analysis using time to first event

## >1 Day

DDDRP+MVP vs. Control DDDR
HR 0.66, 95% CI 0.52-0.85, p=0.001*

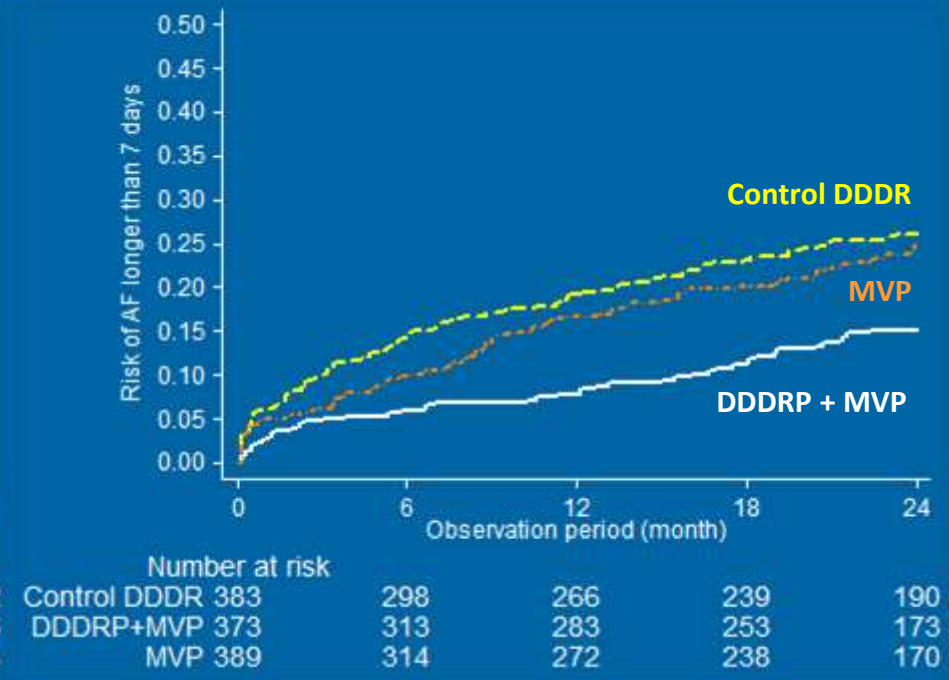
MVP vs. Control DDDR
HR 0.98, 95% CI 0.87-1.10, p=0.71*




## >7 Days

DDDRP+MVP vs. Control DDDR
HR 0.52, 95% CI 0.36-0.73, p<0.001*

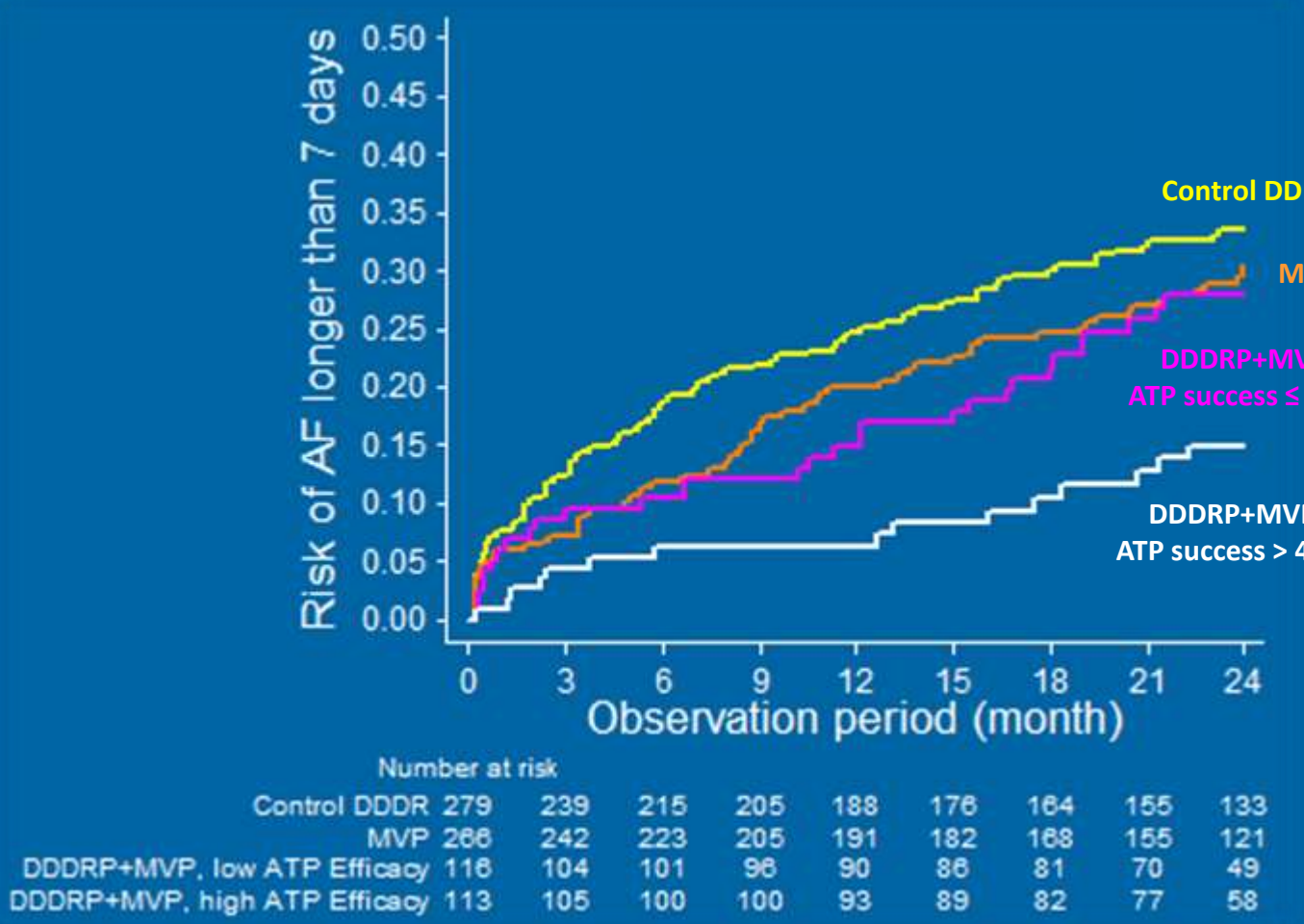
MVP vs. Control DDDR
HR 0.95, 95% CI 0.82-1.10, p=0.49*




*No change after adjustment for gender

# Risk of AF>7 days and aATP efficacy

Median (25th-75th percentile) aATP efficacy: 43% (17%-62%)




Number at risk

| | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| Control DDDR | 279 | 239 | 215 | 205 | 188 | 176 | 164 | 155 | 133 |
| MVP | 266 | 242 | 223 | 205 | 191 | 182 | 168 | 155 | 121 |
| DDDRP+MVP, low ATP Efficacy | 116 | 104 | 101 | 96 | 90 | 86 | 81 | 70 | 49 |
| DDDRP+MVP, high ATP Efficacy | 113 | 105 | 100 | 100 | 93 | 89 | 82 | 77 | 58 |

Log Rank p value comparing
**Control DDDR** vs.

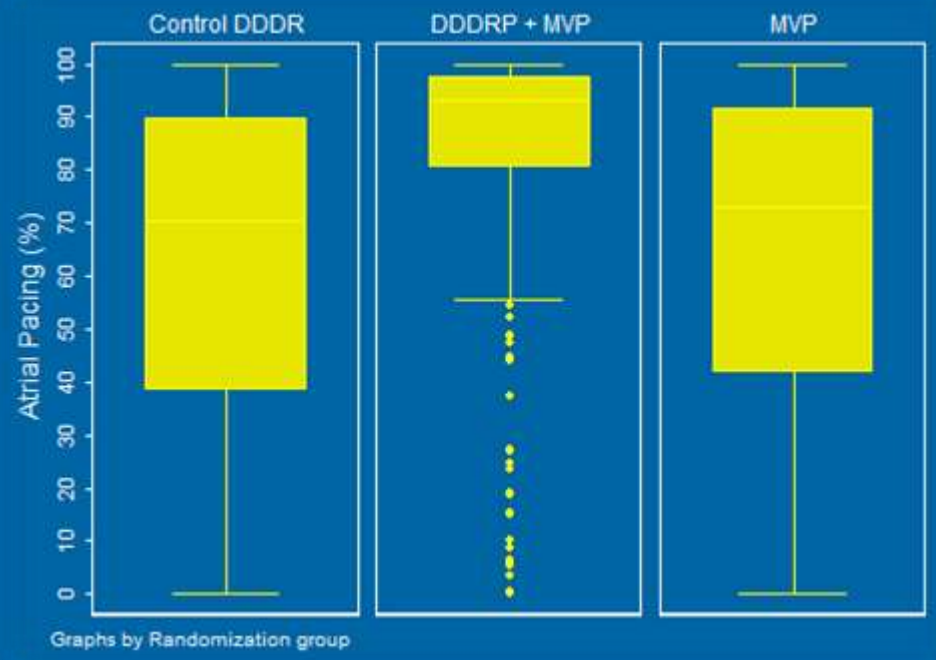
**MVP** **p=0.274**

**DDDRP+MVP (ATP success ≤ 43%) p=0.193**

**DDDRP+MVP (ATP success > 43%) p<0.001**

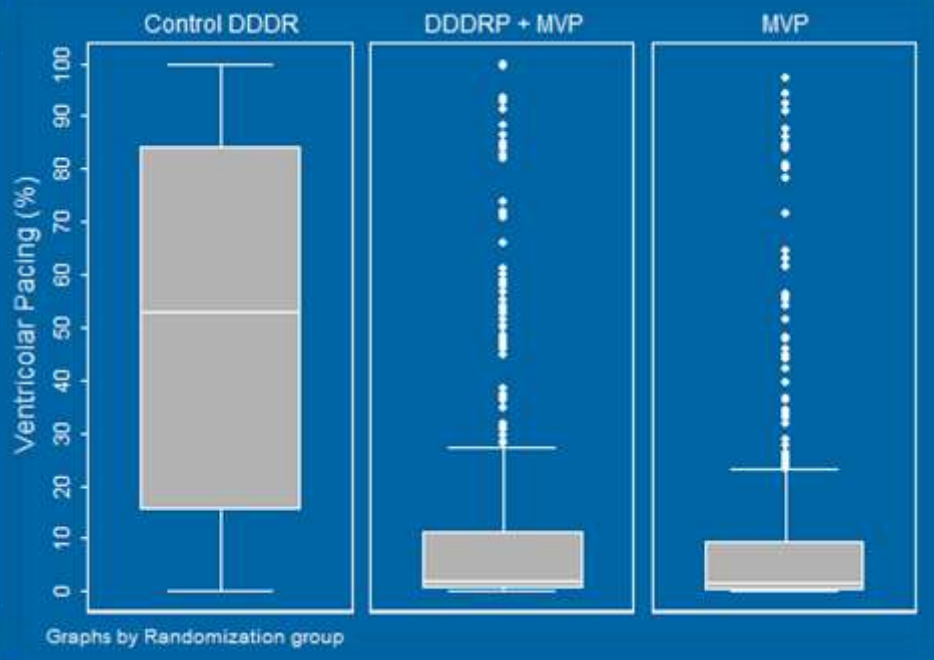
Note: since ATP treated only episodes longer than 2 minutes, to compare the different groups in a correct and balanced way, this analysis considered only patients with at least 2 minutes of AF

# % of Atrial Pacing




| AP% | Control DDDR n=374 | DDDRP + MVP n=370 | p-value Control DDDR vs DDDRP +MVP | MVP n=392 | p-value Control DDDR vs MVP |
|---|---|---|---|---|---|
| **Median (Q1-Q3)** | 70% (39%-90%) | 93% (81%-97%) | <0.001 | 73% (42%-92%) | 0.66 |

# % of Ventricular Pacing




| VP% | Control DDDR n=374 | DDDRP + MVP n=370 | p-value Control DDDR vs DDDRP + MVP | MVP n=392 | p-value Control DDDR vs MVP |
|---|---|---|---|---|---|
| **Median (Q1-Q3)** | 53% (15%-84%) | 2% (0%-11%) | <0.001 | 1% (0%-9%) | <0.001 |

# Conclusions

- In patients with bradycardia, previous atrial tachyarrhythmias and no history of permanent AF or third-degree atrioventricular block, DDDRP+MVP proved superior to standard dual-chamber pacing, in that it led to a significant **26% relative risk reduction** in the combined endpoint of mortality, cardiovascular hospitalizations, and permanent AF.

- DDDRP+MVP positive effect was mainly driven by a significant reduction in the progression of atrial tachyarrhythmias to permanent AF (**61% relative risk reduction**) over 2 years of follow- up.

- For DDDRP+MVP the number needed to treat (NNT) to prevent evolution to permanent AF over 2 years is 20 patients.