Patient selection for AF ablation and impact of risk factor management on treatment success

- *How can the patient contribute?*
- *Life style modifications and outcome of AF ablation*

Hans Kottkamp, M.D.

Hirslanden Hospital
Dept. of Electrophysiology
Zurich, Switzerland

Berlin

January 2019

Presenter Disclosure Information

Hans Kottkamp, M.D.

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Company Name:	Relationship:
Kardium	Consultant/equity interest

Treatment of atrial fibrillation

- The focus is on:

  - Rhythm control therapy (ablation, antiarrhythmic drugs)

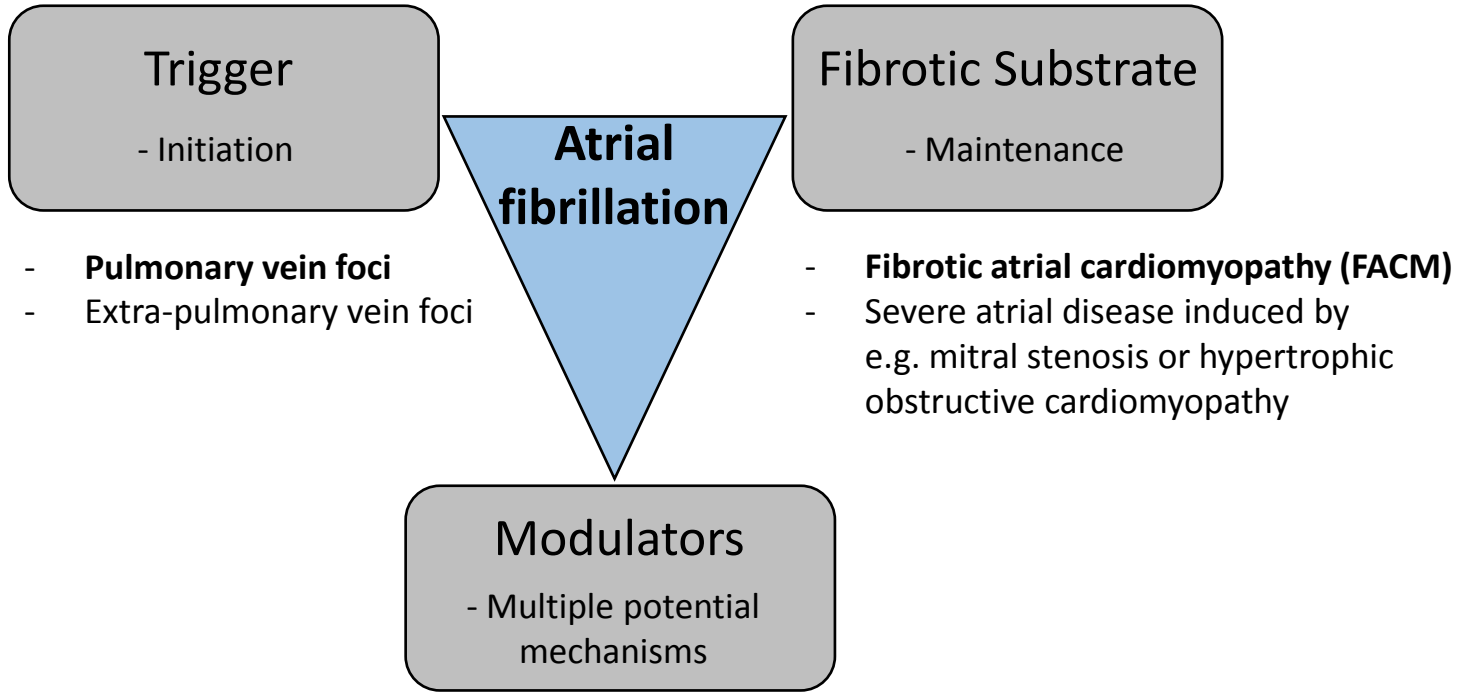
  - Rate control (antiarrhythmic drugs, pace & ablate)

  - Prevention of thromboembolism (oral anticoagulation, LAA occluder)

- **Much less attention on:**

  Primary & secondary prevention with risk factor management/life-style changes

The pathophysiological triangle in atrial fibrillation



Kottkamp H, et al.: JACC EP 2016;2:140-142

The role of obesity in atrial fibrillation

Chrishan Joseph Nalliah[1,2,3], Prashanthan Sanders[3], Hans Kottkamp[4], and Jonathan M. Kalman[1,2*]

- The link of AF with obesity is becoming increasingly clear.
- The mechanistic pathways are multifactorial:

  - left atrial enlargement

  - diastolic dysfunction

  - inflammation

  - role of epicardial fat not fully elucidated (e.g. paracrine effects)

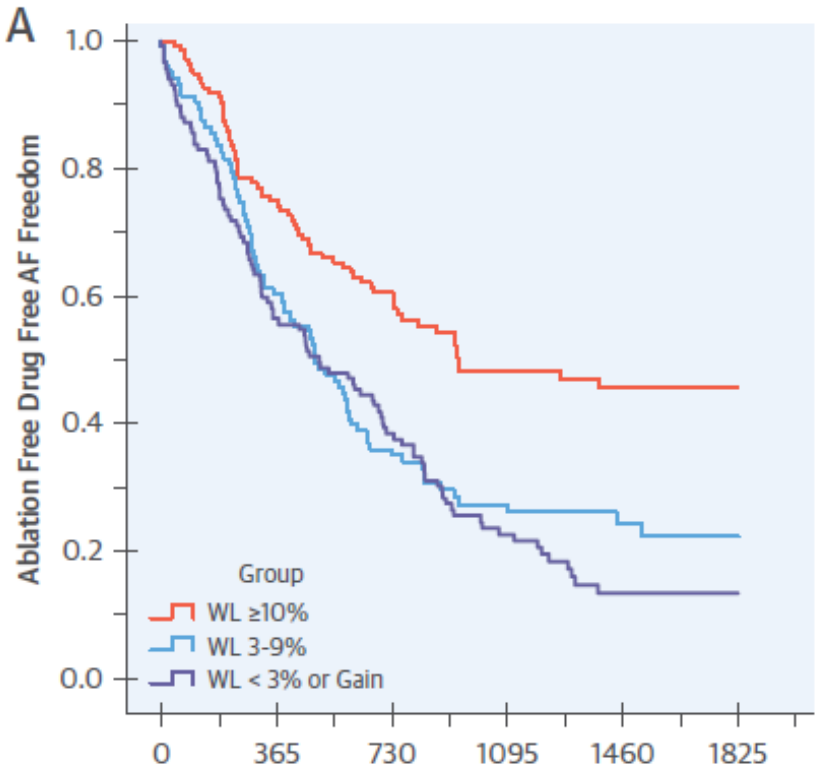
  - frequent combination with other cardiac risk factors

  - others

Nalliah, Sanders, Kottkamp, Kalman: Eur Heart J 2016:37:1565-72

Goal directed weight managment in an atrial fibrillation cohort (LEGACY)

- 355 pts with AF and with BMI ≥27 kg/m2 were offered weight management
- Group 1 weight loss ≥10%, Group 2 WL 3-9%, Group 3 WL <3%

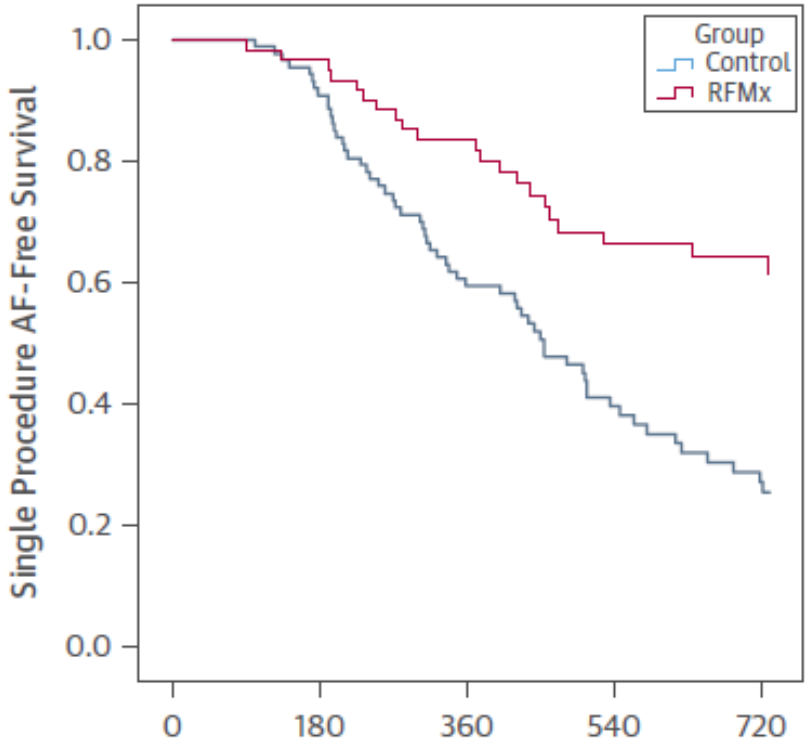


Time (Days)	0	365	730	1095	1460	1825
≥10 WL	135	101	72	42	31	18
3-9% WL	103	62	36	22	13	7
<3% WL or gain	117	66	44	22	11	9

Pathak RK,… , Sanders P: JACC 2015;65:2159-69

Aggressive risk factor reduction … outcome of ablation (ARREST-AF)

- 149 pts with AF and with BMI ≥27 kg/m2 and ≥1 cardiac RF
- Group 1 (n=61) aggressive RFM pts, Group 2 (n=88) control pts
- «aggressive» RFM management: diet, exercise, hypertension, sleep apnoe, alcohol, tobacco,…



Time (days)	0	180	360	540	730
RFM	61	59	48	33	27
Control	88	79	51	28	16

Pathak RK,… , Sanders P: JACC 2014;64:2222-31

Obesity and ablation outcome

- Ablation outcome could be worse because

  - the atria are more «sick» in obese patients

- Ablation outcome could also be worse because

  - the atria are enlarged in obese pts which makes catheter navigation more difficult

  - the whole procedure is more difficult in obese pts (groin puncture, fluoro picture, etc.)

  - the sedation is more difficult in obese pts

- … or a combination

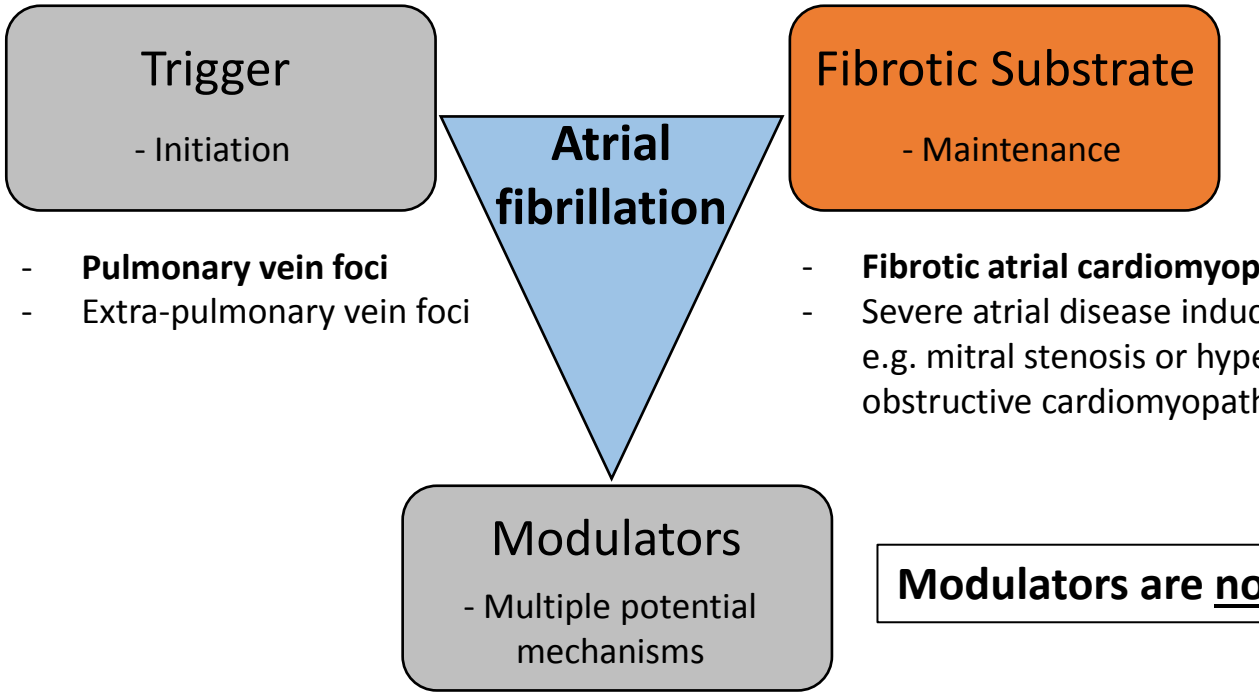
Risk factors vs. Fibrosis (VM) as predictors for ablation outcome

TABLE 5A Univariable analysis of factors associated with single and multiple procedure outcome

Baseline Parameter	Single Procedure	Multiple Procedure
Age	0.943	0.798
Gender	0.899	0.073
Arterial hypertension	0.566	0.398
Coronary artery disease	0.794	0.369
Heart failure (EF < 40%)	0.961	0.501
Obesity	0.295	0.730
Renal insufficiency	0.333	0.134
Diabetes mellitus	0.020	0.099
OSAS	0.740	0.779
CHA_2DS_2VASc	0.935	0.528
Type of AF (PAF vs. PersAF)	0.155	0.723
LA (mm)	0.771	0.759
EF (%)	0.497	0.976
FACM I, II vs. III, IV	<0.001	<0.001
Presence of post. SFAs	0.003	0.003
Presence of ant. SFAs	0.794	0.648
Presence of SFAs ant.+post.	0.002	0.006
Total SFA (cm^2)	0.007	0.006
Maximum LA voltage (mV)	0.012	0.004
SFA > 20 cm^2	0.022	0.005
SFA post. >5 cm^2	0.052	0.024

Schreiber D., … , Kottkamp H.: JCE 2017

Atrial fibrosis is the pathophysiological *key player of the AF substrate*



- **Pulmonary vein foci**
- Extra-pulmonary vein foci

- **Fibrotic atrial cardiomyopathy (FACM)**
- Severe atrial disease induced by e.g. mitral stenosis or hypertrophic obstructive cardiomyopathy

Modulators are <u>not</u> the main fibrosis makers

- Hypertension
- Obesity
- Obstructive sleep apnoe
- Other cardiac risk factors

- Inflammation
- Cancer
- Surgery

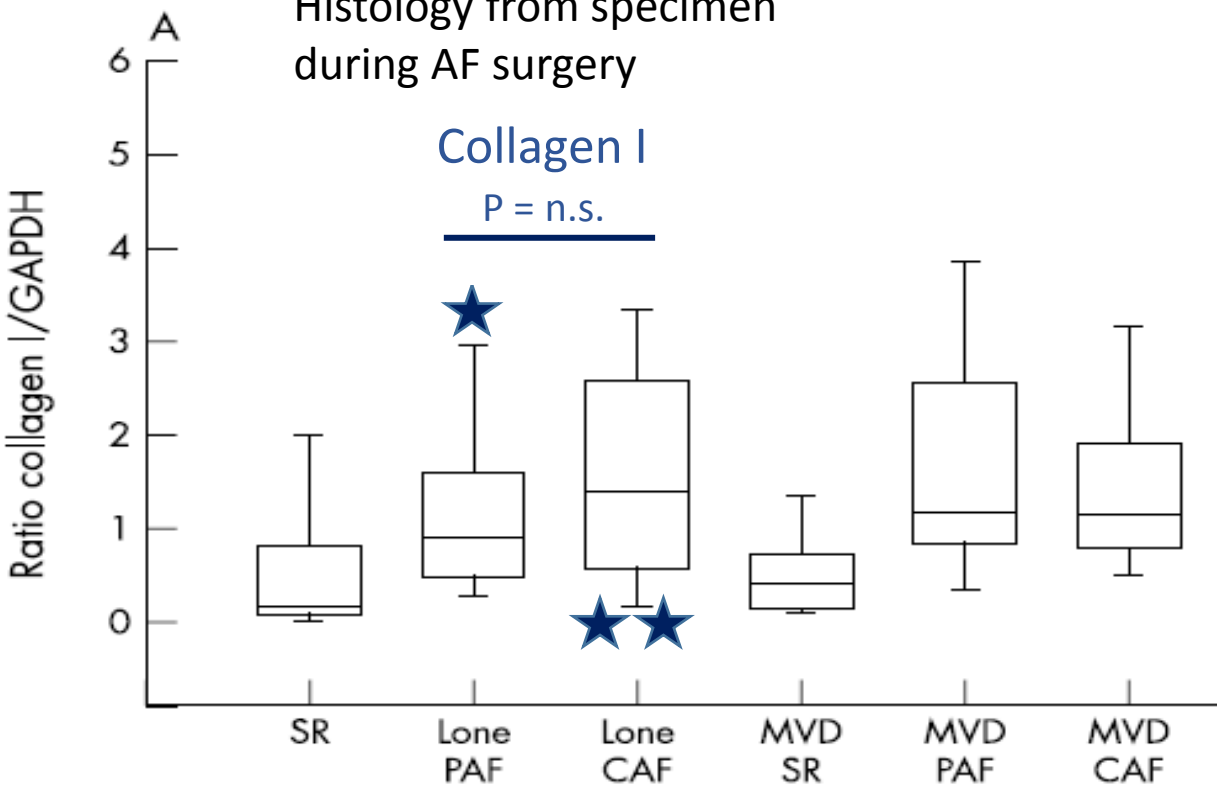
- Electrical remodeling
- Autonomic nervous system
- Endurance sports
- Others

Kottkamp H: JCE 2012;23:797-799

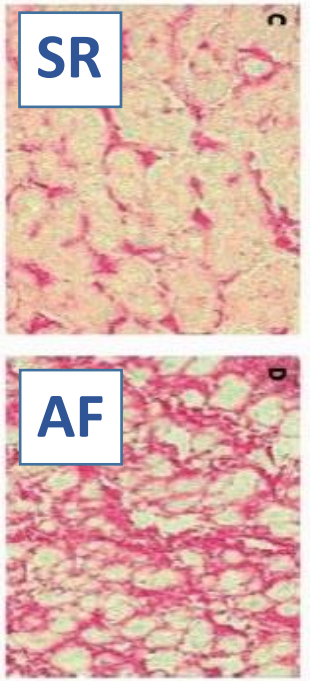
Kottkamp H: Eur Heart J 2013;34:2731-2738

Pathophysiology: Atrial fibrosis is the fundamental histologic finding in AF

Histology from specimen during AF surgery



Immunohistology for collagen type I

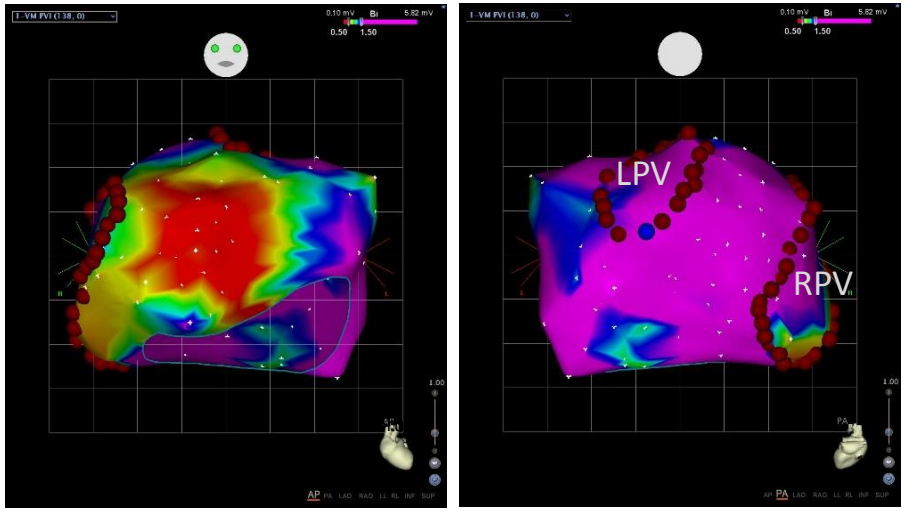


Boldt A, Hindricks G, Kottkamp H, et al.: Heart 2004;90:400-405
Corradi D, et al.: Heart Rhythm 2014;11:1250-58

Classic cardiovasc. risk factors are <u>not</u> the main „fibrosis makers“

- 72-year old pt
- **Persistent** AF for 9 months
- St.p. electrical CV, St.p. Amiodarone
- CAD, St.p. bypass surgery
- Arteriel hypertension
- Diabetes mellitus
- **Obesity**

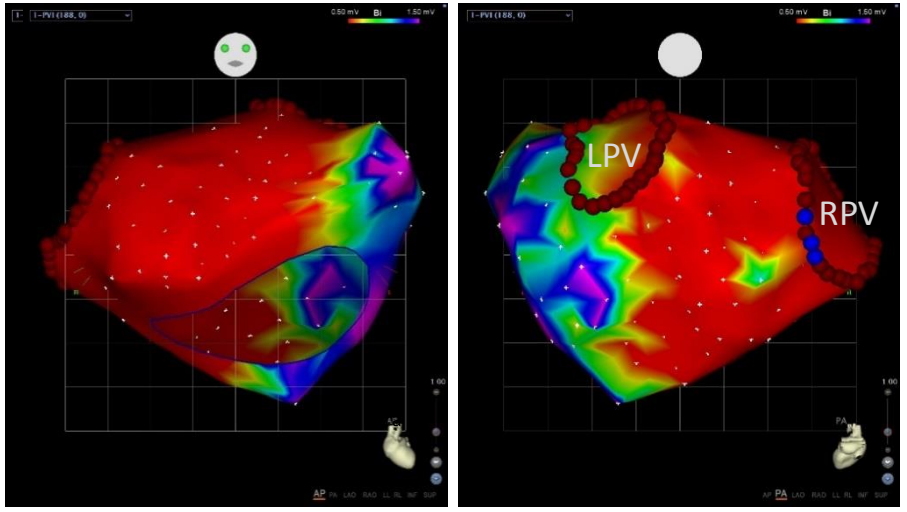
RF
+++



- 72-year old pt
- **Persistent** AF for 8 months

- No risk factors

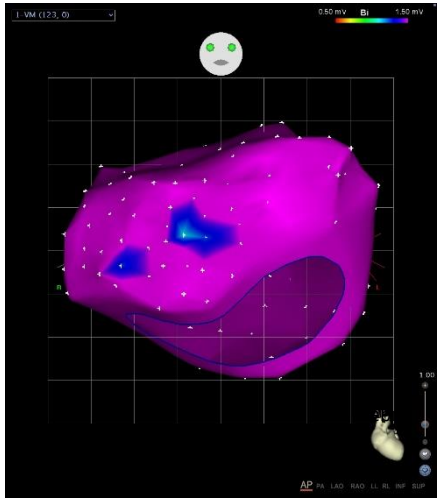
RF
-

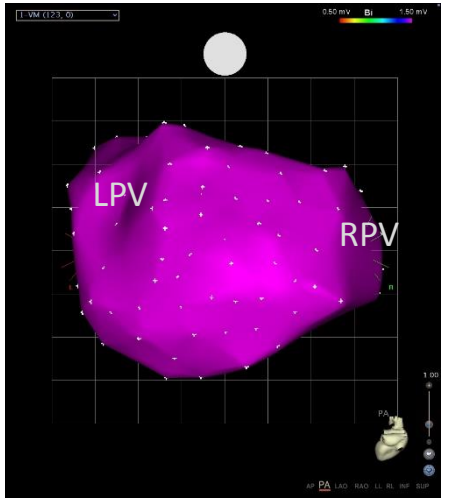


Classic cardiovasc. risk factors are <u>not</u> the main „fibrosis makers“

- 60-year old pt
- **Paroxysmal** AF
- Hypertension
- Diabetes
- **Massive obesity**
- Obstructive sleep apnoe
- Alcohol consumption

RF
+++

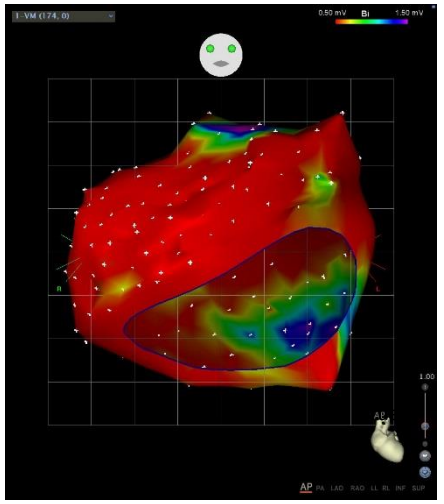


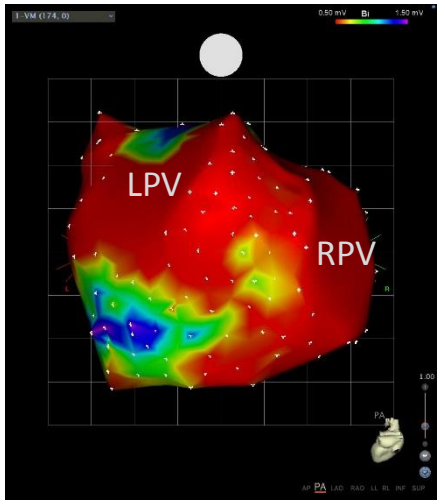


- 69-year old pt
- **Paroxysmal** AF

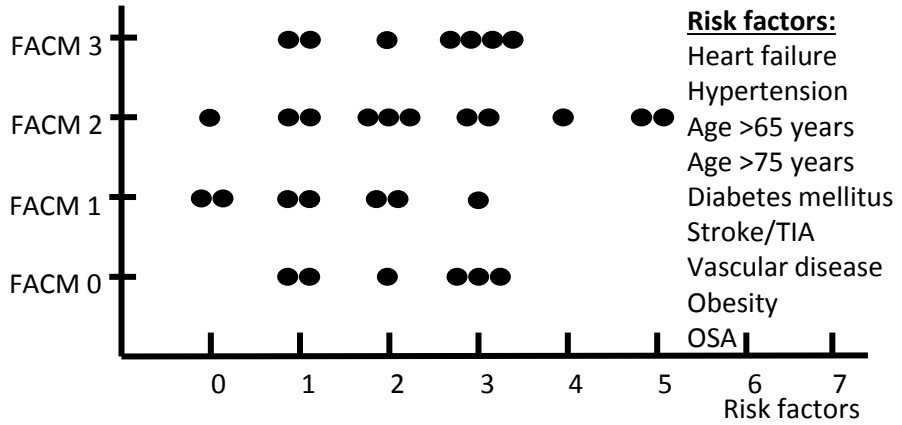
- No risk factors (LA 39mm)

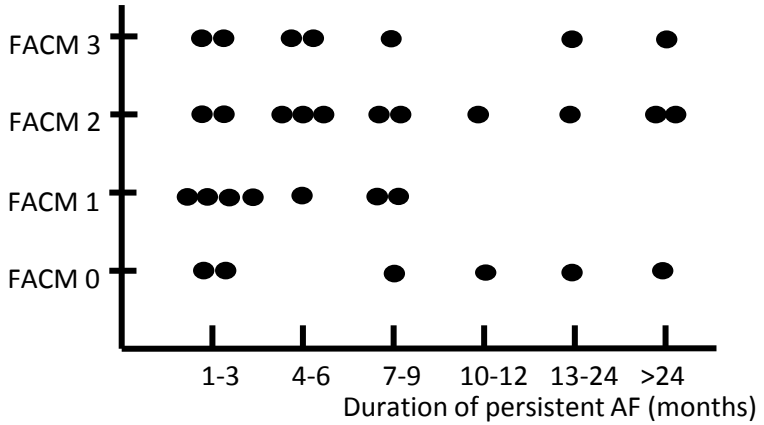
RF
-

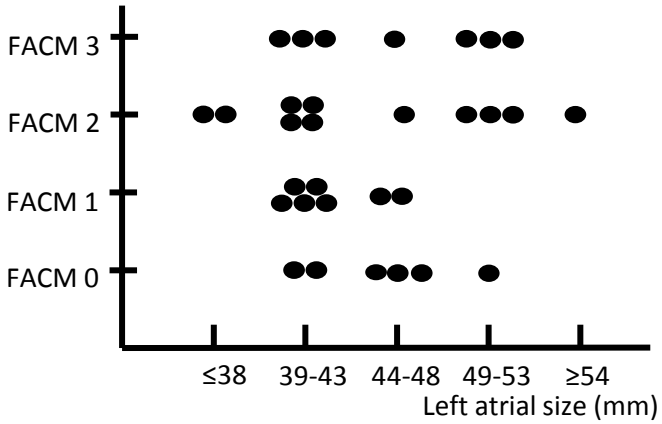




Classic cardiovasc. risk factors are <u>not</u> the main „fibrosis makers“







Kottkamp H, et al.: J Cardiovasc Electrophysiol 2016;27:22-30

Classic cardiovasc. risk factors are not the main „fibrosis makers“

	BIFA Population n = 92	Reference Group n = 49	P
Patients' characteristics			
Age, years {min-max}	67.9 ± 7.9 {38–81}	59.1 ± 11.8 {23–81}	0.789
Gender, m/f	53/39	46/3	<0.001
Type of AF PAF/PersAF	34/58	39/10	<0.001
EF (%){min-max}	57.5 ± 9.9 {25–76}	59.8 ± 6.6 {45–73}	0.803
LA diameter, mm {min-max}	43.9 ± 6.6 {28–60}	41.5 ± 5.2 {30–55}	0.101
CHA_2DS_2VASc {min-max}	2.6 ± 1.3 {0–5}	1.4 ± 1.2 {0–5}	0.108
BMI {min-max}	26.6 ± 5.2 {18.2–43.8}	27.5 ± 4.1{22–39.4}	0.310
Arterial hypertension, n (%)	59 (64.13)	25 (51.02)	0.131
CAD, n (%)	17 (18.48)	5 (10.20)	0.197
Diabetes, n (%)	10 (10.87)	3 (6.12)	0.354
Structural HD other CAD, n (%)	10 (10.9)	2 (4.08)	0.171
Heart failure (EF < 45%), n (%)	9 (9.8)	0 (0)	0.024
Cerebrovascular event, n (%)	4 (4.4)	2 (4.1)	0.941
Renal insufficiency, n (%)	11 (12.0)	1 (2.0)	0.045
OSAS, n (%)	4 (10.9)	3 (6.1)	0.644

Schreiber D., … , Kottkamp H.: JCE 2017

Classic cardiovasc. risk factors are not the main „fibrosis makers“

Parameter	FACM I+II n = 63	FACM III+IV n = 29	P
Age (years)	66.9 ± 8.8	70.3 ± 4.6	0.080
Gender ♂: ♀	41:22	12:17	0.022
EF (%)	58.5 ± 9.6	55.4 ± 10.5	0.245
LA (mm)	43.5 ± 6.4	44.8 ± 7.0	0.392
CHA_2DS_2VASc	2.4 ± 1.3	3.1 ± 1.2	0.023
CHA_2DS_2VASc corr. (female gender)	2.1 ± 1.3	2.5 ±1.1	0.146
AF diagnosis (months)	37.9 ± 55.9	45.8 ± 50.4	0.675
PersAF, n (%)	35 (55.6)	23 (79.3)	0.028
BMI	26.6 ± 5.0	26.7 ± 5.6	0.954
Arterial hypertension, n (%)	40 (63.5)	19 (65.5)	0.851
Diabetes, n (%)	8 (12.7)	2 (6.9)	0.406
TIA/stroke, n (%)	0 (0)	4 (13.8)	0.003
CAD, n (%)	11 (17.5)	6 (20.7)	0.711
Heart failure, n (%)	7 (11.1)	2 (6.9)	0.527
Renal insufficiency, n (%)	6 (9.5)	5 (17.2)	0.289
OSAS, n (%)	3 (4.8)	1 (3.4)	0.774

Schreiber D., … , Kottkamp H.: JCE 2017

Classic cardiovasc. risk factors are not the main „fibrosis makers“

Table 2 Patient population characteristics for patients with non-lone atrial fibrillation

	Total (n = 293)	Utah I (n = 17)	Utah II (n = 187)	Utah III (n = 67)	Utah IV (n = 22)
Age, y	68.8 ± 6.9	67.7 ± 8.8	66.1 ± 9.2	67.6 ± 11.8	70.2 ± 7.7
Gender, n (%)					
Female	110 (37.54)	5 (29.41)	59 (31.56)	33 (49.25)	11 (50)
Male	183 (62.46)	12 (70.59)	128 (68.44)	34 (50.75)	11 (50)
Hypertension, n (%)	193 (65.87)	13 (76.47)	125 (66.84)	41 (61.19)	15 (68.18)
Diabetes mellitus, n (%)	46 (15.7)	3 (17.65)	25 (13.37)	14 (20.90)	5 (22.73)
CAD, n (%)	48 (16.38)	5 (29.41)	24 (12.83)	16 (23.88)	3 (13.64)
CABG, n (%)	24 (8.19)	4 (23.53)	14 (7.49)	4 (5.97)	2 (9.09)
MI, n (%)	16 (5.46)	2 (11.76)	9 (4.81)	4 (5.97)	1 (4.55)
History of smoking, n (%)	48 (16.38)	3 (17.65)	31 (16.58)	10 (14.93)	4 (18.18)
Implanted device, n (%)	23 (7.85)	0 (0)	9 (4.81)	10 (14.93)	4 (18.18)
CHF, n (%)	30 (10.24)	3 (17.65)	17 (9.09)	8 (11.94)	3 (13.64)
CMP, n (%)	30 (10.24)	0 (0)	19 (10.16)	7 (10.45)	5 (22.73)
MVR, n (%)	15 (5.12)	0 (0)	8 (4.28)	6 (8.96)	1 (4.55)
Valve surgery, n (%)	8 (2.73)	0 (0)	4 (4.14)	2 (2.99)	2 (9.09)
Stroke, n (%)	26 (8.87)	2 (11.76)	12 (6.41)	9 (13.43)	3 (13.64)
Duration (months)	68.4 ± 93.6				

Mahnkopf C, et al.: Heart Rhythm 2010;7:1475-81

Classic cardiovasc. risk factors are not the main „fibrosis makers“

Table 2 Patient population characteristics for patients with non-lone atrial fibrillation

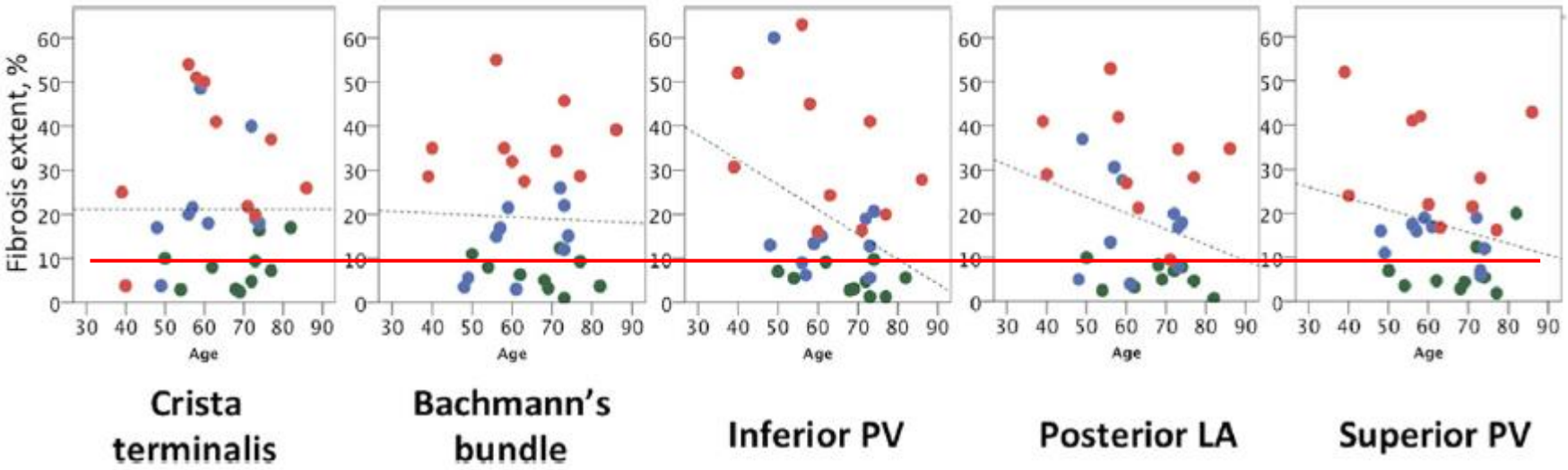
	Total (n = 293)	Utah I (n = 17)	Utah II (n = 187)	Utah III (n = 67)	Utah IV (n = 22)
Age, y	68.8 ± 6.9	67.7 ± 8.8	66.1 ± 9.2	67.6 ± 11.8	70.2 ± 7.7
Gender, n (%)					
Female	110 (37.54)	5 (29.41)	59 (31.56)	33 (49.25)	11 (50)
Male	183 (62.46)	12 (70.59)	128 (68.44)	34 (50.75)	11 (50)
Hypertension, n (%)	193 (65.87)	13 (76.47)	125 (66.84)	41 (61.19)	15 (68.18)
Diabetes mellitus, n (%)	46 (15.7)	3 (17.65)	25 (13.37)	14 (20.90)	5 (22.73)
CAD, n (%)	48 (16.38)	5 (29.41)			
CABG, n (%)	24 (8.19)	4 (23.53)			
MI, n (%)	16 (5.46)	2 (11.76)			
History of smoking, n (%)	48 (16.38)	3 (17.65)			
Implanted device, n (%)	23 (7.85)	0 (0)			
CHF, n (%)	30 (10.24)	3 (17.65)			
CMP, n (%)	30 (10.24)	0 (0)			
MVR, n (%)	15 (5.12)	0 (0)			
Valve surgery, n (%)	8 (2.73)	0 (0)			
Stroke, n (%)	26 (8.87)	2 (11.76)			
Duration (months)	68.4 ± 93.6				

Table 3 Distribution in Utah I to IV

	Total (n = 333)	Lone AF (n = 40)	Non-lone AF (n = 293)	*P* value
Utah I, n (%)	21		17 (5.8)	.298
Utah II, n (%)	141		187 (63.82)	.884
Utah III, n (%)	148		67 (22.87)	.959
Utah IV, n (%)	23		22 (7.51)	.334

Mahnkopf C, et al.: Heart Rhythm 2010;7:1475-81

Autopsy data on fibrosis in AF: No correlation to age and risk factors



Blue circles = paroxysmal AF
Red circles = permanent AF
Green circles = no AF

- *No correlation at all* could be detected between patient age and increase in the extent of fibrosis or fatty changes in atrial tissue, in either total material or subgroup analysis.

- Atrial samples taken from age-matched AF-free pts contained *negligibly low amounts of fibrofatty tissue* despite similar clinical profile (No-AF group CHA2DS2-VASc Score 4.3±1.9).

Platonov PG, et al.: JACC 2011;58:2225-32

Is one risk factor/modulator enough to result in AF?

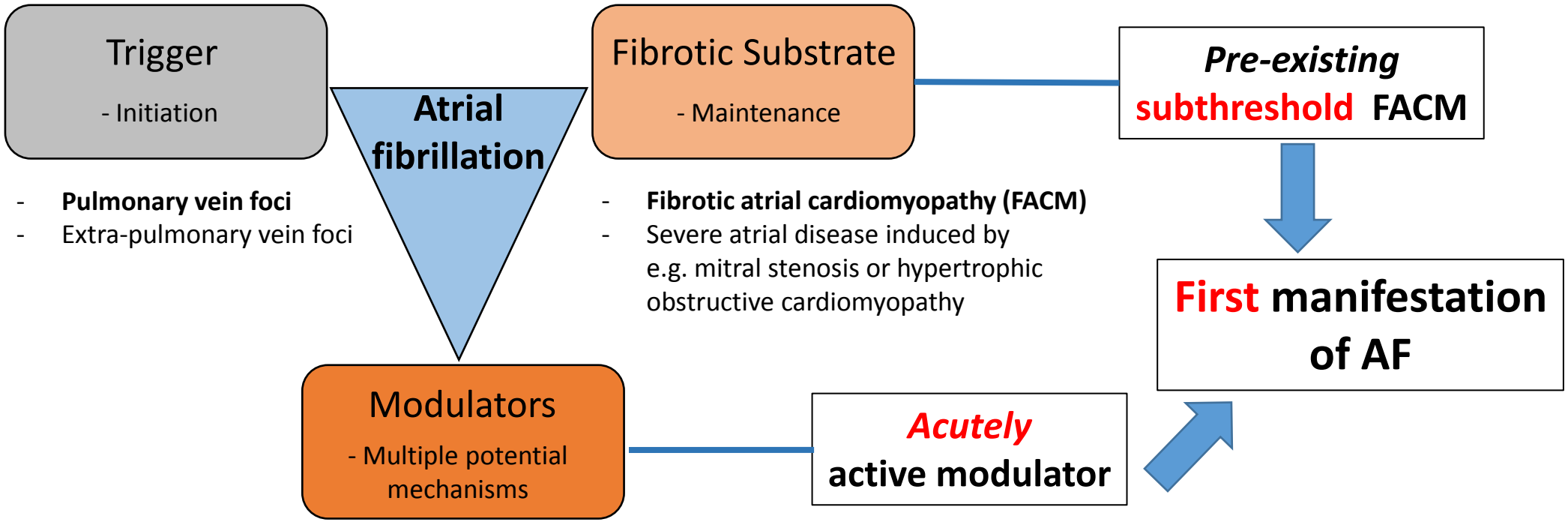
Example: Why do some pts after cardiac surgery get AF but most do not?

- 54 pts having cardiac surgery without a history of AF
- Pre-operative blood draw (serum markers for collagen) plus left and right atrial biopsies
- 18 pts developed AF, 36 pts remained in normal SR

- LA fibrosis and serum markers for collagen were both significantly higher in pts who developed AF vs. pts with stable SR

Swartz MF, et al.: JACC 2012;60:1799-806

Modulator surgery brings sub-threshold fibrosis to manifestation of AF

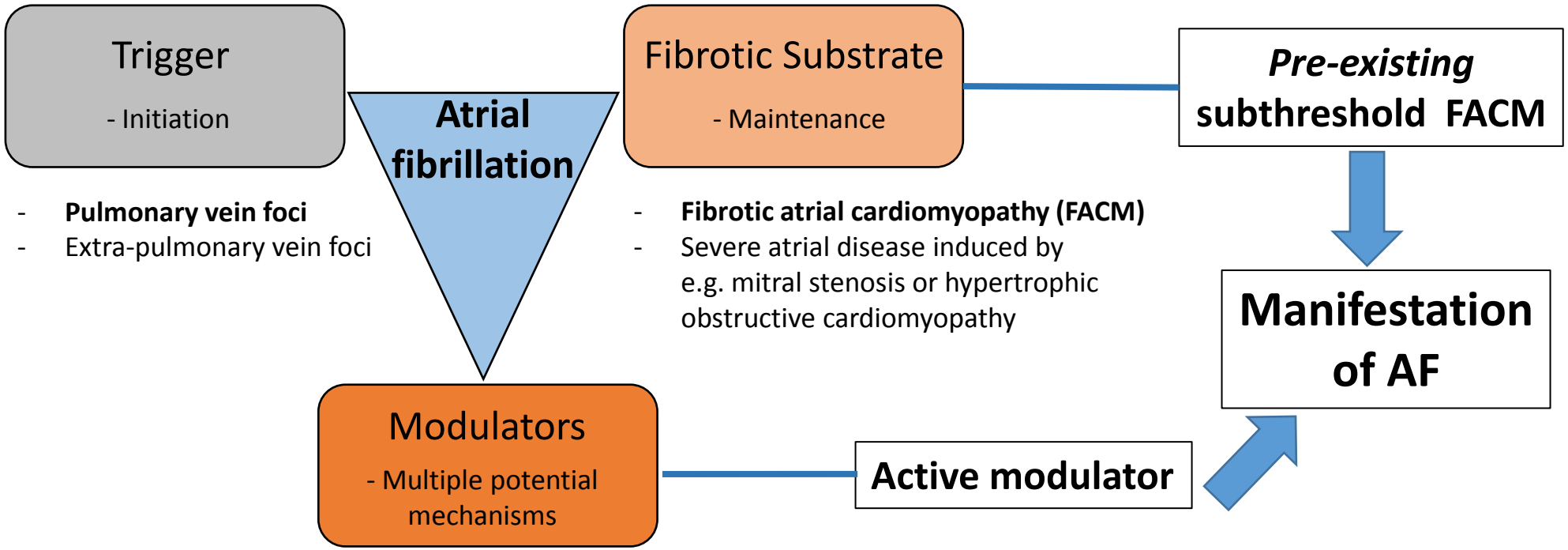


Kottkamp H: JCE 2012;23:797-799

Kottkamp H: Eur Heart J 2013;34:2731-2738

Kottkamp H, et al.: JACC EP 2016;2:140-142

Modulator surgery brings sub-threshold fibrosis to manifestation of AF



- **Pulmonary vein foci**
- Extra-pulmonary vein foci

- **Fibrotic atrial cardiomyopathy (FACM)**
- Severe atrial disease induced by e.g. mitral stenosis or hypertrophic obstructive cardiomyopathy

- Hypertension
- **Obesity**
- Obstructive sleep apnoe
- Other cardiac risk factors

- Inflammation
- Cancer
- Surgery

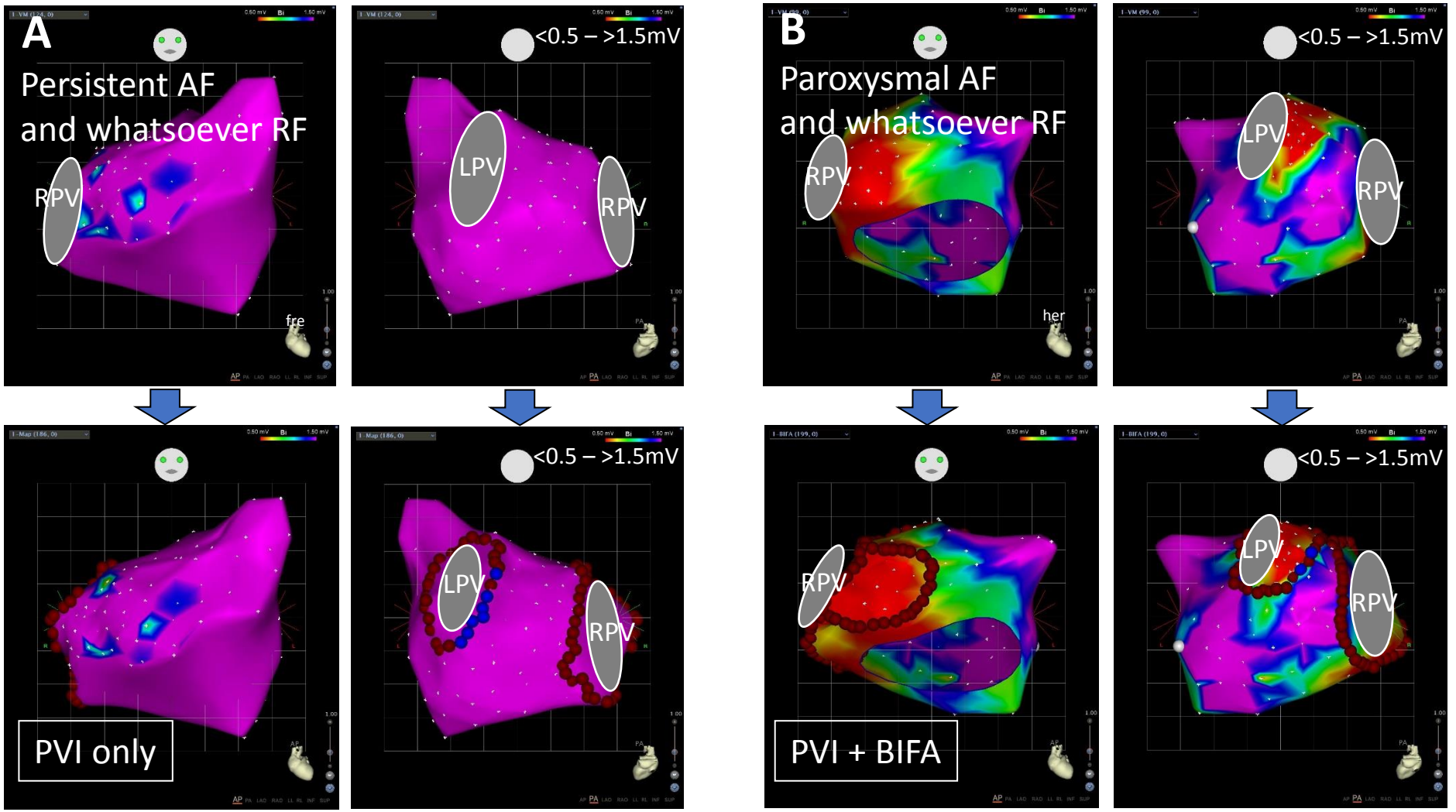
- Electrical remodeling
- Autonomic nervous system
- Endurance sports
- Others

Kottkamp H: JCE 2012;23:797-799

Kottkamp H: Eur Heart J 2013;34:2731-2738

Kottkamp H, et al.: JACC EP 2016;2:140-142

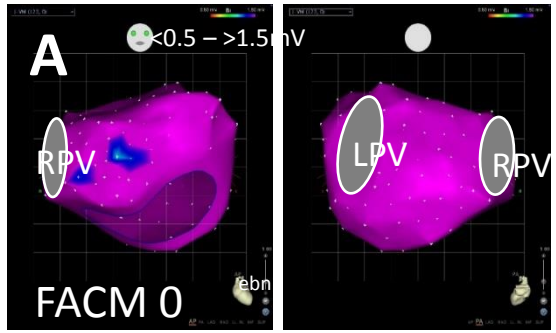
Ablation according to the *substrate*, not according to risk factors or PAF vs. Non-PAF



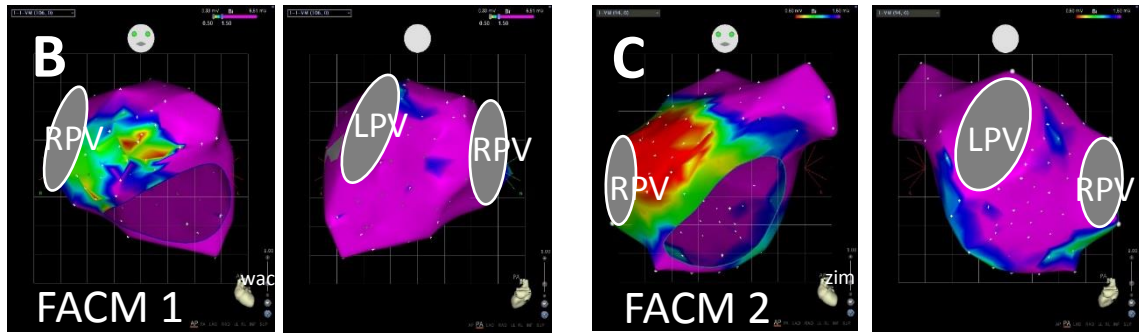
Kottkamp H, et al.: J Am Coll Cardiol 2015;65:196-206
Kottkamp H, et al.: JACC EP 2017;3:643-653

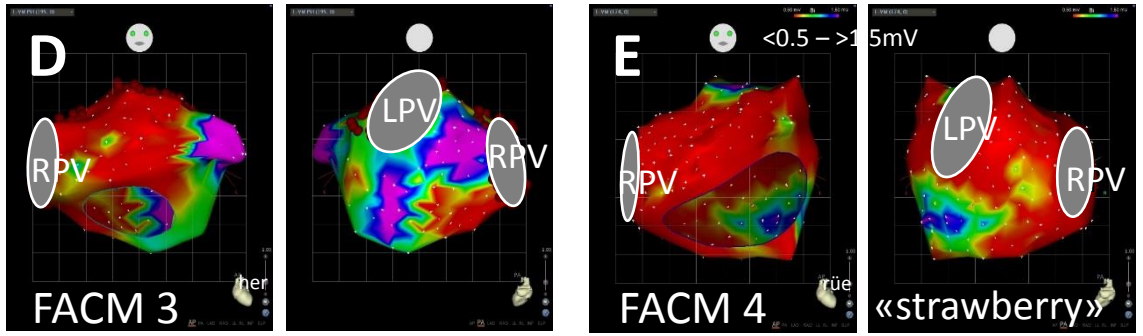
Ablation according to the *substrate*, not according to risk factors or PAF vs. Non-PAF

PVI only

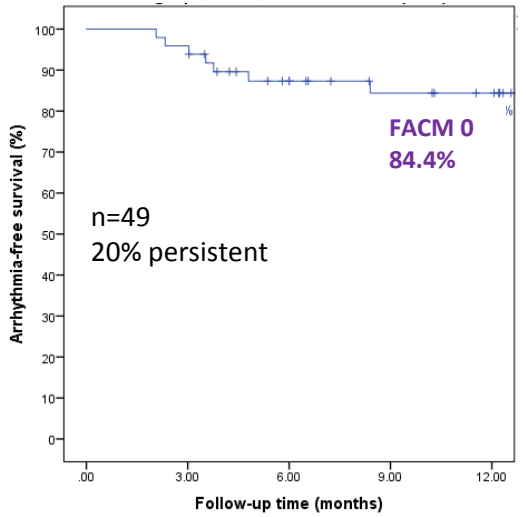


PVI + BIFA

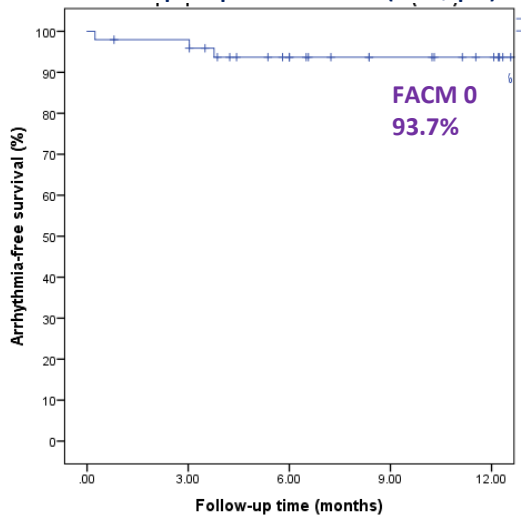




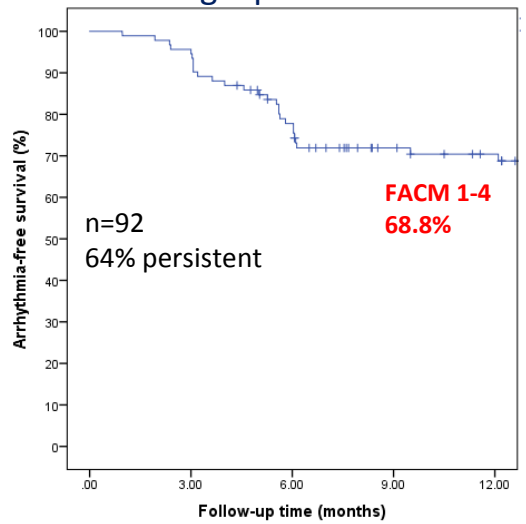
Single procedure



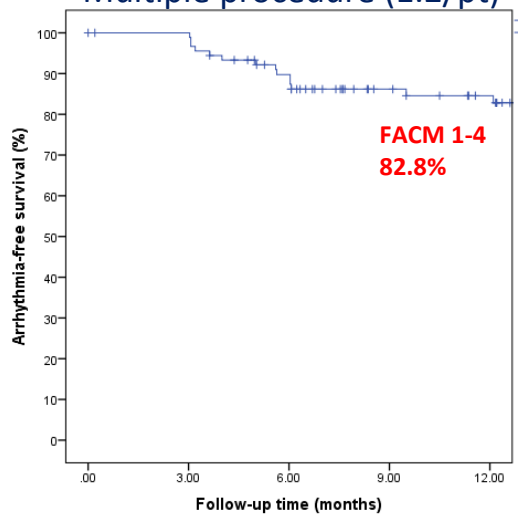
Multiple procedure (1.1/pt)



Single procedure



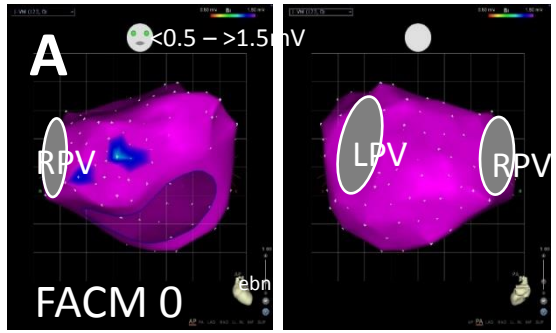
Multiple procedure (1.2/pt)



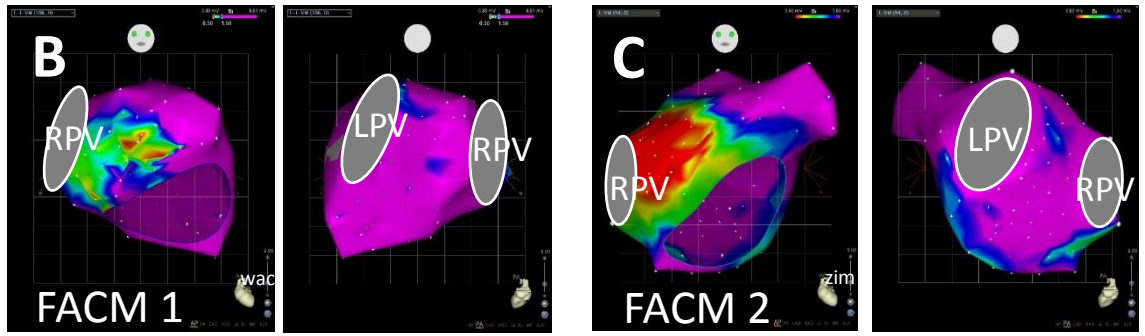
Schreiber D., … , Kottkamp H.: JCE 2017

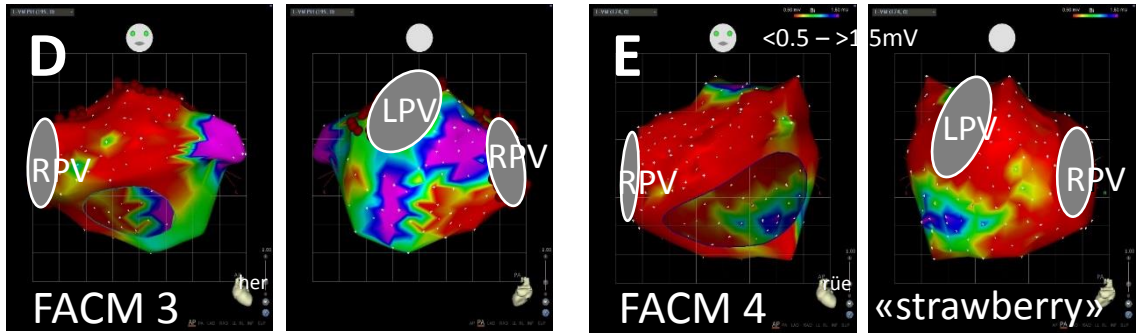
Ablation according to the *substrate*, not according to risk factors or PAF vs. Non-PAF

PVI only

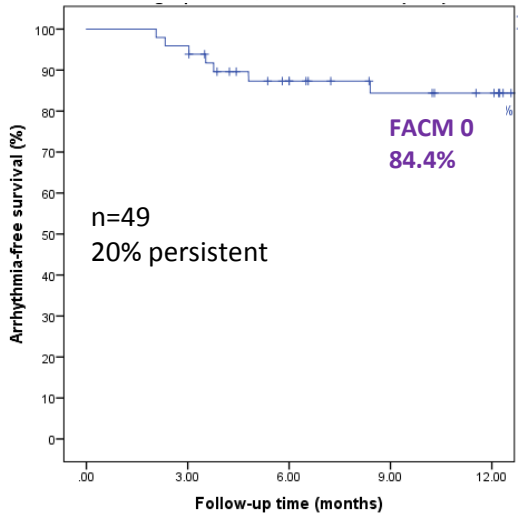


PVI + BIFA

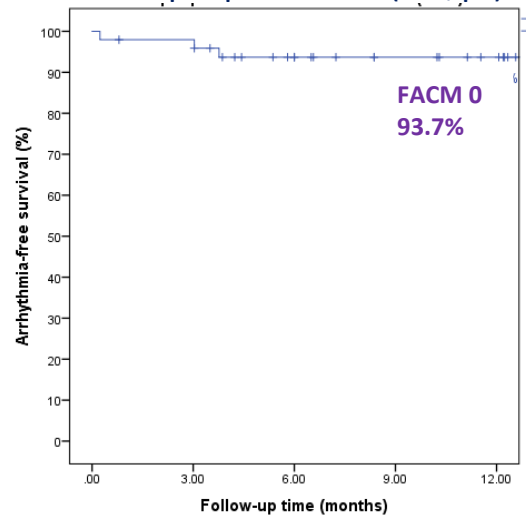




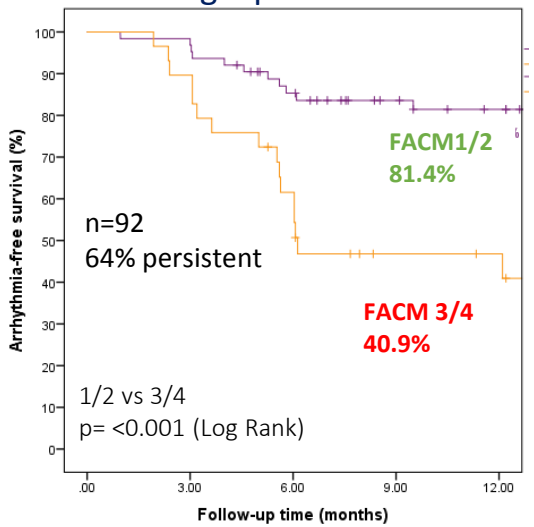
Single procedure



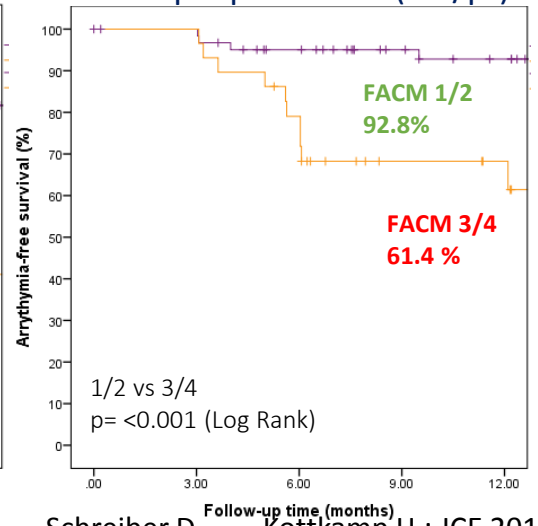
Multiple procedure (1.1/pt)



Single procedure



Multiple procedure (1.2/pt)



Schreiber D., … , Kottkamp H.: JCE 2017

Bariatric surgery and the risk of *new-onset* AF in Swedish obese subjects

BACKGROUND Obesity is a risk factor for atrial fibrillation, which in turn is associated with stroke, heart failure, and increased all-cause mortality.

OBJECTIVES The authors investigated whether weight loss through bariatric surgery may reduce the risk of new-onset atrial fibrillation.

METHODS SOS (Swedish Obese Subjects) is a prospective matched cohort study conducted at 25 surgical departments and 480 primary healthcare centers in Sweden. The cohort was recruited between 1987 and 2001. Among 4,021 obese individuals with sinus rhythm and no history of atrial fibrillation, 2,000 underwent bariatric surgery (surgery group), and 2,021 matched obese control subjects received usual care (control group). The outcome, first-time atrial fibrillation, was ascertained by crosschecking the SOS database with the Swedish National Patient Register on inpatient and outpatient diagnosis codes.

RESULTS During a median follow-up of 19 years, first time atrial fibrillation occurred in 247 patients (12.4%) in the surgical group, and in 340 (16.8%) control subjects. The risk of developing atrial fibrillation was 29% lower in the surgery group versus the control group (hazard ratio: 0.71; 95% confidence interval: 0.60 to 0.83; $p < 0.001$). Younger individuals benefited more from surgical intervention than those who were older (p value for interaction 0.001). Also, those with a high diastolic blood pressure benefitted more from surgery than did those with a low diastolic blood pressure (p for interaction = 0.028).

CONCLUSIONS Compared with usual care, weight loss through bariatric surgery reduced the risk of atrial fibrillation among persons being treated for severe obesity. The risk reduction was more apparent in younger people and in those with higher blood pressure. (J Am Coll Cardiol 2016;68:2497-504) © 2016 The Authors. Published by Elsevier

Jamaly J, et al.: JACC 2016;68:2497-504

AF treatment: Life-style change first or ablation first?

- Clear evidence: In pts with massive obesity and moderate burden of AF, substantial weight loss will very likely result in lower burden of AF and perhaps even freedom of AF

- Option 1: Pts with symptomatic AF and metabolic syndrome should be advised to undergo life-style changes prior to scheduling an ablation procedure
  - but most of these pts hate that…
  - and the AF burden may simply be too large to recommend such a strategy

- Option 2 reverse approach: Ablation first with elimination of AF, allowing return to more active life-style resulting in effective and long-lasting risk factor management

Patient selection for AF ablation and impact of risk factor management on treatment success

- *How can the patient contribute?*
- *Life style modifications and outcome of AF ablation*

Hans Kottkamp, M.D.

Hirslanden Hospital
Dept. of Electrophysiology
Zurich, Switzerland

Multimodal substrate examination: PBP, FAM, and MRI

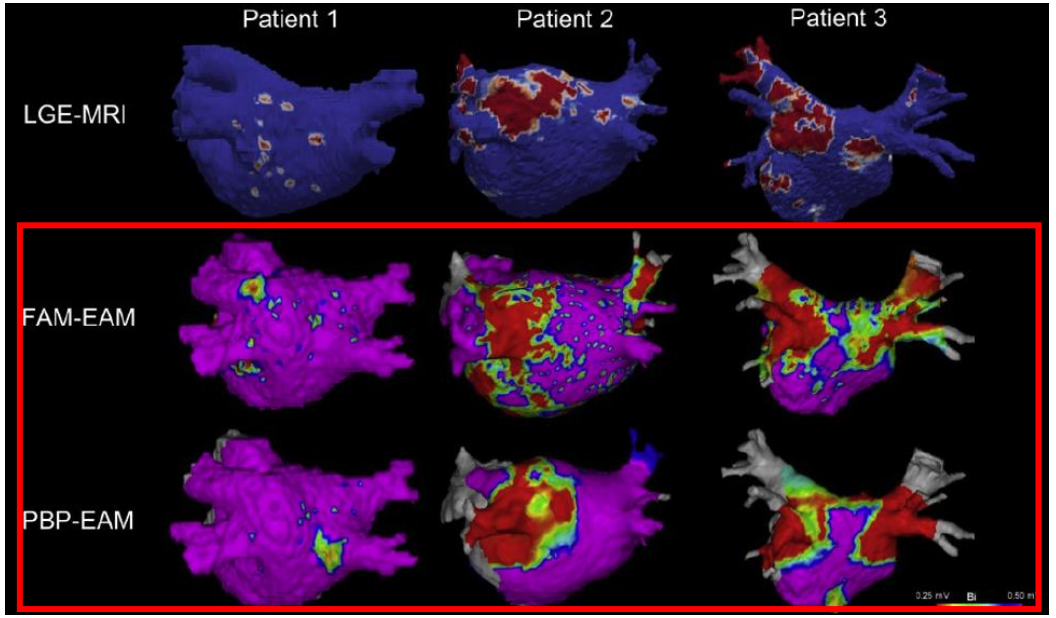
- Mapping during sinus rhythm
- Point-by-point mapping PBP, mean 82 points
- Fast automated mapping (FAM with CMC), mean 734 points

- Mean bipolar voltage FAM 1.20 ± 1.36mV
  Mean bipolar voltage PBP 0.91 ± 0.99mV

- 20th percentile, FAM 0.08 vs. PBP 0.18mV
- 40th FAM 0.25 vs. PBP 0.42mV

- 60th FAM 0.69 vs. PBP 0.73mV
- 80th FAM 1.52 vs. PBP 1.54mV

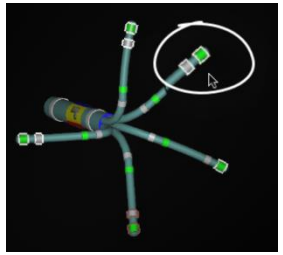
- 99th FAM 6.26 vs. PBP 4.65mV



Tarek Zghaib, Saman Nazarian, et al.: JACC EP 2018;4:59-68

High resolution mapping in normal and diseased left atria

- 10 pts with structurally normal atria
- 20 pts with scar-related atrial arrhythmias



- 3.5-mm tip electrode (Thermocool) vs. 1-mm multi-electrode-mapping catheter (Pentaray)
- LA Mapping points in scar group: mean 1858 vs. 472 points
- Normal bipolar voltage similar: fifth percentile 0.48 vs. 0.52mV
- In pts with scar-related arrhythmias, area of bipolar voltage <0.5 mV was smaller with 1-mm electrode catheter: 14.7 vs. 20.4cm2.
- The mean bipolar voltage amplitude in these areas was higher with 1-mm electrode catheter: 0.28 vs. 0.17 mV

Anter E, et al.: Circ AE 2015;8:537-545