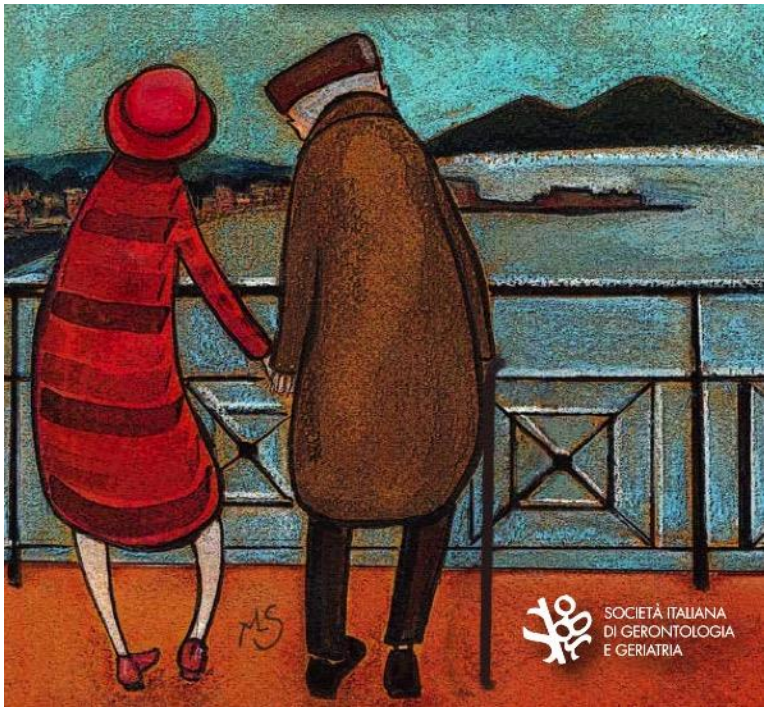
62° CONGRESSO NAZIONALE SIGG

INVECCHIAMENTO: SCENARIO 2.0

NAPOLI 2017
29 novembre - 2 dicembre



SIMPOSIO

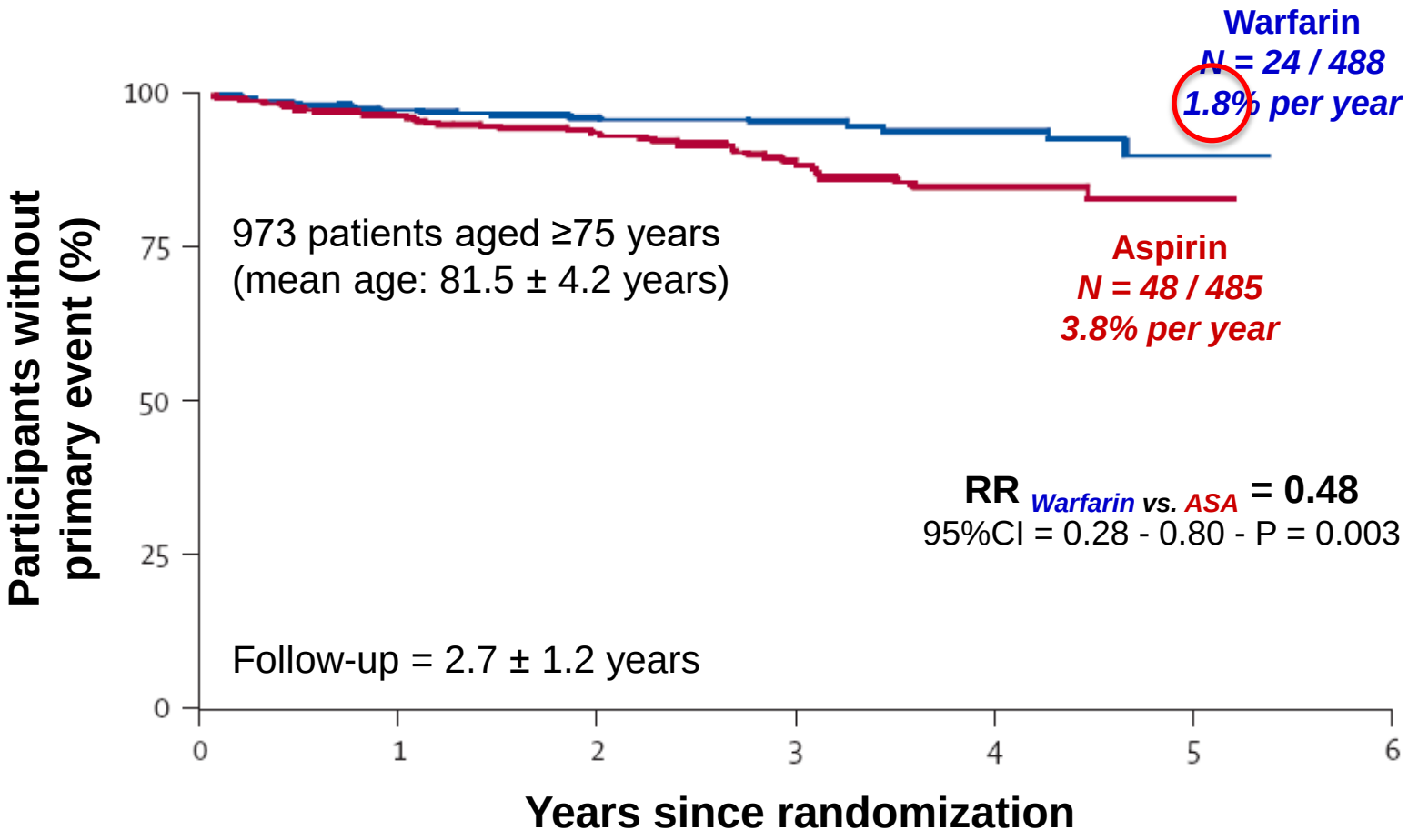
ANTICOAGULAZIONE NELL'ANZIANO:
INDICAZIONI, CONTROINDICAZIONI, ALTERNATIVE

Quali opzioni alternative nell'anziano con fibrillazione atriale che non può essere anticoagulato?

Stefano Fumagalli, MD, PhD, FEHRA

Unità di Terapia Intensiva Geriatrica e Unità di Aritmologia Geriatrica, AOU Careggi e Università di Firenze

Warfarin versus aspirin for stroke prevention in an elderly community population with atrial fibrillation (the Birmingham Atrial Fibrillation Treatment of the Aged Study, BAFTA): a randomised controlled trial



Primary endpoint: fatal / disabling stroke (ischemic / hemorrhagic), intracranial hemorrhage, or clinically significant arterial embolism

Mant J et al. Lancet 2007

Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation

The ACTIVE-A (Effect of Clopidogrel Added to Aspirin in Patients with Atrial Fibrillation) Investigators

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

- ✓ VKA therapy prevents S/SE, myocardial infarction, and vascular death better than single or dual antiplatelet therapy
- ✓ Antiplatelet therapy increases bleeding risk, especially DAPT with bleeding rates that are similar to those on OAC
- ✓ Thus, antiplatelet therapy cannot be recommended for stroke prevention in AF patients
- ✓ Antiplatelet mono-therapy is not recommended for stroke prevention in AF patients, regardless of stroke risk (Class III, Harm)

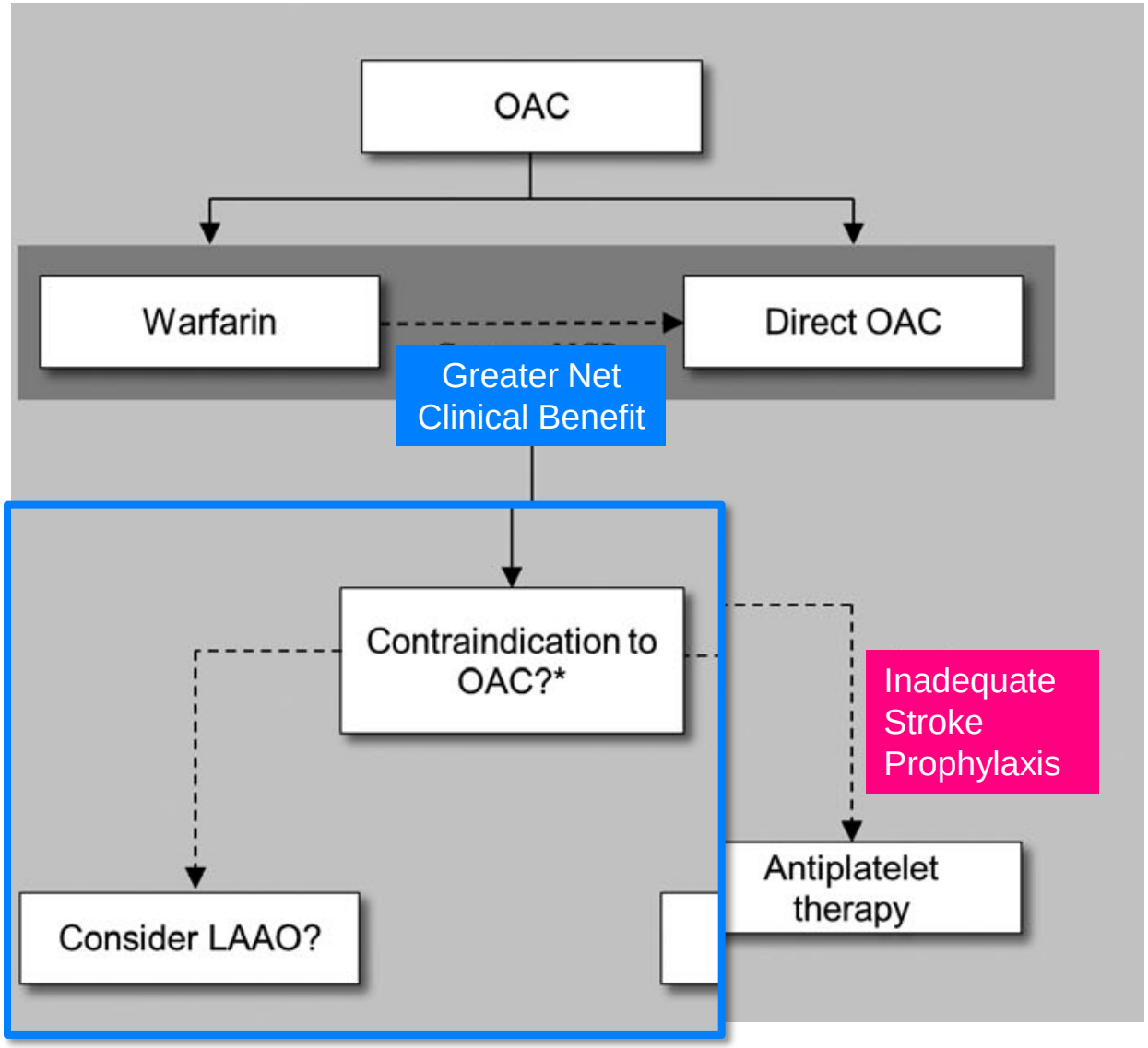
The NEW ENGLAND JOURNAL of MEDICINE

Years

Connolly SJ, 2009

Management of Atrial Fibrillation in Elderly Adults

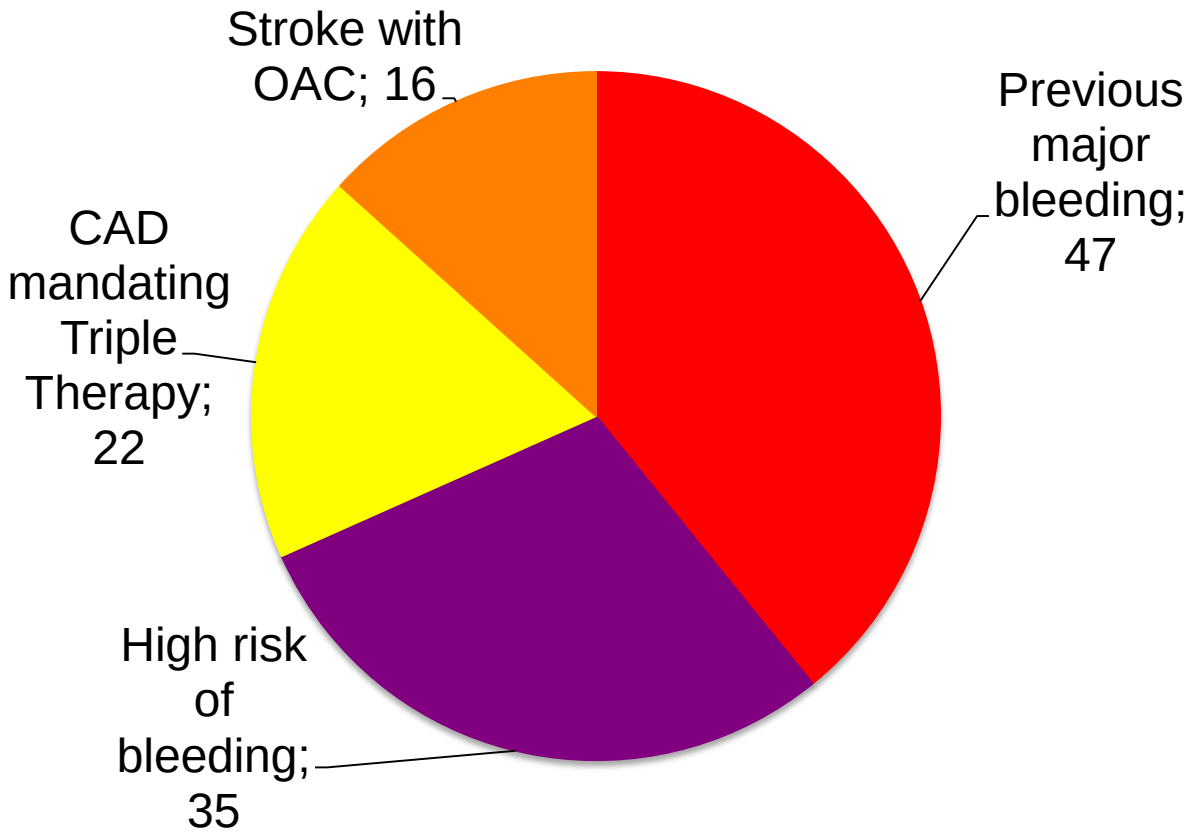
Approach to AF stroke risk reduction in elderly adults



Desai Y,
JAGS 2017

Characterization of Cerebrovascular Events After Left Atrial Appendage Occlusion

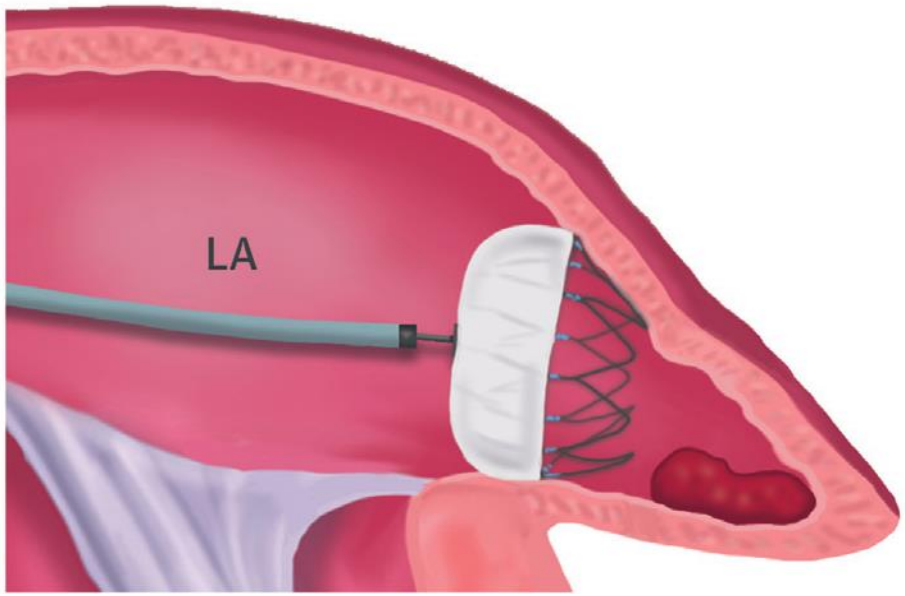
The main indication for LAAO in the AMPLATZER Cardiac Plug - ACP Registry (N=1047; Age: 75±8 years; CHA_2DS_2-VASc: 4.5±1.6; 2008-13)



Freixa X,
Am J Cardiol 2016

Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

Placement of the Watchman device to sequester the left atrial appendage from the systemic circulation



The device is a self- expanding nickel titanium structure available in 5 sizes.

The atrial surface is covered by a permeable polyester fabric and affixed to the LAA ostium by anchors to minimize the possibility of embolization.

Implantation is performed via a trans-septal approach.

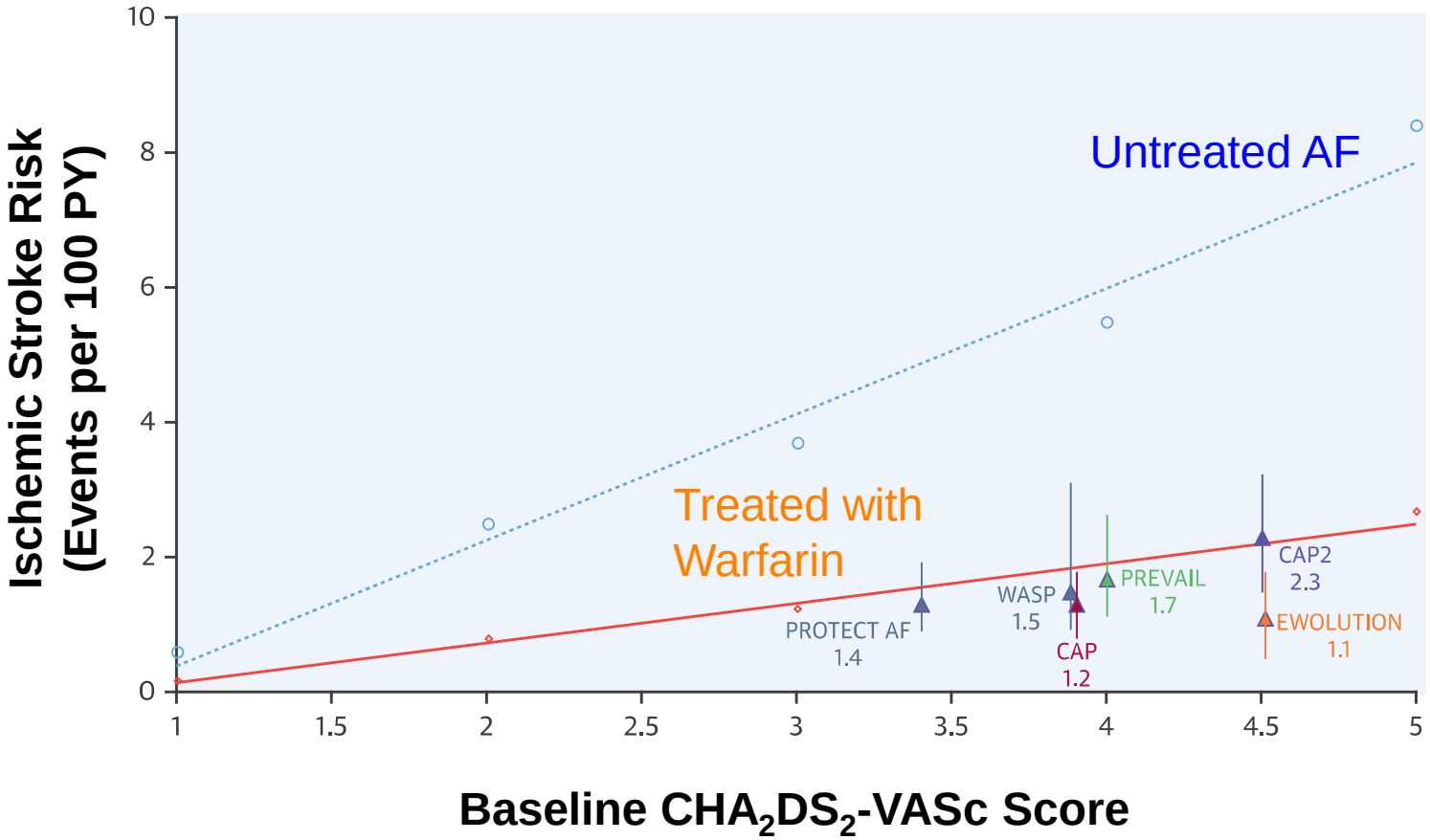
Reddy VY,
JACC 2017

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Reddy VY,
JACC 2017

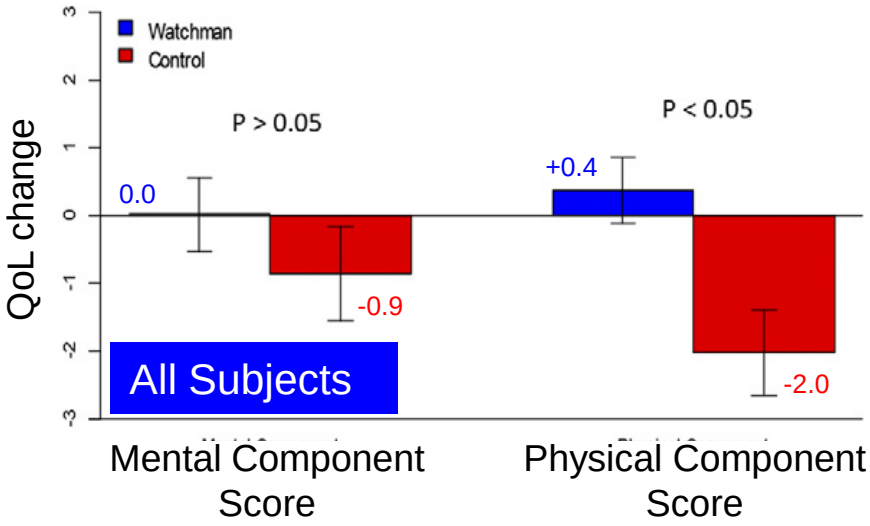
Stroke Prevention in NVAF With LAA Closure. The ischemic stroke rates of NVAF patients are shown as a function of the baseline CHA_2DS_2-VASc score

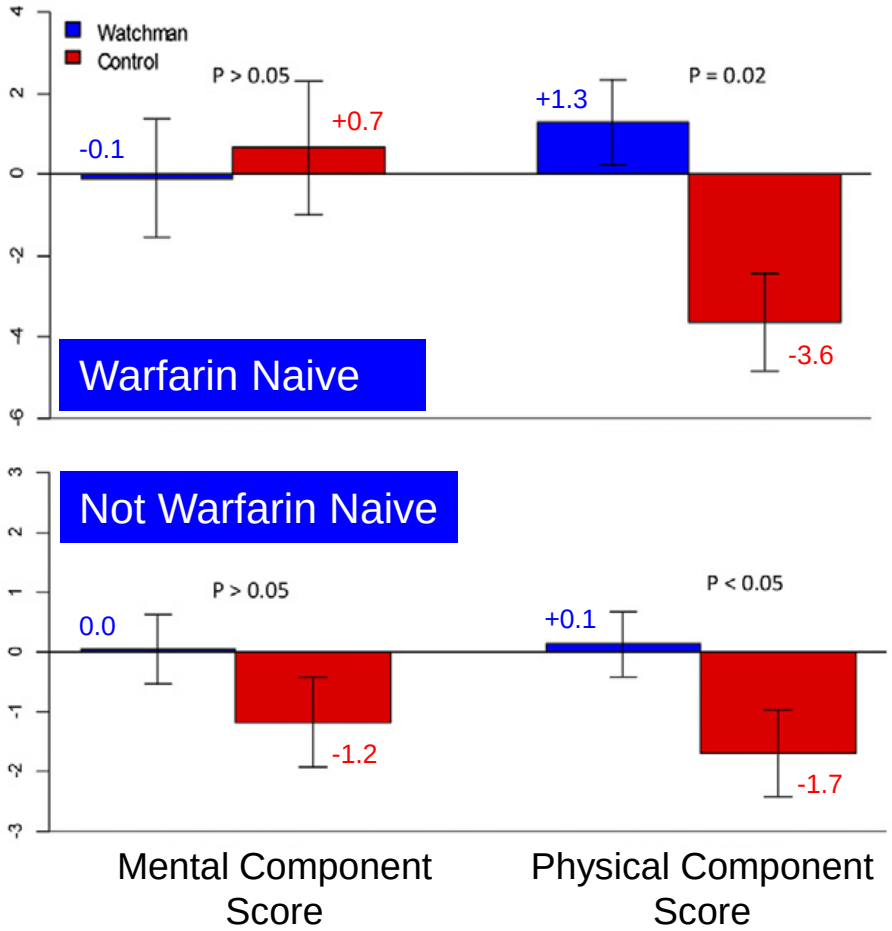


Quality of Life Assessment in the Randomized PROTECT AF (Percutaneous Closure of the Left Atrial Appendage Versus Warfarin Therapy for Prevention of Stroke in Patients With Atrial Fibrillation) Trial of Patients at Risk for Stroke With Nonvalvular Atrial Fibrillation

Alli O,
JACC 2013

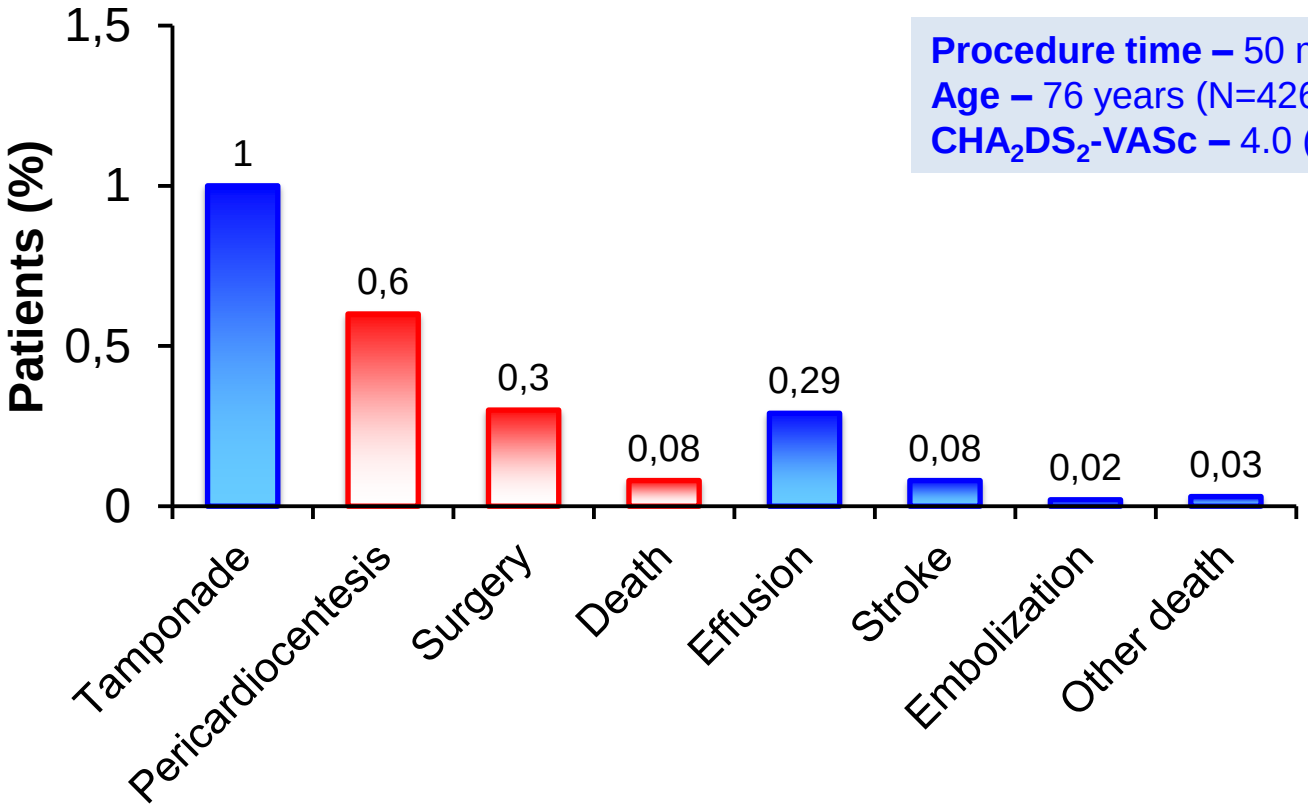
Change in QOL by Treatment - Device (N=361) vs. Warfarin (N=186) - as Evaluated with the SF-12 (Baseline vs. 12 months; Age: 72 y; $CHADS_2$: 2.2)





Post-Approval U.S. Experience With Left Atrial Appendage Closure for Stroke Prevention in Atrial Fibrillation

Procedural complications post-FDA approval of Watchman (2015-2016; N=3822; successful: 95.6%)



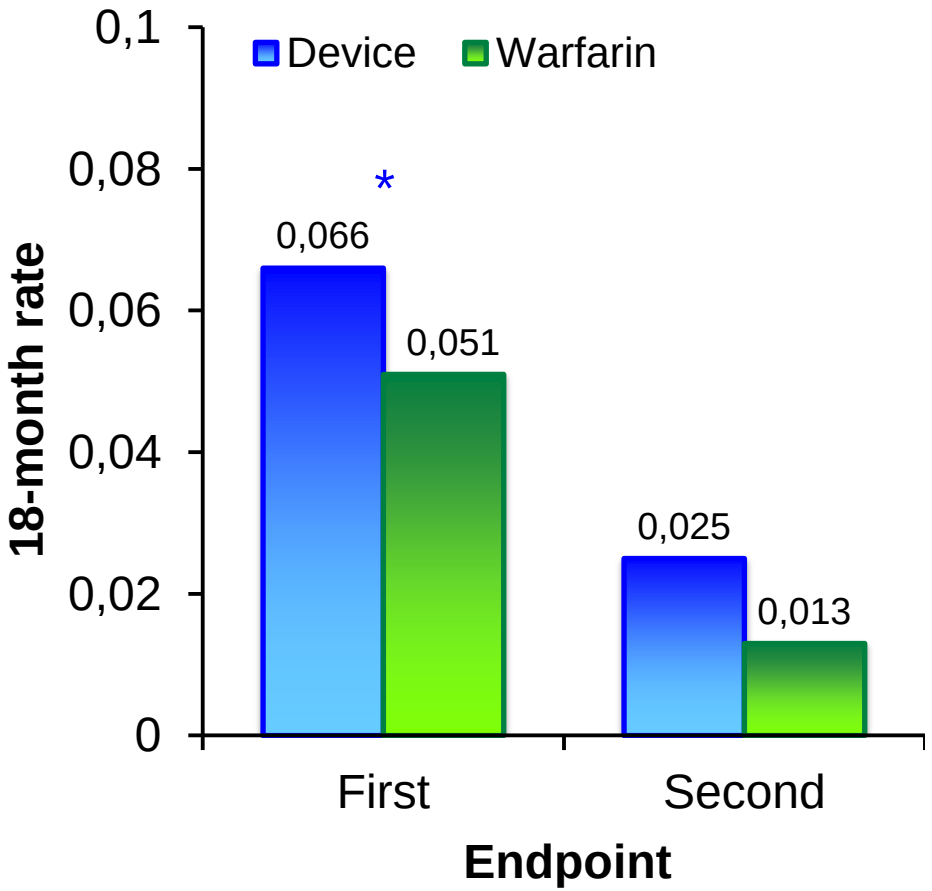
Procedure time – 50 minutes
Age – 76 years (N=426)
CHA_2DS_2-VASc – 4.0 (N=426)

Reddy VY,
JACC 2017

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

PREVAIL Primary Efficacy Endpoints as evaluated at the final 5-year analysis (N=407; randomization – D 2 : W 1)



Endpoint
First Primary - Stroke, SE, and CV/Unexplained Death
Second Primary - Ischemic Stroke or SE >7 Days

*: Statistical non-inferiority NOT achieved

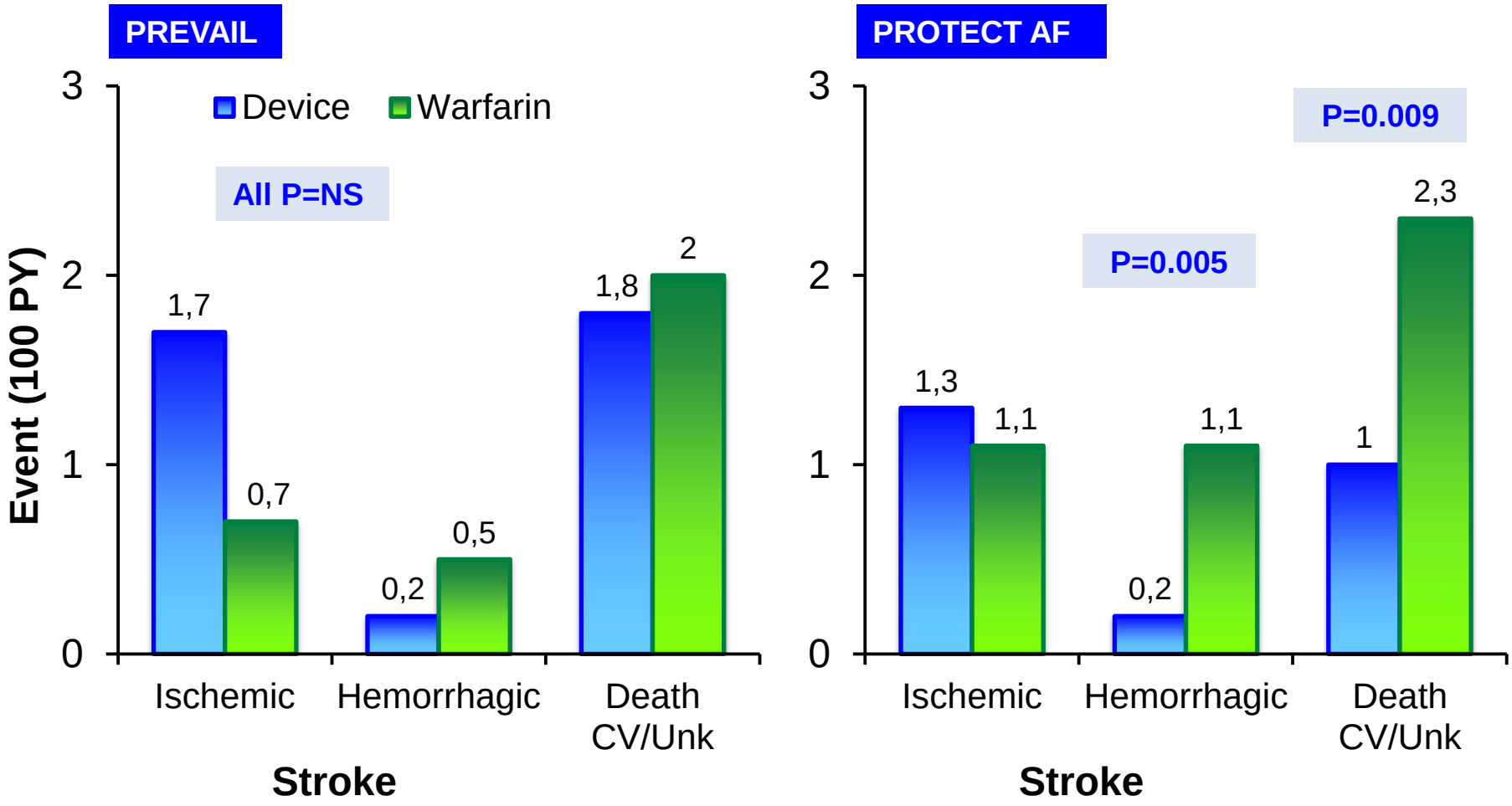
Reddy VY, JACC 2017

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Reddy VY,
JACC 2017

Efficacy rates as evaluated at the final 5-year analysis in the PREVAIL (N=407) and in the PROTECT AF (N=707) studies (randomization – 2:1)

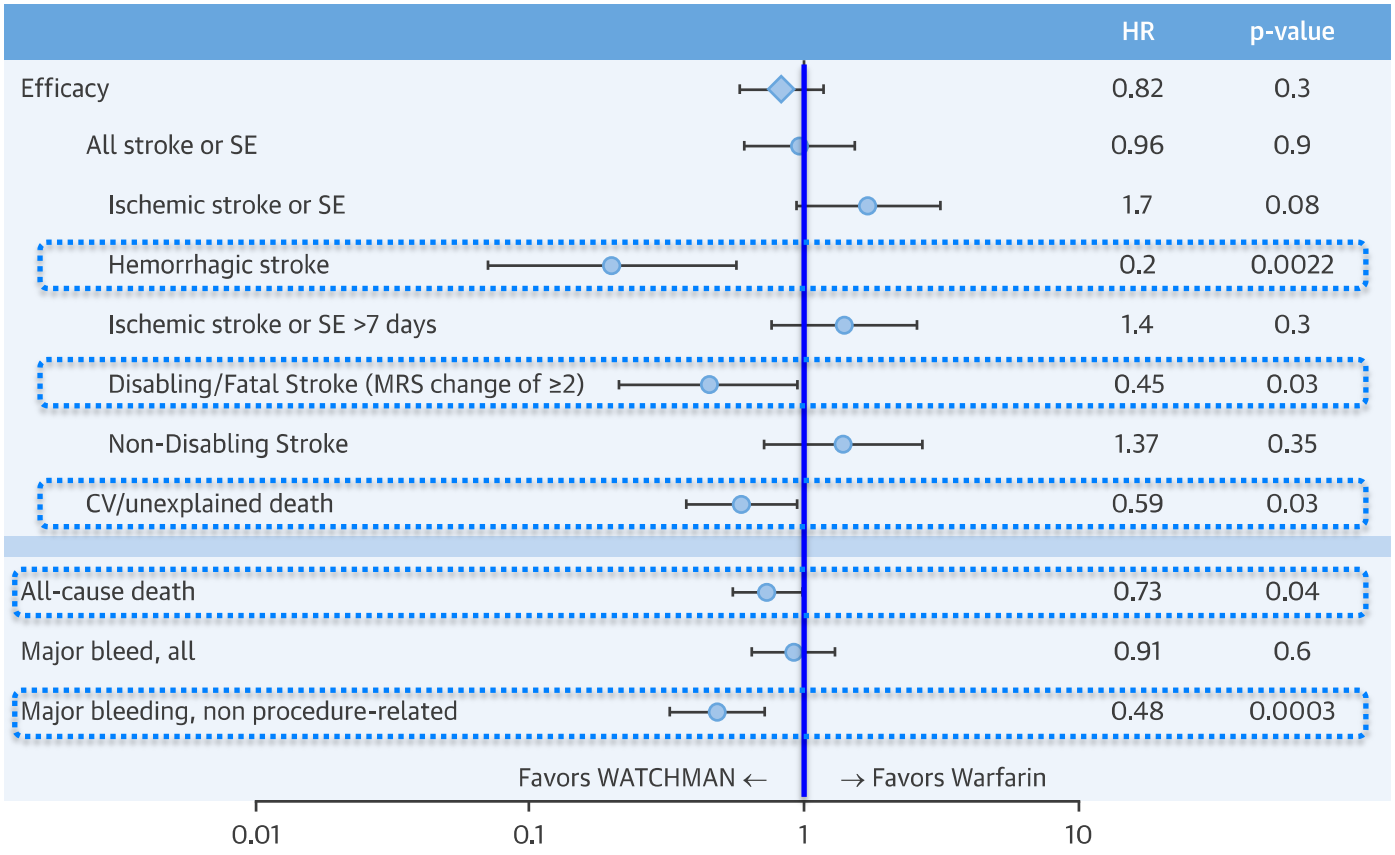


5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Reddy VY,
JACC 2017

Stroke Prevention in NVAF With LAA Closure, in a meta-analysis combining the randomized PROTECT AF (N=707) and PREVAIL (N=407) trial cohorts (Age – WATCHMAN: 73 years; Warfarin: 73 years; FU: 4.3 PY)



Hazard Ratio (95% CI)

CHA_2DS_2-VASc
WATCHMAN: 3.6±1.4
Warfarin: 3.9±1.5
P=0.02

5-Year Outcomes After Left Atrial Appendage Closure

From the PREVAIL and PROTECT AF Trials

Reddy VY,
JACC 2017

Antithrombotic therapy in the PROTECT AF (N=707) and the PREVAIL (N=407) trials

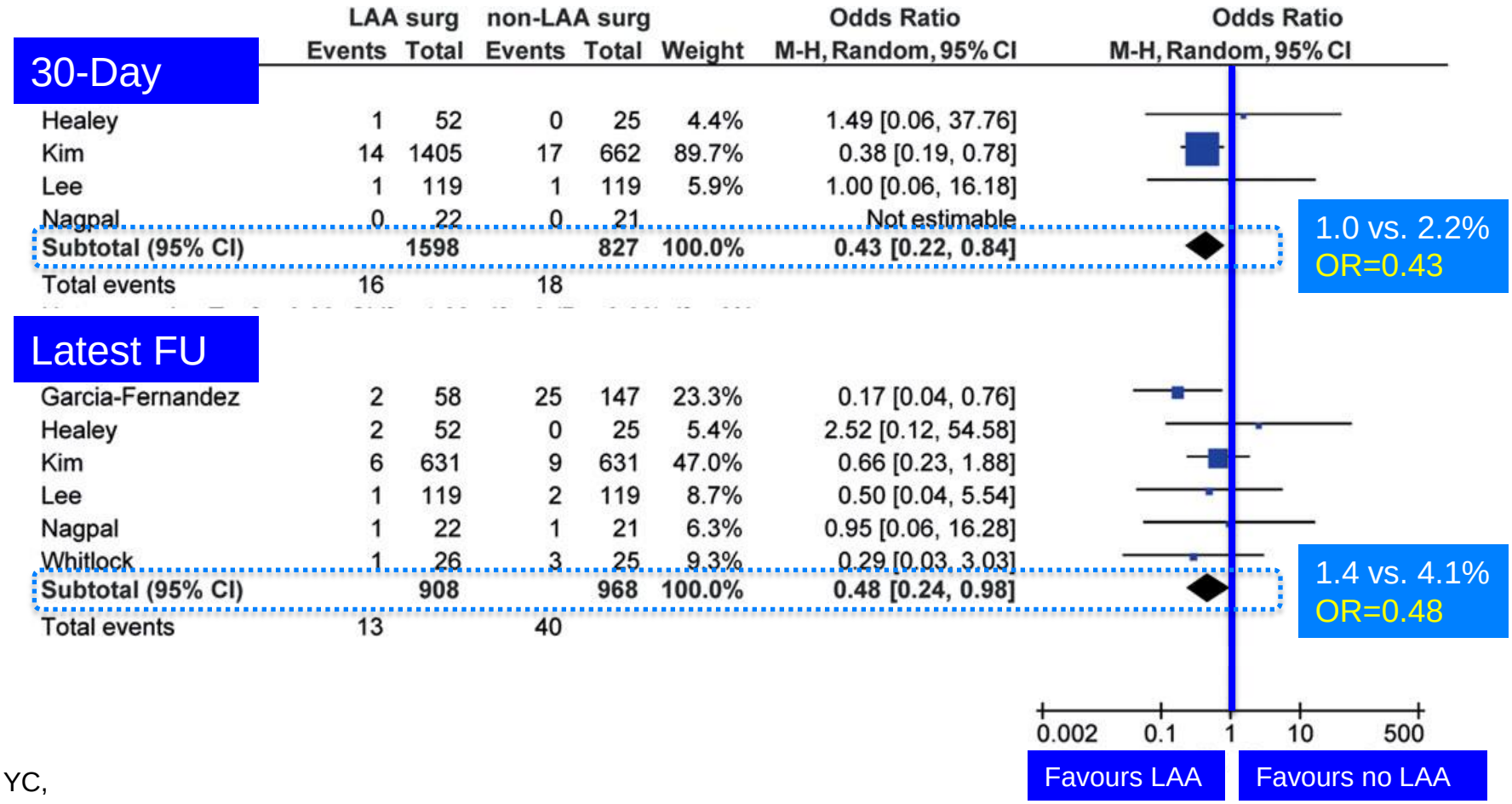
After implantation, patients were treated with an antithrombotic regimen to allow time for device endothelialization:

1) warfarin with a goal INR between 2.0 to 3.0 and aspirin (81 mg) for 45 days;
2) following TEE demonstrating adequate LAAC (no peridevice leak), warfarin was discontinued, and clopidogrel (75 mg) and aspirin (81-325 mg) were instituted until the 6-month timepoint;
3) clopidogrel was discontinued and aspirin (325 mg) was continued indefinitely.

In the warfarin arms, the target INR remained between 2.0 to 3.0 throughout follow-up

Surgical left atrial appendage occlusion during cardiac surgery for patients with atrial fibrillation: a meta-analysis

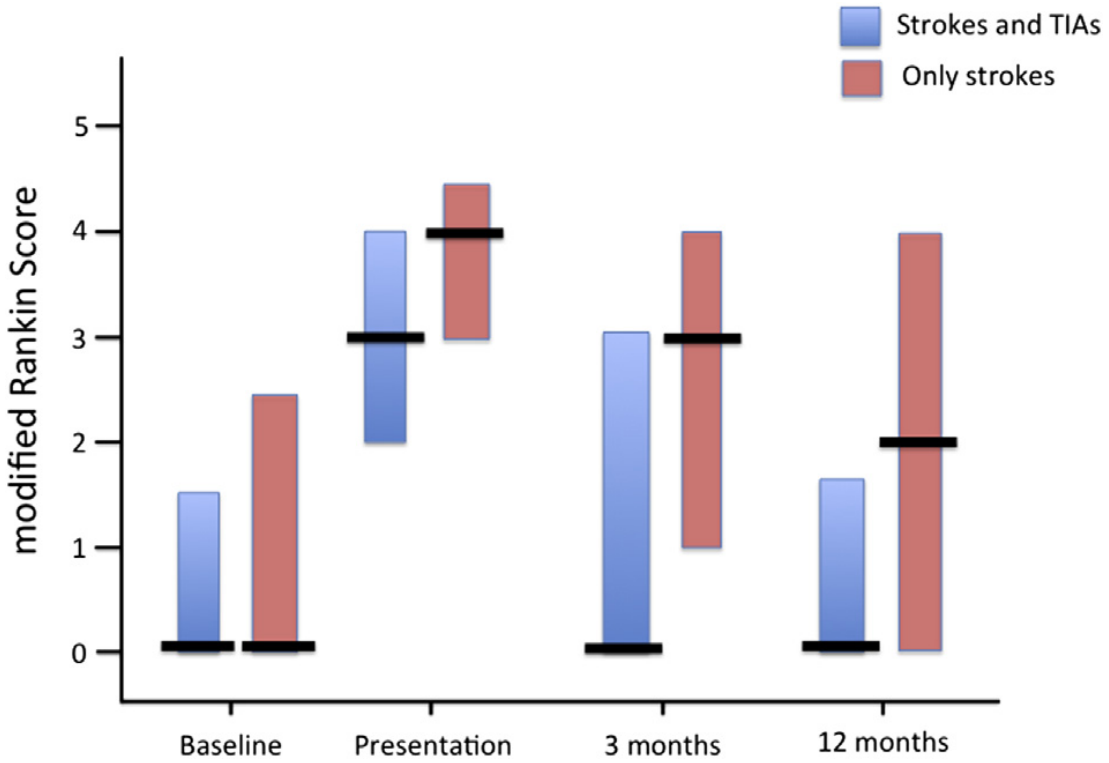
Forest plot of the ORs of embolic stroke incidence on Day 30 and at the latest follow-up by group (7 studies; LAA – N=1716, 65 y; non-LAA – N=1937, 64 y)



Tsai YC,
European Journal of Cardio-Thoracic Surgery 2015

Characterization of Cerebrovascular Events After Left Atrial Appendage Occlusion

Median and interquartile values of the modified Rankin score at baseline, stroke presentation, 3 and 12 months after the cerebrovascular event
In the ACP Registry (follow-up: 13 months)



Stroke – 9/1047 (0.9%)
TIA – 9/1047 (0.9%)
ICH - 0
Death – 45/1047 (4.3%)

The median time of stroke or TIA presentation was **420 days** (IQR 234-671) after LAAO

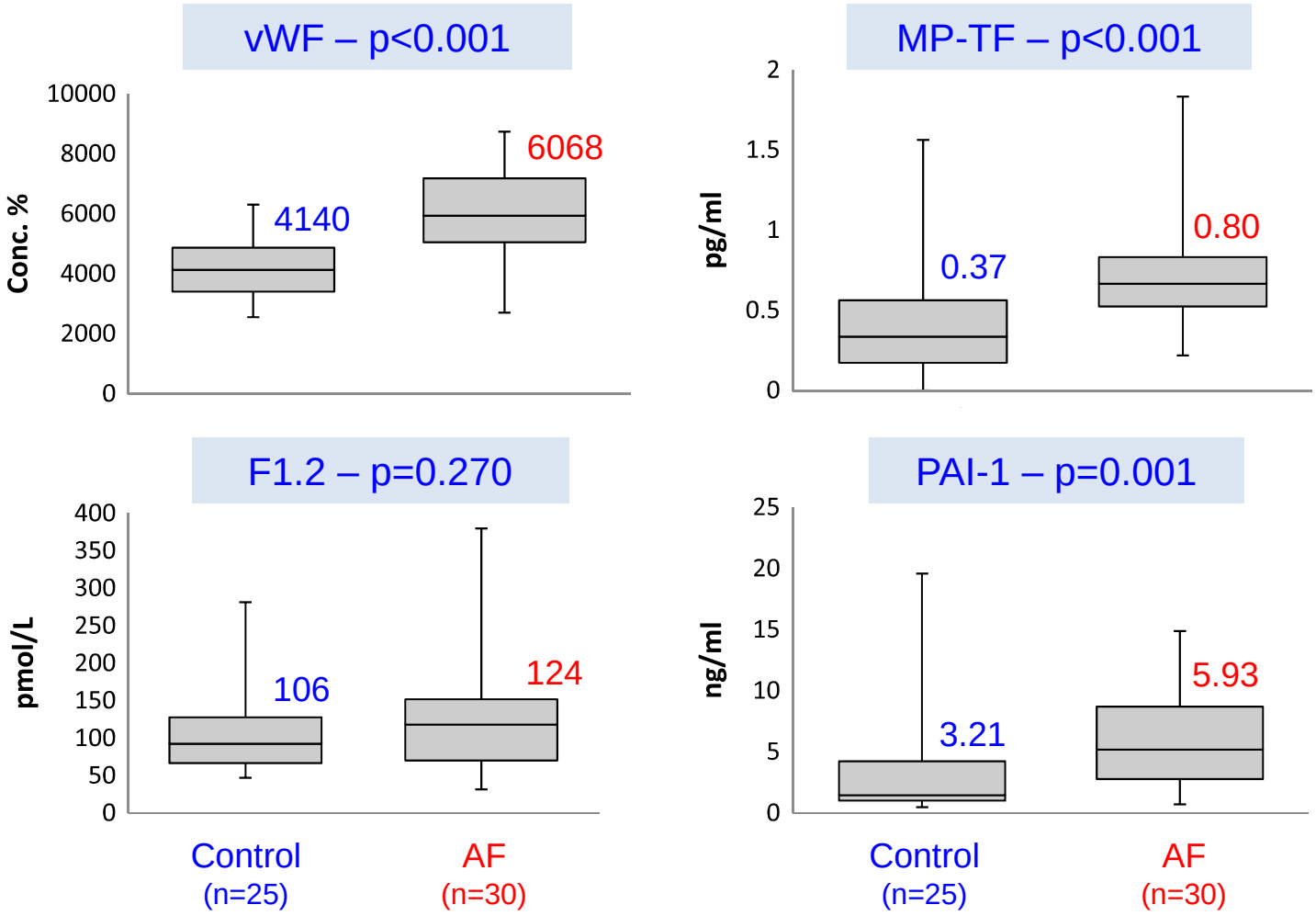
N=17 **(94%)** were on **single-antiplatelet therapy when the event occurred**

Freixa X,
Am J Cardiol 2016

Increased Level of Thrombotic Biomarkers in Patients with Atrial Fibrillation Despite Traditional and New Anticoagulant Therapy

Clinical and Applied Thrombosis/Hemostasis

Levels of biomarkers in control and AF groups



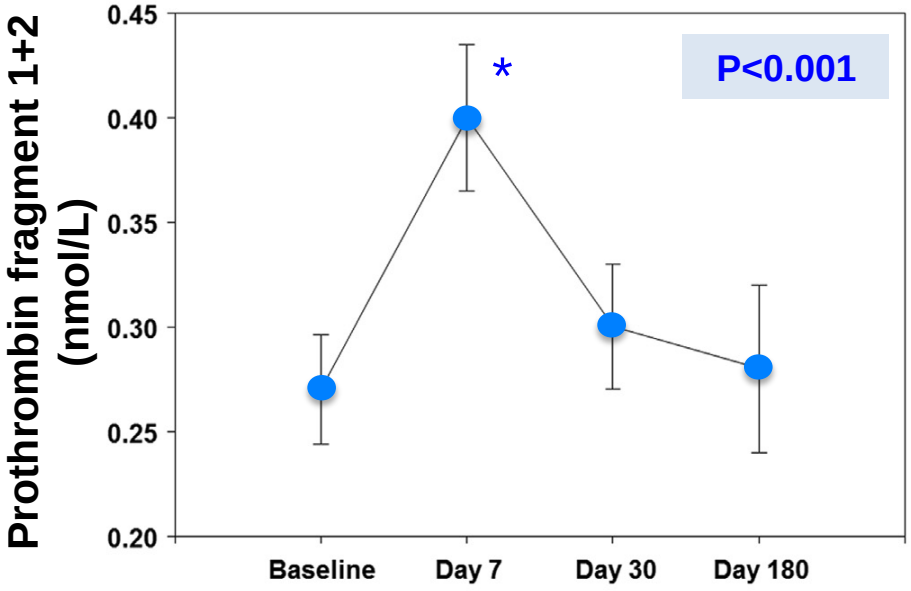
vWF: von Willebrand Factor
MP-TF: Microparticle tissue factor
F1.2: Prothrombin fragment 1+2
PAI-1: Plasminogen activator inhibitor

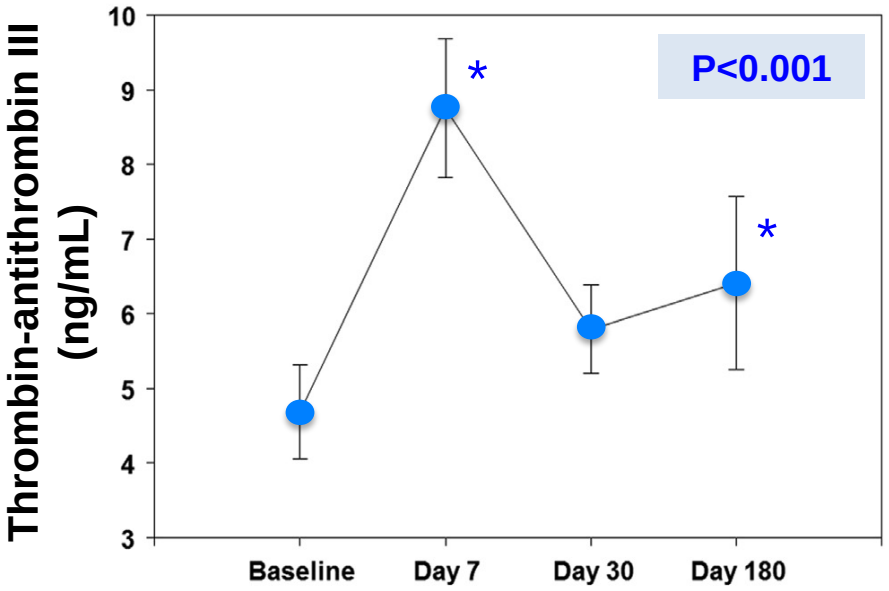
Liles J, 2016

Changes in Coagulation and Platelet Activation Markers Following Transcatheter Left Atrial Appendage Closure

Changes in the markers of coagulation activation after LAAC (N=43; Age: 76±9 years; CHA_2DS_2-VASc: 4)

*: p<0.05 vs. Baseline





Antithrombotic Tx
ASA – 30%
Clopidogrel – 7%
ASA and Clopidogrel – 63%

Rodés-Cabau J,
Am J Cardiol 2017

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

Recommendations for occlusion or exclusion of the LAA

Recommendations	Class	Level
After surgical occlusion or exclusion of the LAA, it is recommended to continue OAC in at-risk patients with AF for stroke prevention	I	B
LAA occlusion may be considered for stroke prevention in patients with AF and contra-indications for long-term OAC treatment (e.g. those with a previous life-threatening bleed without a reversible cause)	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients with AF undergoing cardiac surgery	IIb	B
Surgical occlusion or exclusion of the LAA may be considered for stroke prevention in patients undergoing thoracoscopic AF surgery	IIb	B

Kirchhof P,
Europace 2017

2016 ESC Guidelines for the management of atrial fibrillation developed in collaboration with EACTS

9.3 Left atrial appendage occlusion and exclusion

Still unsolved issues …

Adequately powered controlled trials are urgently needed to inform the best use of these devices, including

1. LAA occluders in patients who are truly unsuitable for OAC or in patients who suffer a stroke on OAC,
2. randomized comparisons of LAA occluders with NOACs, and
3. assessment of the minimal antiplatelet therapy acceptable after LAA occlusion.

Kirchhof P,
Europace 2017

Conclusioni

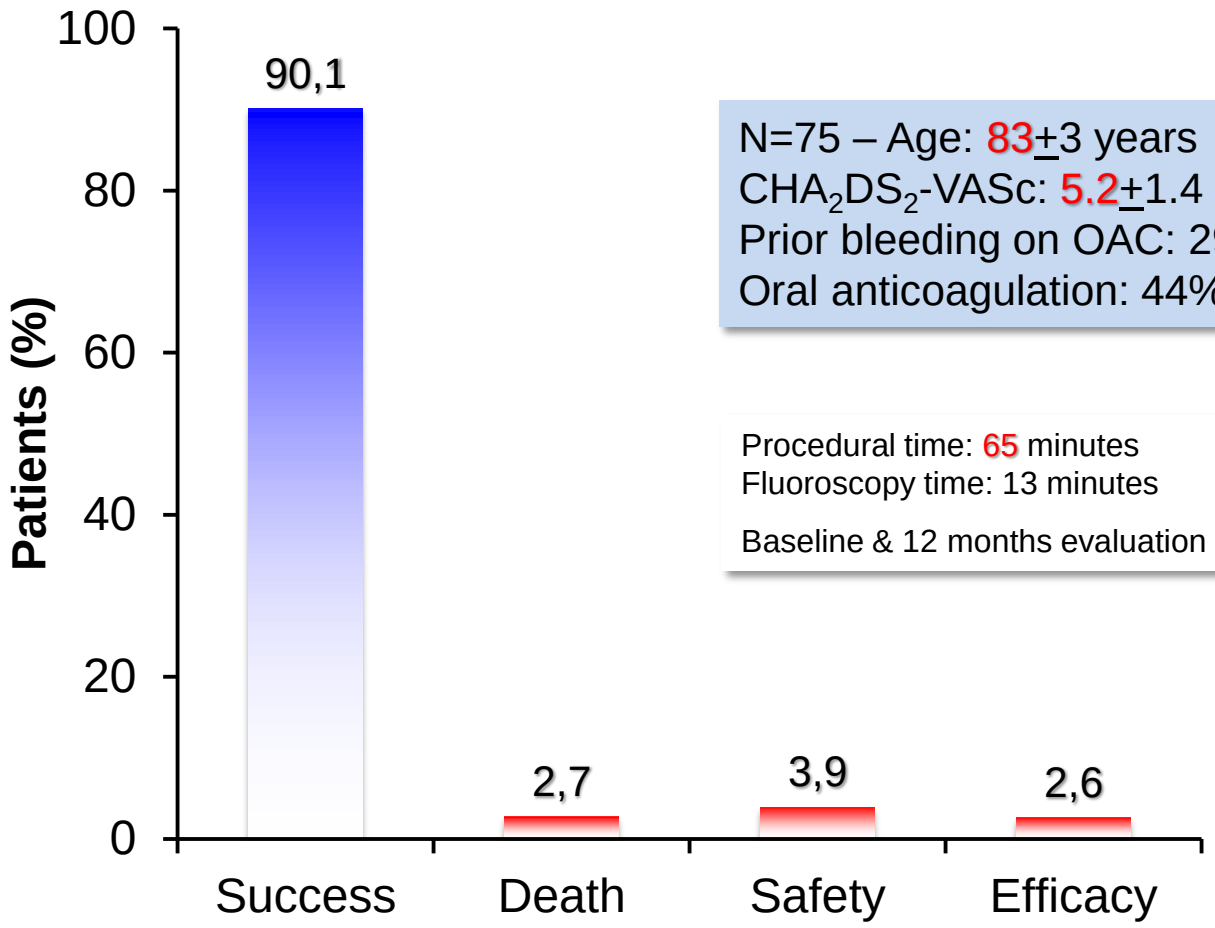
I risultati dei principali "trial" clinici e degli studi di mondo reale dimostrano che, per la CVE, i NOACs hanno efficacia e sicurezza sovrapponibili a quelle degli AVK

I NOACs sarebbero già preferibili per le loro proprietà "note" (1- rapidi inizio e termine del loro effetto, 2- comportamento prevedibile senza necessità di monitoraggio, 3- minori interazioni farmacologiche)

Ulteriori vantaggi dei NOACs da prendere in considerazione per la CVE sono: la "maggiore" aderenza alla terapia, il non dover ritardare lo svolgimento della procedura, una efficacia sovrapponibile a quella degli AVK nella dissoluzione della trombosi in auricola, una minor compromissione della funzione renale

Left Atrial Appendage Occlusion in Octogenarians: Short-Term and 1-Year Follow-Up

Success of the procedure and incidence of safety and efficacy events



N=75 – Age: 83±3 years
CHA_2DS_2-VASc: 5.2±1.4
Prior bleeding on OAC: 29.3%
Oral anticoagulation: 44%

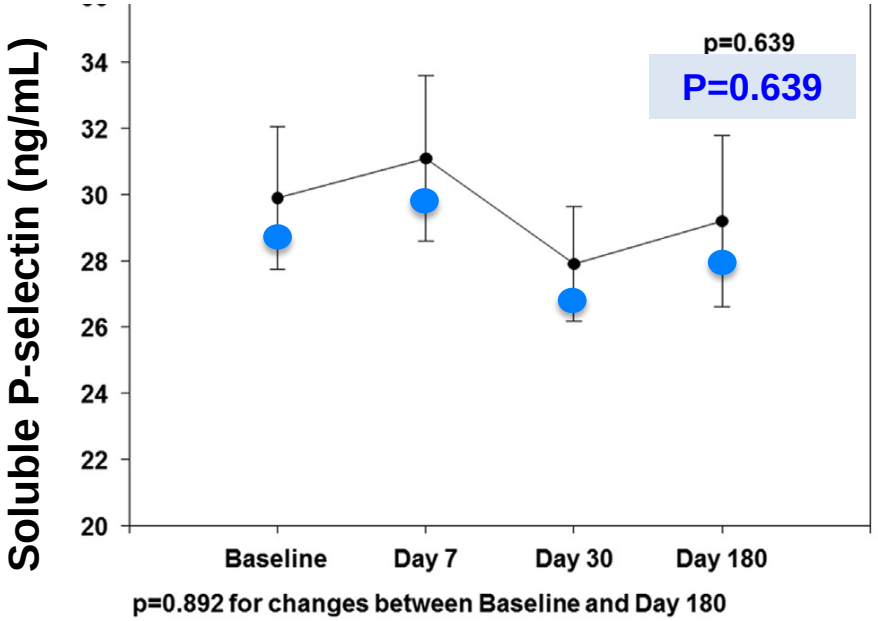
Procedural time: 65 minutes
Fluoroscopy time: 13 minutes

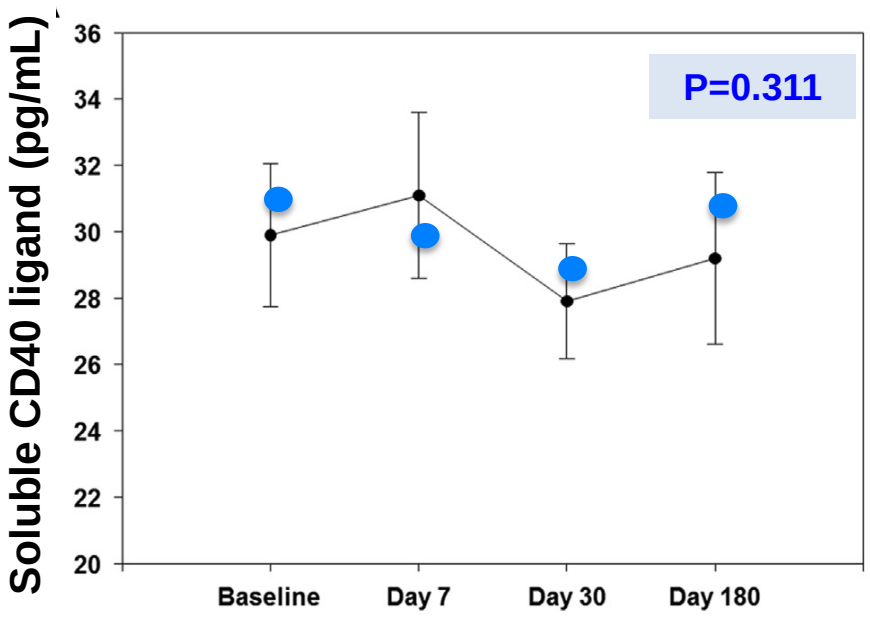
Baseline & 12 months evaluation

Gafoor S, Catheter and Cardiov Interv 2014

Changes in Coagulation and Platelet Activation Markers Following Transcatheter Left Atrial Appendage Closure

Changes in the markers of platelet activation after LAAC
(N=43; Age: 76±9 years; CHA_2DS_2-VASc: 4)





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Rodés-Cabau J,
Am J Cardiol 2017

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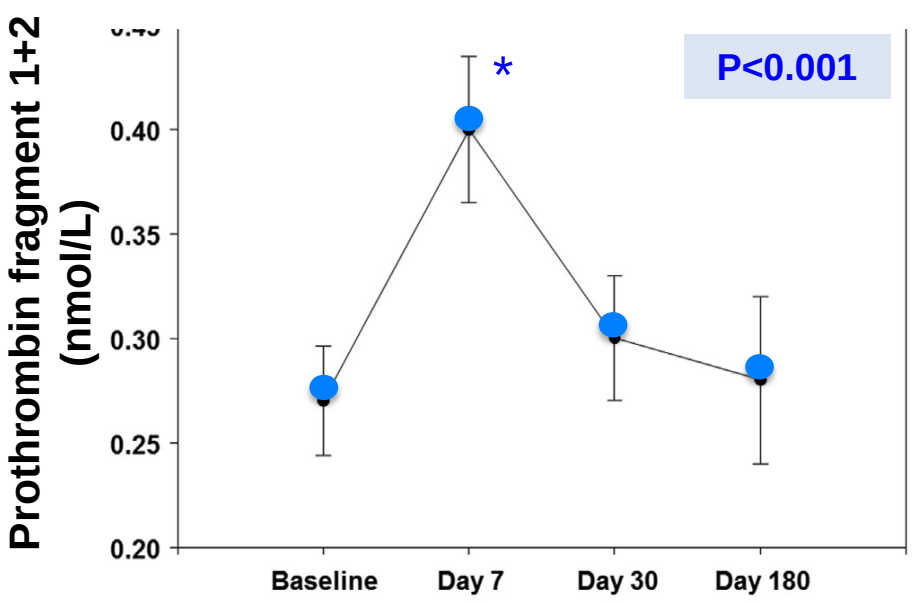

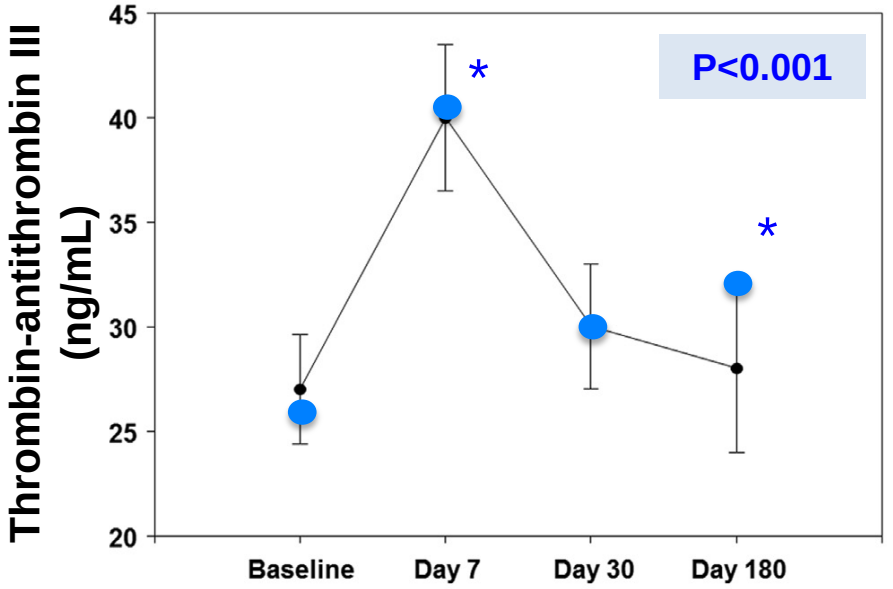

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Rodés-Cabau J,
Am J Cardiol 2017

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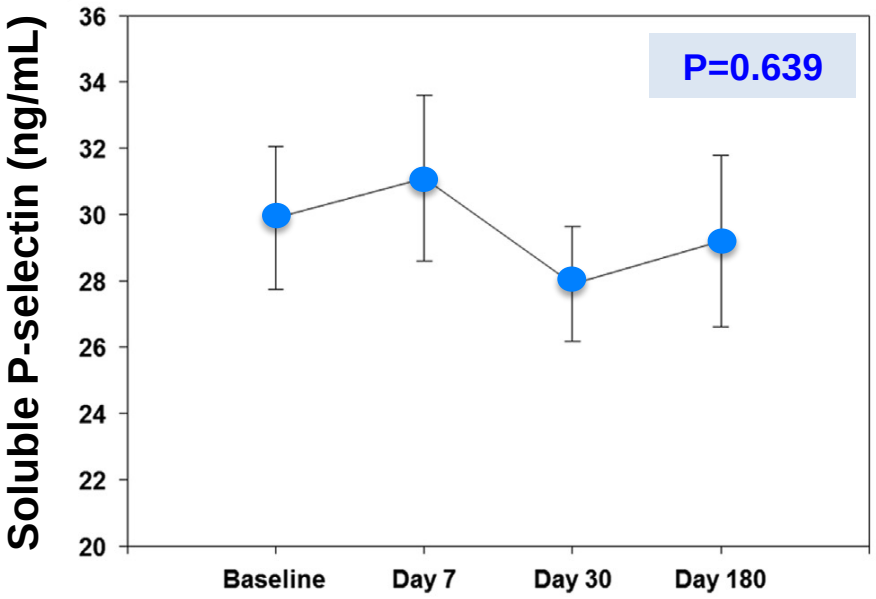

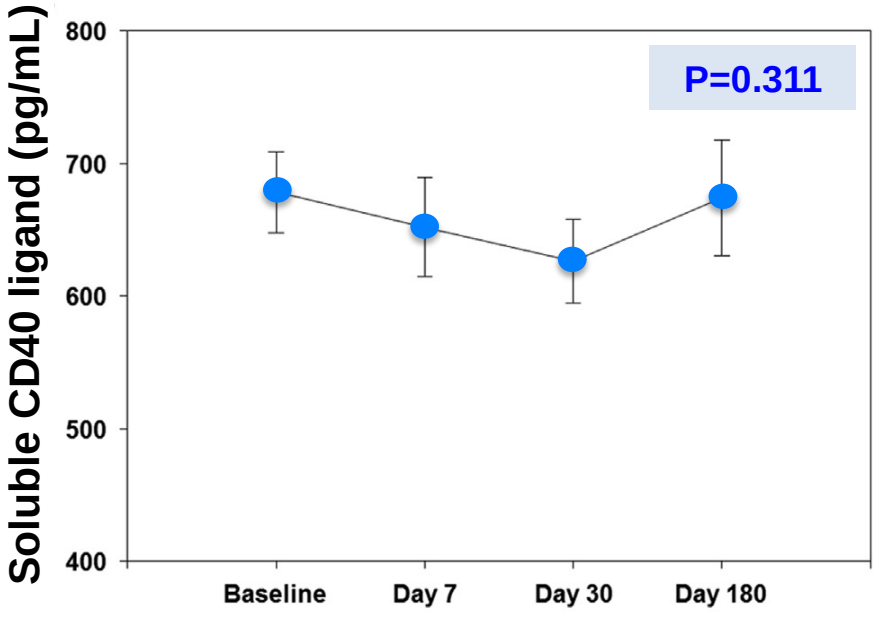

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Rodés-Cabau J,
Am J Cardiol 2017