7° AP-HRS Scientific Session, New Dehli, India - Oct 29 to Nov 1, 2014

# Causal relationship between AF & stroke

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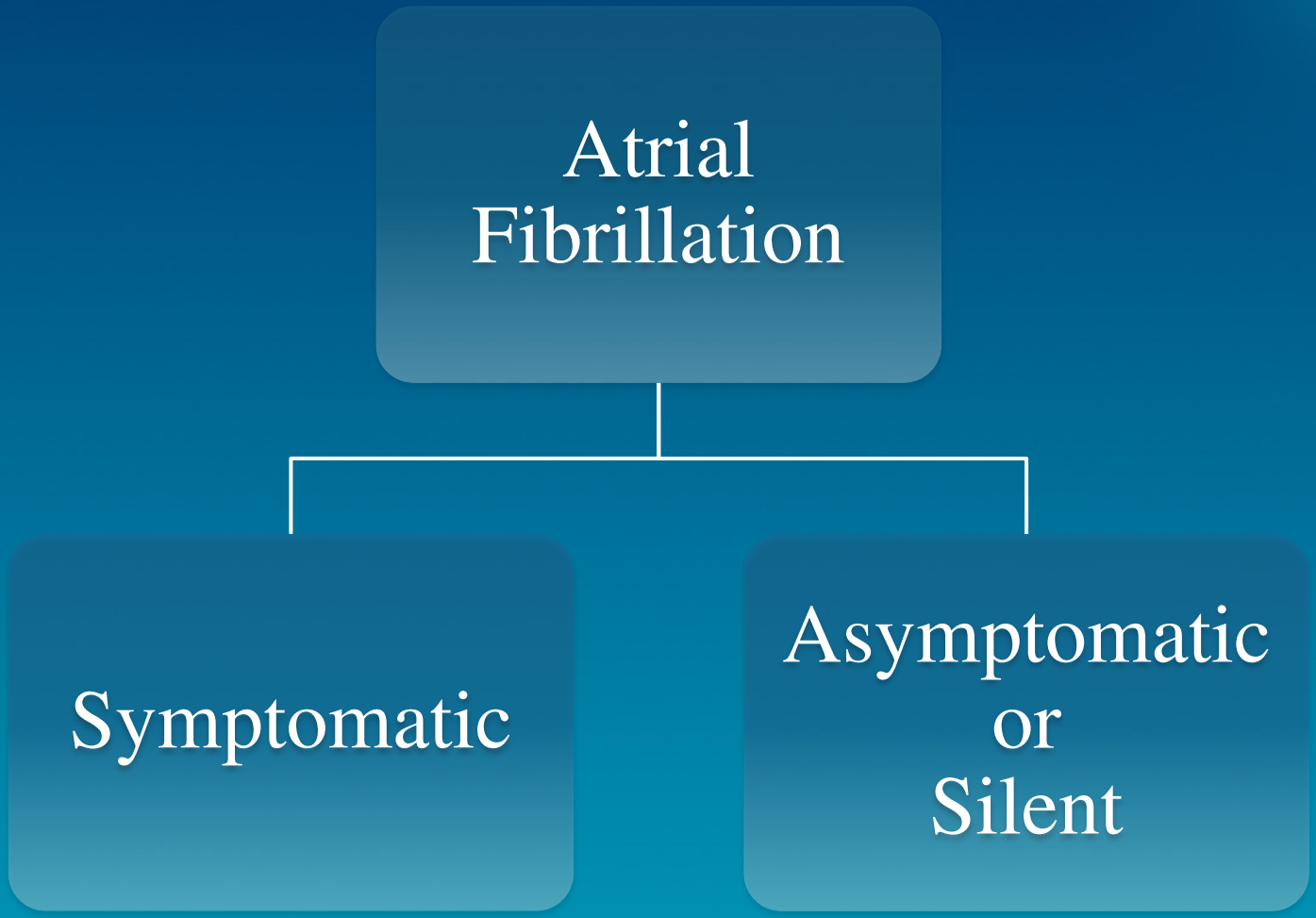
# AF & Symptoms

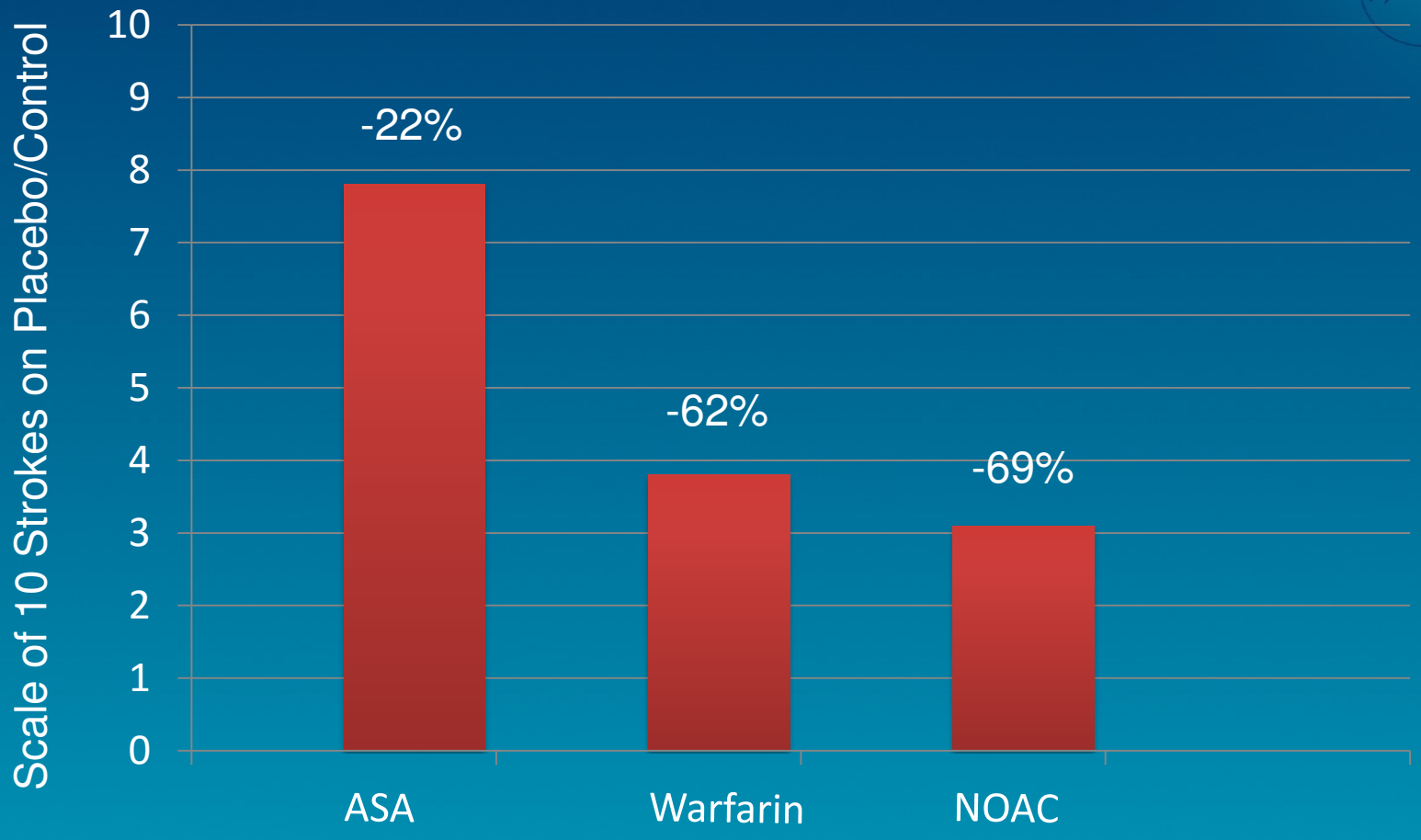


# Risk of Thromboembolic Events / Stroke

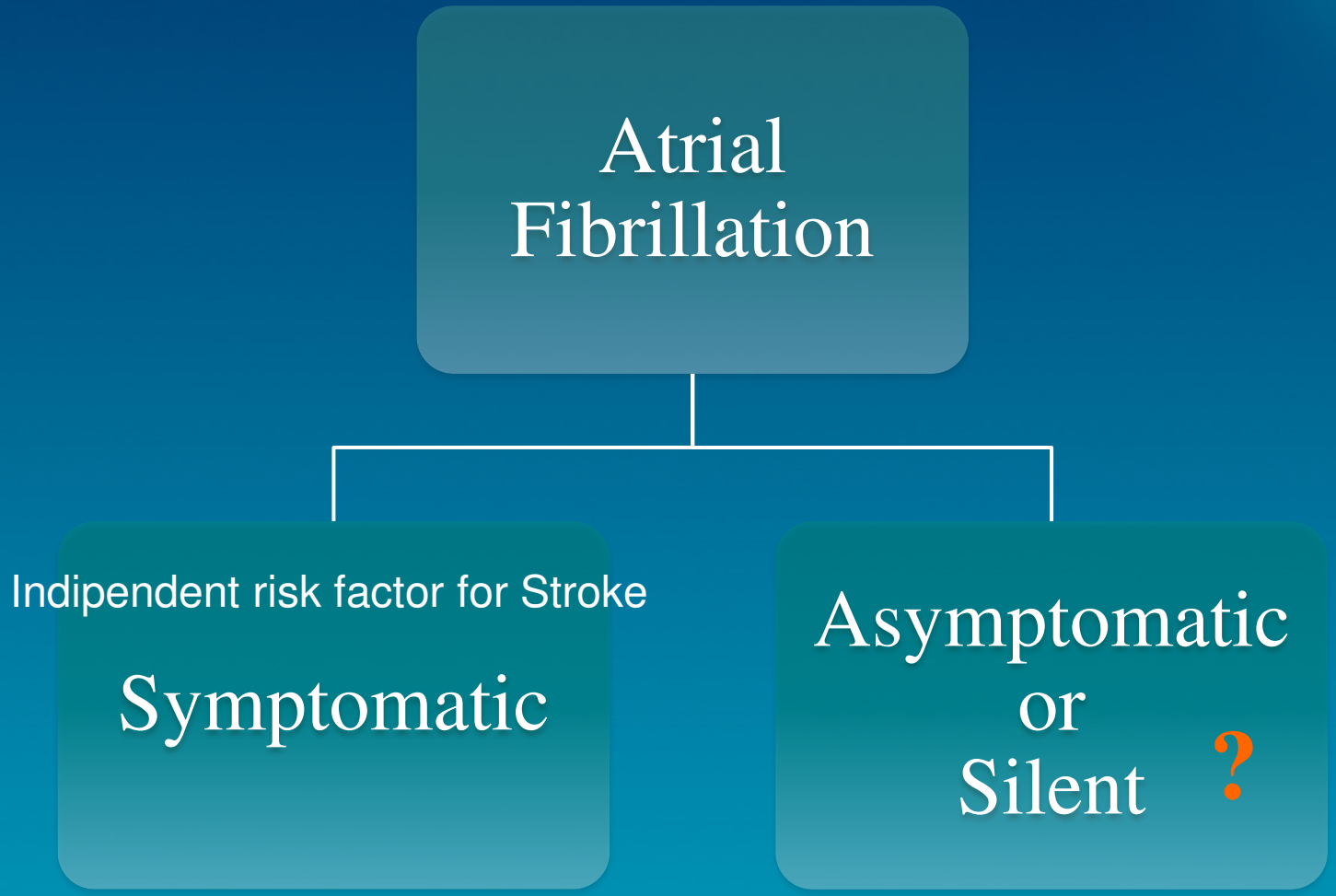
**AFib** → **five-fold ↑** → **Controls**

**(The SPAF Investigators. Ann Intern Med 1992; 116: 1 – 5)**

# Stroke risk reductions from randomized trials of antithrombotic agents in atrial fibrillation.



# AF & Risk of Stroke



# Asymptomatic AF / Detection Methods

## Intermittent AF monitoring

- Standard-12 lead ECG
- 24-h / 7-d Holter monitoring
- In-hospital telemetry
- Mobile continuous outpatient telemetry
- Event recorder / Intermittent TTEM

## Continuous AF monitoring

- PM - ICD Device memory
- External & Implantable loop recorder

# EURObservational Research Programme-AF (EORP-AF) Pilot General Registry

| | Total | EHRA I (%) | EHRA II (%) | EHRA III (%) | EHRA IV (%) |
|---|---|---|---|---|---|
| N° of Patients | 3119 | 1237 **(39.7%)** | 963 **(30.9%)** | 746 (23.9%) | 173 (5.5%) |

Boriani G et al. Am J Med. 2015 May;128(5):509-18

# Prevalence of Asymptomatic AF

| Clinical Settings | Percent |
|---|---|
| Incidental finding at standard ECG<br>ECG | **16-25** |
| Pts treated with AADs<br>TTEM | **56-70** |
| PM – ICD recipients<br>Device memory | **51-74** |
| Pts with criptogenetic ischemic stroke<br>HM - ILR | **0-42** |
| Pts after AF ablation<br>HM - MCOT - PM/ICD - ILR | **0-31** |

Raviele A. CircArrhythmElectrophysiol 2015; 8: 249-251

# Silent AF / Main Issues

- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

**Table 4** Summary of studies on AF detected by dual-chamber cardiac implantable electronic devices and thromboembolic risk

| Year | Trial | No. of patients | Duration of follow-up | Atrial rate cutoff | AF burden threshold | Hazard ratio for TE event | TE event rate (below vs above AF burden threshold) |
|---|---|---|---|---|---|---|---|
| 2003 | Ancillary MOST[47] | 312 | 27 months (median) | >220 bpm | 5 minutes | 6.7 ($P = .020$) | 3.2% overall (1.3% vs 5%) |
| 2005 | Italian AT500 Registry[49] | 725 | 22 months (median) | >174 bpm | 24 hours | 3.1 ($P = .044$) | 1.2% annual rate |
| 2009 | Botto et al[50] | 568 | 1 year (mean) | >174 bpm | $CHADS_2$ + AF burden | N/A | 2.5% overall (0.8% vs 5%) |
| 2009 | TRENDS[51] | 2486 | 1.4 years (mean) | >175 bpm | 5.5 hours | 2.2 ($P = .060$) | 1.2% overall (1.1% vs 2.4%) |
| 2012 | Home Monitor CRT[52] | 560 | 370 days (median) | >180 bpm | 3.8 hours | 9.4 ($P = .006$) | 2.0% overall |
| 2012 | ASSERT[31] | 2580 | 2.5 years (mean) | >190 bpm | 6 minutes | 2.5 ($P = .007$) | (0.69% vs 1.69%) |

AF = atrial fibrillation; TE = thromboembolic event.

Glotzer TV et al. Heart Rhythm 2014; Epub before Print

# Silent AF / Significance

- It is not yet known what is the length of asymptomatic AF episodes or the amount of asymptomatic AF burden that convey a substantial risk.

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# Silent AF / Significance

- The duration of the longest episode and the burden of asymptomatic AF that are the best predictors for subsequent stroke are still matter of debate and need to be assessed by future studies

# Silent AF / Main Issues

- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

# Silent AF & Stroke

- Direct cause of stroke ?
- Marker of an increased risk ?

**Table 5** Temporal relationship of device-detected AF to thromboembolic events

| Year | Trial | No. of patients with TE event | Definition of AF episode | Any AF detected before TE event | AF detected only after TE event | No AF in 30 days before TE event | Any AF in 30 days before TE event |
|---|---|---|---|---|---|---|---|
| 2011 | TRENDS[53] | 40 | 5 minutes | 20/40 (50%) | 6/40 (15%) | 29/40 (73%) | 11/40 (27%) |
| 2014 | ASSERT[54] | 51 | 6 minutes | 18/51 (35%) | 8/51 (16%) | 47/51 (92%) | 4/51 (8%) |
| 2014 | IMPACT[55] | 69 | 36/48 atrial beats ≥200 bpm | 20/69 (29%) | 9/69 (13%) | 65/69 (94%) | 4/69 (6%) |

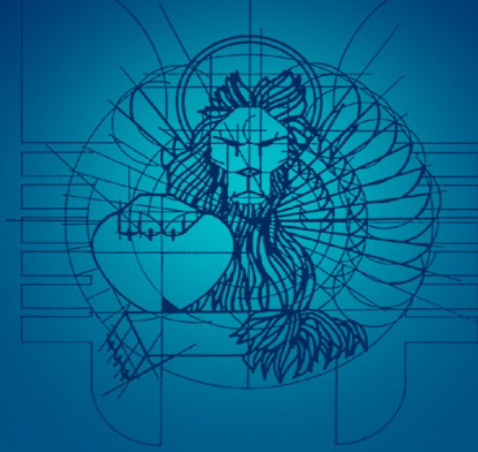
AF = atrial fibrillation; TE = thromboembolic event.

Glotzer TV et al. Heart Rhythm 2014; Epub before Print

# Silent AF & Stroke

- These results indicate that a proximate temporal relationship does not exist between asymptomatic AF and stroke occurrence and that silent AF is not the direct cause of the stroke in the majority of patients with device-detected AF.
- They also call into question our current understanding of how AF causes embolic events.

# Silent AF & Stroke



- It is likely that multiple mechanisms contribute to stroke in patients with asymptomatic AF.
- In some cases stroke may due to stasis from an actual AF episode; in other cases to chronic atrial and endothelial changes caused by multiple prior AF episodes; in other more cases to non-AF mechanisms

# Silent AF & Stroke

- In these latter cases, AF probably represents simply a marker of increased stroke from any cause because of its relationship to other comorbidities, such as presence of heart failure, hypertension, diabetes mellitus, occult atrial myopathy, endothelial dysfunction, and/or other vascular disease risk factors summarized by the CHA2DS2-VASc scoring system.

# Silent AF / Main Issues

- **Clinical / prognostic significance**
- **Causal relationship with stroke**
- **Therapeutical implications**

# Asymptomatic AF / Therapy

- Need for Oral Anticoagulation

# Asymptomatic AF / Need for OAC

- Detection of asymptomatic AF especially in PM-ICD recipients and in patients with critpogenetic stroke theoretically could allow for early initiation of anticoagulation, assuming that device-detected AF imparts a stroke risk similar to symptomatic AF.
- However, whether pts with subclinical AF have to be anticoagulated currently remains an unanswered question.

# Asymptomatic AF / Need for OAC

- Indeed, no prospective randomized trials using OAC have been performed in this field so far.
- Furthermore, the lack of proximate temporal relationship between asymptomatic AF and stroke observed in the majority of patients in the ASSERT, TRENDS, and IMPACT trials suggests that oral OAC may not be systematically required for stroke prevention in asymptomatic patients

# Randomized trial of atrial arrhythmia monitoring to guide anticoagulation in patients with implanted defibrillator and cardiac resynchronization devices

David T. Martin[1], Malcolm M. Bersohn[2], Albert L. Waldo[3], Mark S. Wathen[4], Wassim K. Choucair[5], Gregory Y.H. Lip[6], John Ip[7], Richard Holcomb[8], Joseph G. Akar[9], and Jonathan L. Halperin[10]*, on behalf of the IMPACT Investigators

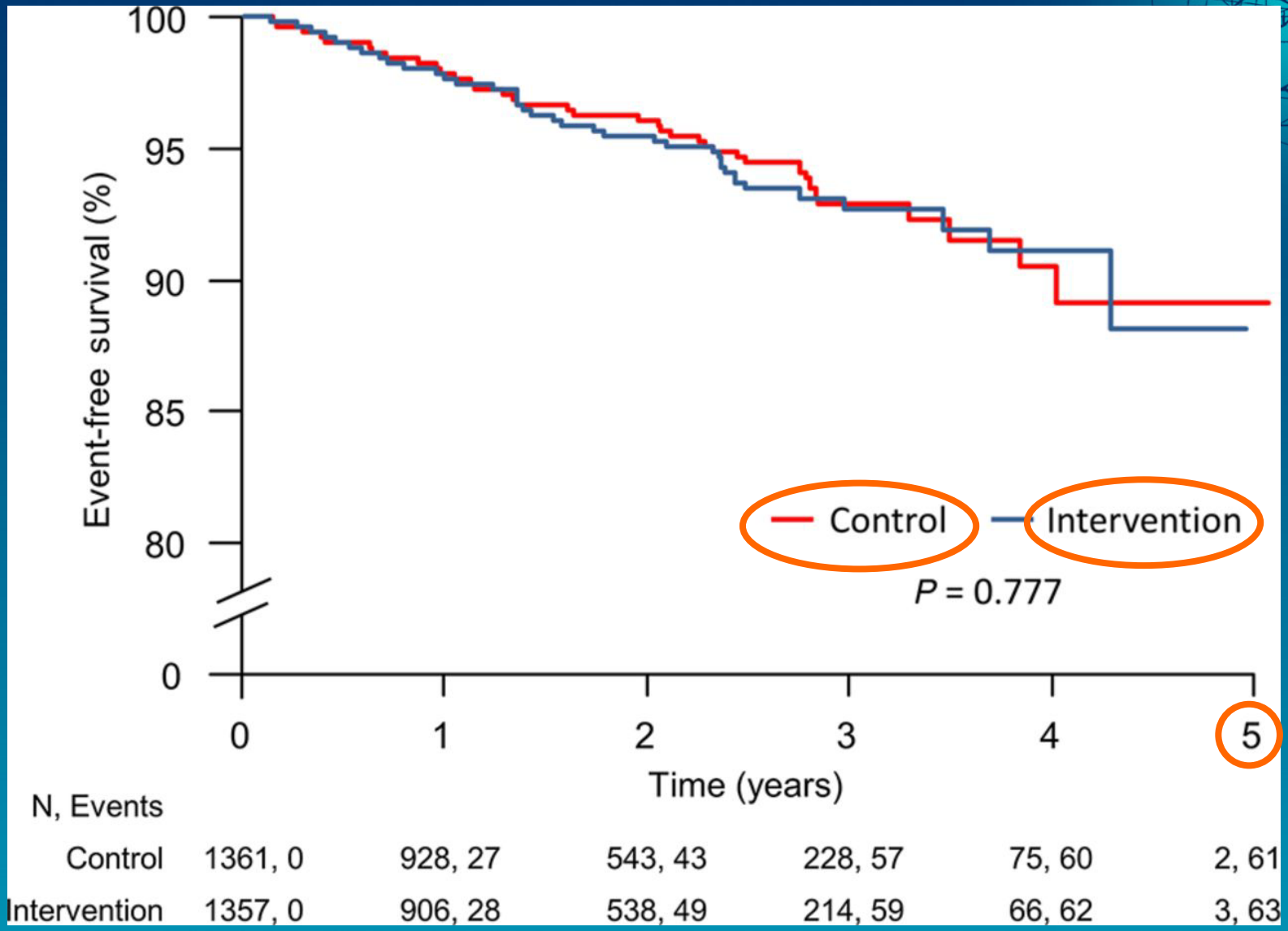
Eur Heart J 2015; 36: 1660-1668

# IMPACT / Study Hypothesis

- The trial was designed to test the hypothesis that initiation and withdrawal of OAC guided by continuous ambulatory monitoring of subclinical AF would reduce the rate of stroke and major bleeding compared to conventional clinical management.

# Primary Outcome Events

(Stroke, systemic embolism or major bleed)




| N, Events | | | | | | |
|---|---|---|---|---|---|---|
| Control | 1361, 0 | 928, 27 | 543, 43 | 228, 57 | 75, 60 | 2, 61 |
| Intervention | 1357, 0 | 906, 28 | 538, 49 | 214, 59 | 66, 62 | 3, 63 |

Martin DT, et al. Eur Heart J 2015; 36: 1660-1668

# Conclusions (1)

- Asymptomatic or silent AF is a common finding in different clinical settings when prolonged ECG monitoring is performed.

# Conclusions (2)

- Patients with asymptomatic AF seem to have the same prognosis than patients with symptomatic AF.
- However, the length of silent AF episodes and the burden of the arrhythmia that convey a greater risk of stroke are still uncertain and need to be clarified by further large prospective studies

# Conclusions (3)

- In the majority of patients with device-detected AF, there is no proximate temporal relationship between asymptomatic AF and stroke occurrence. This suggest that silent AF is not the direct cause of the stroke, but rather represents only a marker of increased thromboembolism

# Conclusions (4)

- Future studies have to establish if and when patients with asymptomatic AF really benefit from oral anticoagulant therapy.