Atriyal fibrilasyonda inflamasyon ve fibrosis

Özgür Aslan

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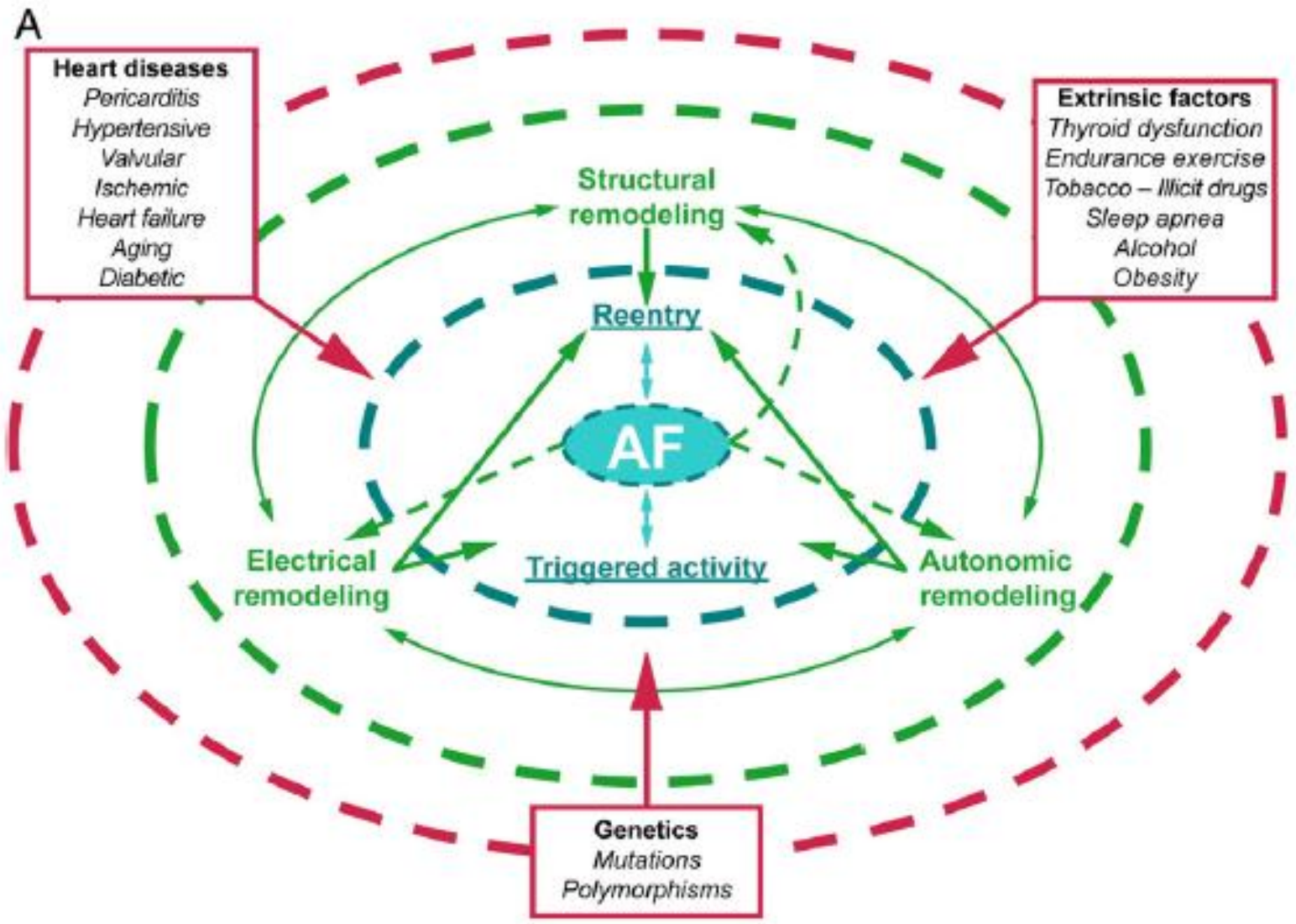
AF zirvesi 2014, Mayıs ,Antalya



Camm et al

American Heart Journal
September 2012

Atriyal fibrilasyonda inflamasyon ve fibrosis

- AF'nin nedeni olarak Fibrozis
  - AF etiyopatogenezi
  - «Yapısal» yeniden biçimlenme
  - AF'nin elektrofizyolojik zemininde fibrozisin rolü
  - Bir AF nedeni olarak «Fibrotik atriyal kardiyomiyopati»
- AF'nin sonucu olarak Fibrozis
  - «Elektriksel» yeniden biçimlenme
- AF'de İnflamasyon
  - Neden ? / Sonuç ?

- Fibrozisin / İnflamasyonun belirlenmesi/ortaya konulması
  - Lab «Belirleyicileri»
  - Görüntüleme
    - MR !!

- *Fibrozisi hedefleyen yaklaşımlar*
  - *İlaçlar ?*
    - *«Upstream» ilaçlar*
    - *İnflamasyon önleyici*
    - *Fibrozis önleyici*
  - *Fibrozise dayanan stratejiler*

AF'de fibrozis
- neden mi, sonuç mu ? -

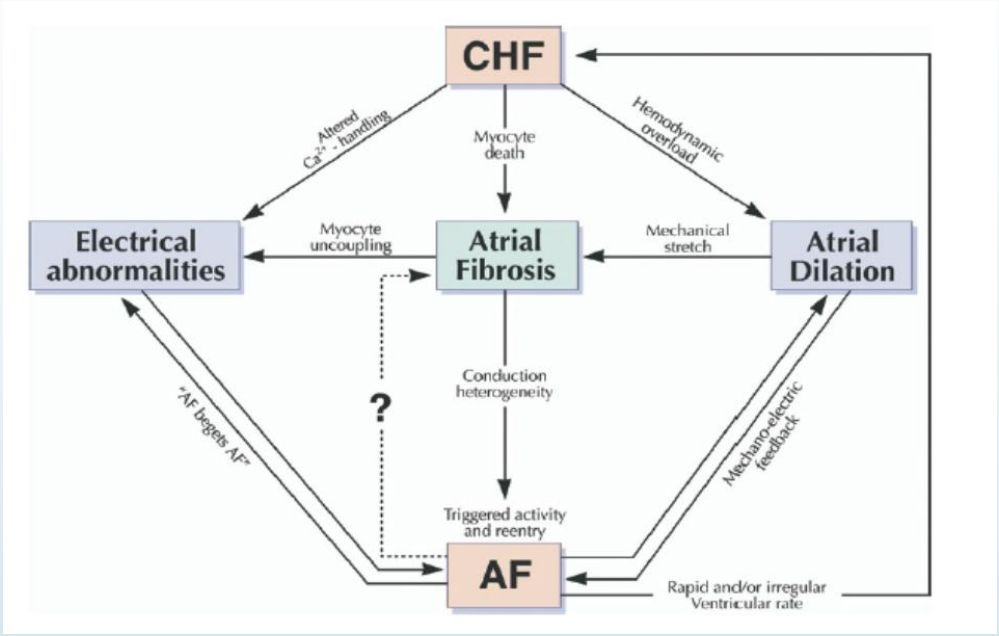
- AF insanların yaklaşık %70'inde bir yapısal (kalp) hastalığının sonucu ! x
- "Lone" AF olgularının atriyumlarında sinüs ritmindeki kontrol olgularına göre daha fazla kollajen depolanması ! xx
- Mitral kapak hastalığı ve kardiyomiyopati gibi yapısal hastalıklarla birlikte olan AF'de de fibrozis daha çok ! xxx, xxxx
  - Ekstrasellüler matriks hacmi ve konpozisyonu AF nin kalıcılaşmasıyla ilişkilidir ! xxxx
- AF ablasyonu yapılan hastalarda hem işlem başarısını hem de nüksü öngörmede MR ile ortaya konulan sol atriyum fibrozis derecesi belirleyici olabilir ! xxxx, xxxxx

x Levy S. Pacing Clin Electrophysiol. 1997;20:2670–2674.
xx Frustaci A, et al. Circulation. 1997;96: 1180–1184.
xxx Boldt A, et al. Heart. 2004;90:400–405.
xxxx Oakes RS, et al. Circulation. 2009; 119:1758–1767.
xxxxx Mahnkopf C, et al. Heart Rhythm. 2010 Jul 2

AF'nin nedeni olarak Fibrozis

- Kalp yetersizliği /mitral hastalığı ve yaşlanma modelleri
  - Yapısal "yeniden biçimlenme"
    - **Fibrozis – lokalize iletim yavaşlaması ve heterojenite artışı – reentry**
    - Atriyal iyonik akım değişiklikleri ve Ca2+ kullanım özellikleri !
    - **"Stabil bir yüksek frekanslı alan"**
    - Daha az oranda "fokal tetiklenmiş aktivite alanları"

Tan AY, Zimetbaum P. J Cardiovasc Pharmacol 2011;57:625–629



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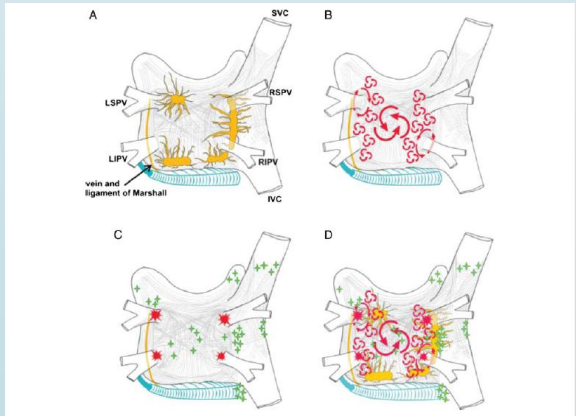
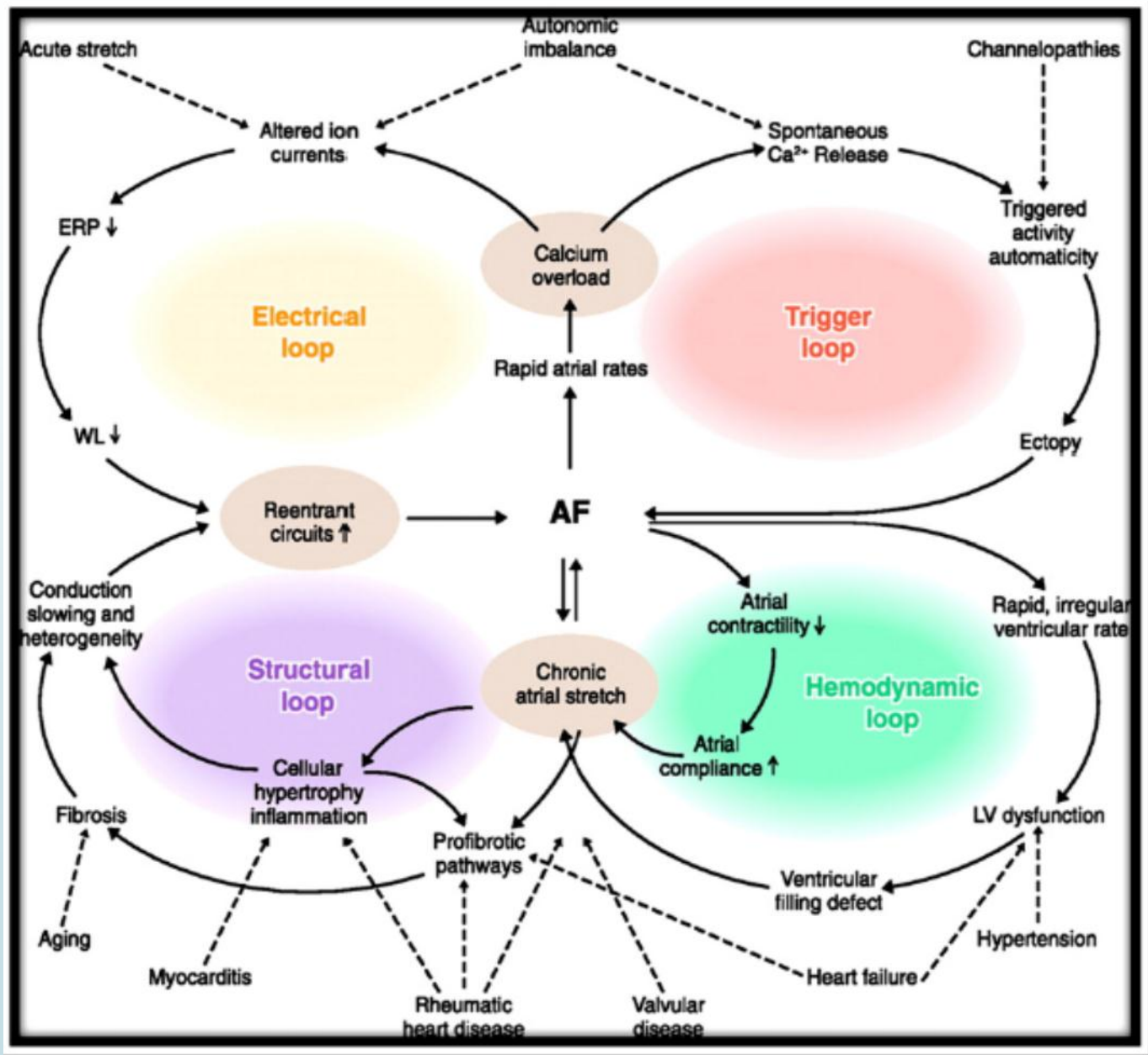


AF'nin elektrofizyolojik temelleri

AF'nin nedeni olarak Fibrozis

- AF Fizyopatolojisi

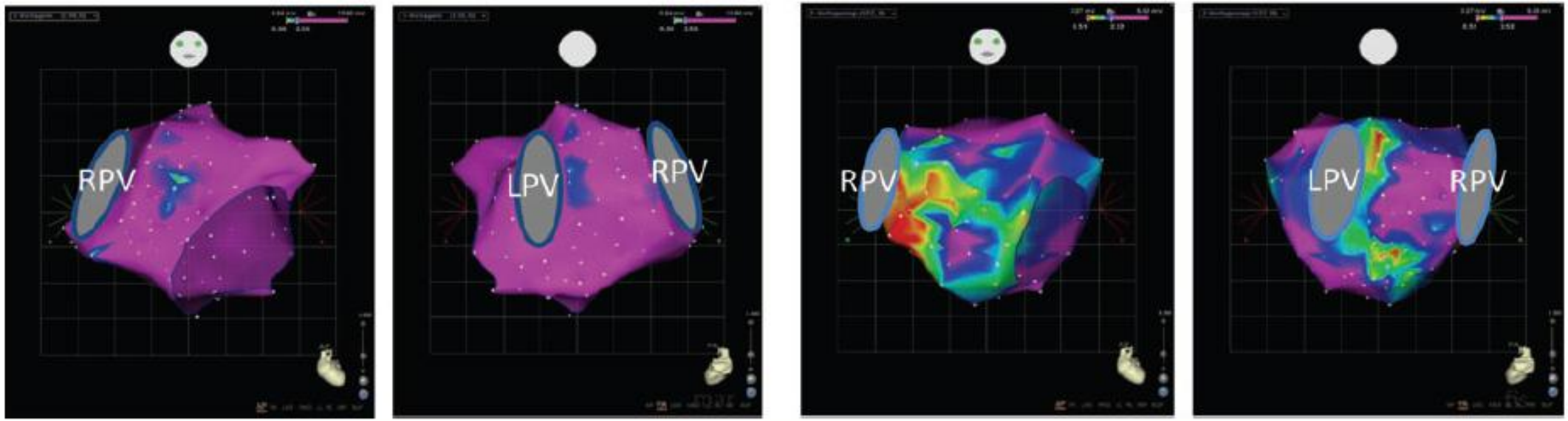


AF'nin nedeni olarak Fibrozis

- Bir AF nedeni olarak «**Fibrotik Atriyal Kardiyomiyopati**»

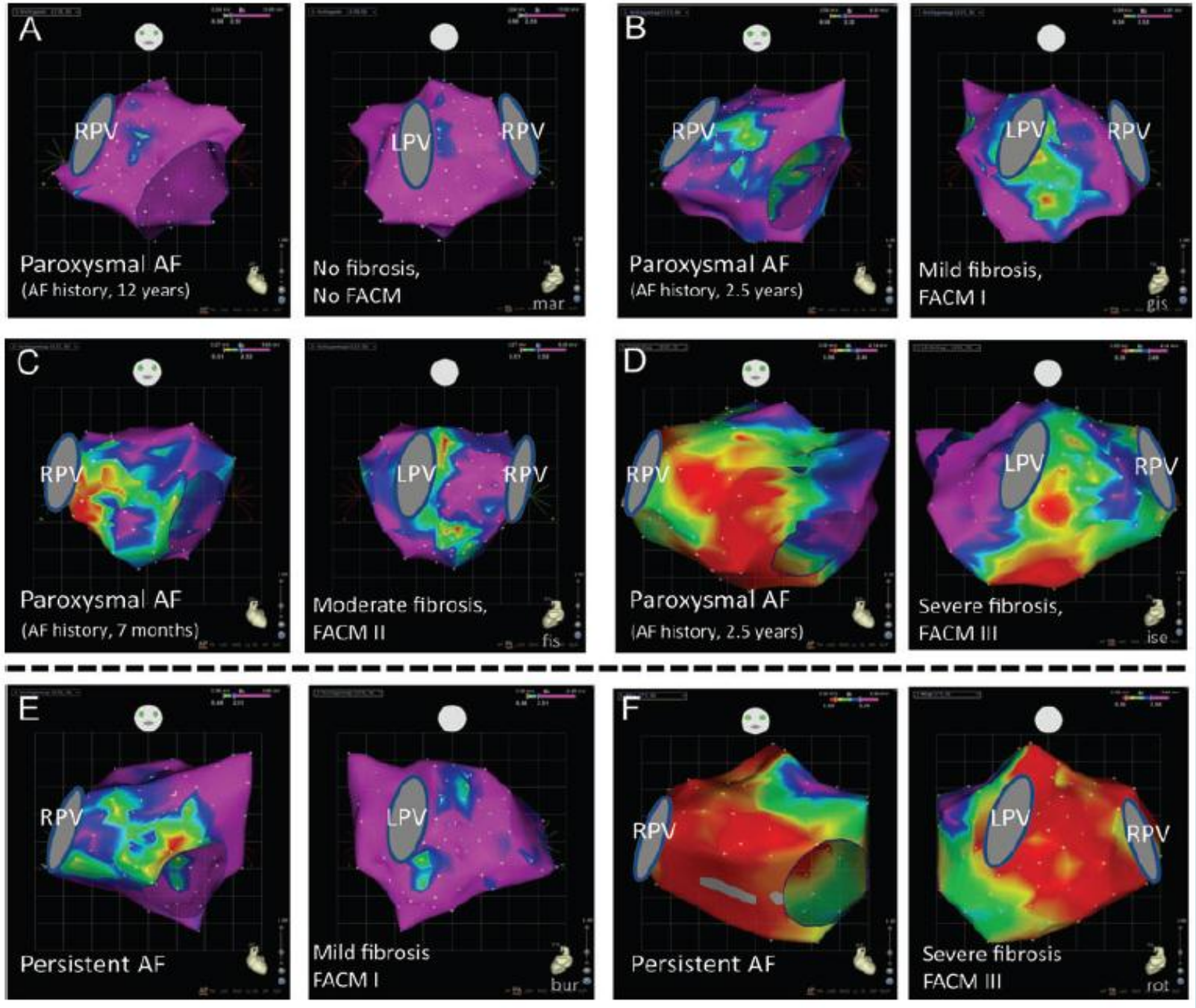
A
- Patient with „focal AF"/no atrial fibrosis
- Age, 47 years
- No structural heart disease
- Paroxysmal AF for 12 years (in the last 2 years almost daily episodes)
- AF episode length minutes to maximal 2 h

B
- Patient with moderate atrial fibrosis
- Age, 49 years
- No structural heart disease
- Paroxysmal AF for only 7 months (estimated overall 10 – 12 AF episodes)
- AF episode length directly 24 – 36 h



Kottkamp H. European Heart Journal (2013) 34, 2731–2738

- Fibrotik atriyal Kardiyomiyopati (FAKM)



Kottkamp H. Heart Rhythm 2012;9:481–482
Kottkamp H. European Heart Journal (2013) 34, 2731–2738

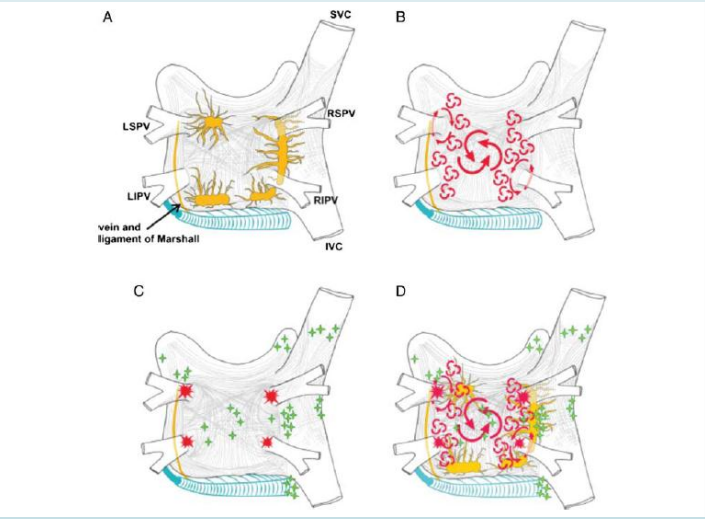
AF'nin nedeni olarak Fibrozis

- «**Fibrotik atriyal kardiyomiyopati**»
  - «Lone AF» olgularının önemli bir kısmı ?
    - Taşikardi-Bradikardi sendromu ?
  - Tanı ?
    - Elektroanatomik haritalama
      - Girişimsel !
    - «Delayed Enhancement» (DE) - MRI
    - Kollajen sentezinin serum belirleyicileri ?
      - PICP
    - Genetik ?
    - C-reaktif protein ?

Kottkamp H. European Heart Journal (2013) 34, 2731–2738

AF'nin sonucu olarak Fibrozis

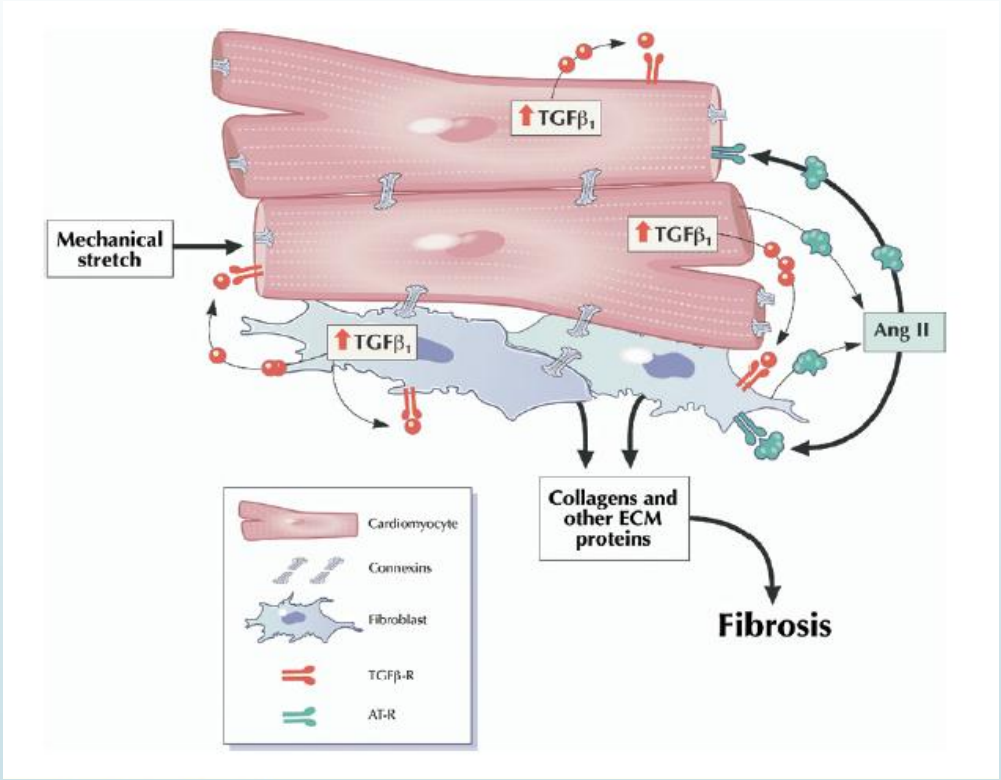
- «Elektriksel Yeniden Biçimlenme»
  - Hızlı atriyal uyarılar (pacing / taşikardiler)
  - Fibrozis daha az !
  - Elektrofizyolojik değişim belirgin !
    - Ical ve potasyum akımlarında «downregülasyon»
    - Atriyal refrakter periyodda (ARPD) kısalma
  - **Multipl yüksek frekanslı "wavelets" !**



AF'nin elektrofizyolojik temelleri

AF ve Fibrozis

- Atriyal Fibrozisin mekanizmaları ?
  - "Renin-Anjiyotensin-Aldosteron sistemi"
    - Aldosteron
    - Anjiyotensin II
  - "Transforming growth factor-b1"
    - Anjiyotensin II ile TGF-b1 expresyonu ve kollajen üretimi
  - PDGF
    - Fibroblast proliferasyonu ve diferensiyasyonu
  - "Oksidatif stres yolakları"



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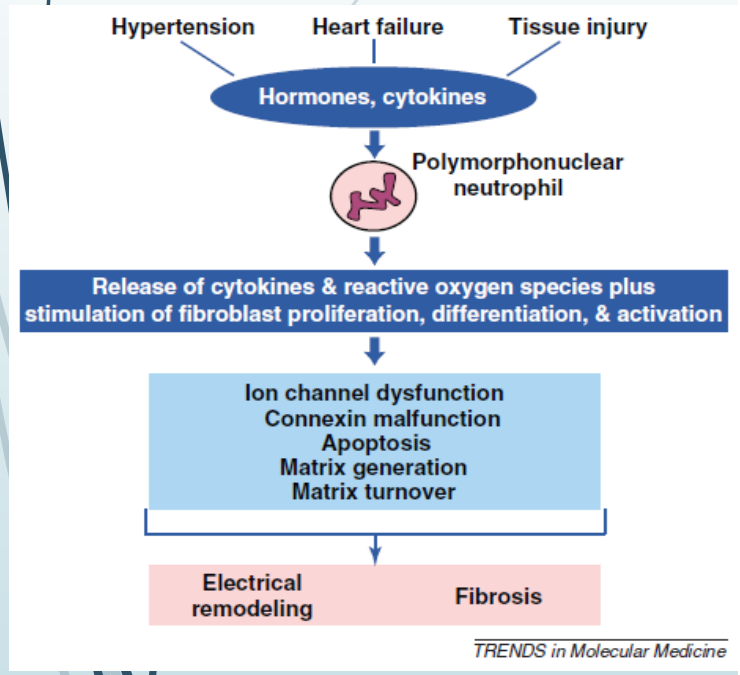
Tan AY, Zimetbaum P. J Cardiovasc Pharmacol 2011;57:625–629

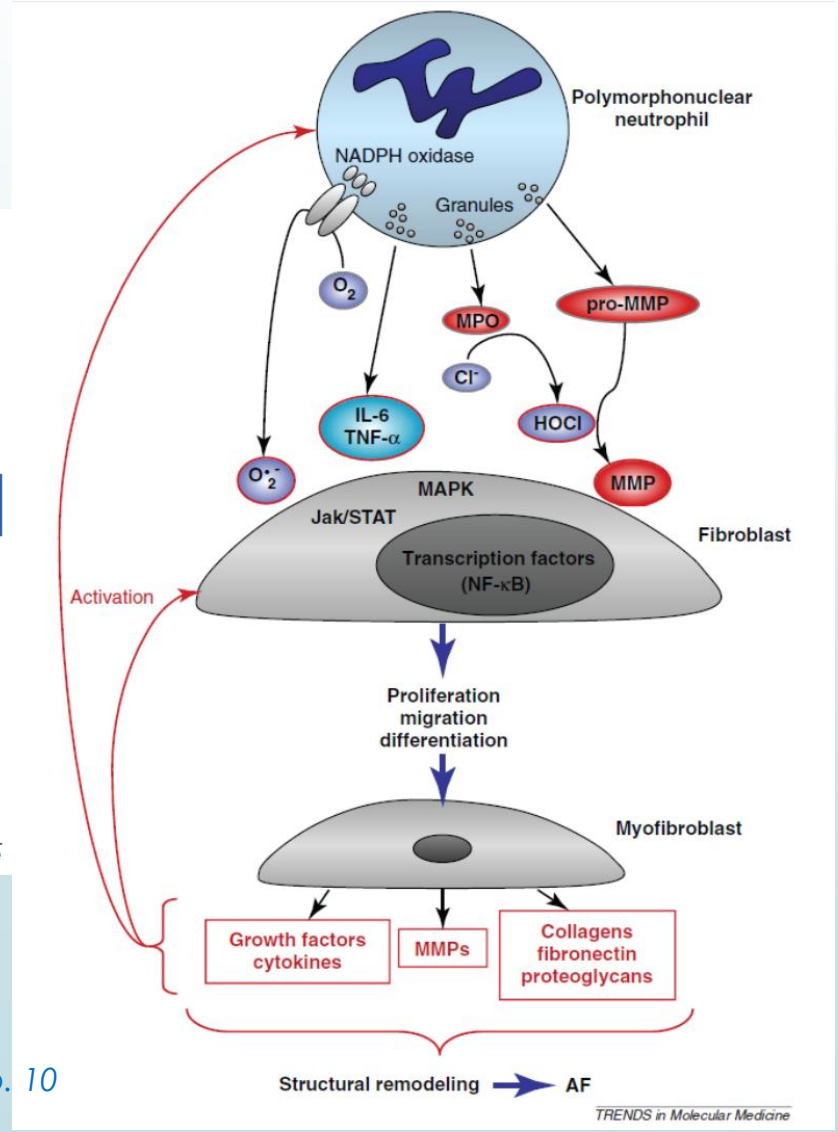
İnflamasyon – AF ilişkisi
- neden mi sonuç mu ? -

- İnflamasyonun AF'yi tetiklemesi ?
  - İnflamatuar durumlarda AF !
    - Miyokardit, perikardit, postop, vb…
  - Epidemiyolojik çalışmalar
    - Women's Health Study
      - AF –CRP ilişkisi
- AF'nin inflamatuar durumu tetiklemesi ?
  - Sinüs ritmine dönüşle CRP düşüşü
  - Ablasyon sonrası CRP düşüşü !
  - AF'nin trombotik sonuçlarıyla inflamasyon ilişkisi !

Guo Y et al. J Am Coll Cardiol 2012;60:2263–70)

AF ve inflamasyon





- **Lökosit aktivasyonu**
- **«C-reactive protein»**
  - Hepatositlerden akut faz reaktanı olarak sentezlenir.
  - Monositlerde «MCP-1–mediated» kemotaksis
  - Doku faktörü sekresyonunun indüklenmesi ve prokoagülan aktivite
  - CRP-AF ilişkisi ?
    - AF tekrarının belirleyicisi ?
    - AF oluşmasının belirleyicisi ?
- **«Tumor necrosis factor»**
  - Monosit ve makrofajlarldan sentez
  - Proinflamatuar
  - AF'de LA çapı ve fibrozis ile ilişki ?
    - AF'nin kalıcılaşmasıyla ilişki ?
- **«Interleukin-2»**
  - Aktive T lenfositlerince sentez
  - Post op AF ile ilişki ?
  - Düşük düzeyleri KV başarısıyla ilişkili ?
- **«Interleukin-6»**
  - Proinflamatuar
  - Akut faz reaktanslarının sentezini uyarır
  - AF'nin oluşması ve kalıcılaşmasıyla ilişki ?

Friedrichs K et al. Trends in Mol Med 2011;17, No. 10
Guo Y et al. J Am Coll Cardiol 2012;60:2263–70)

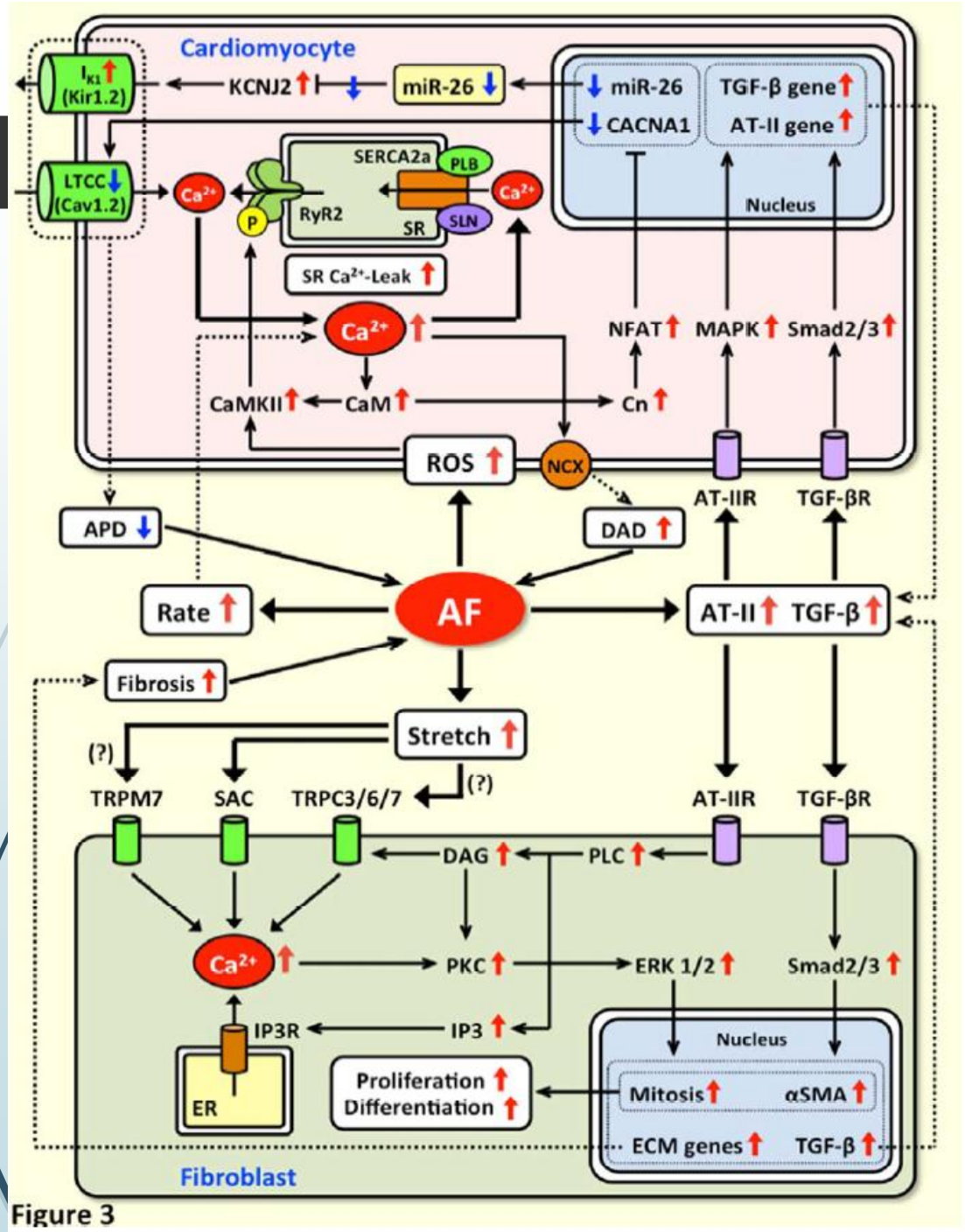
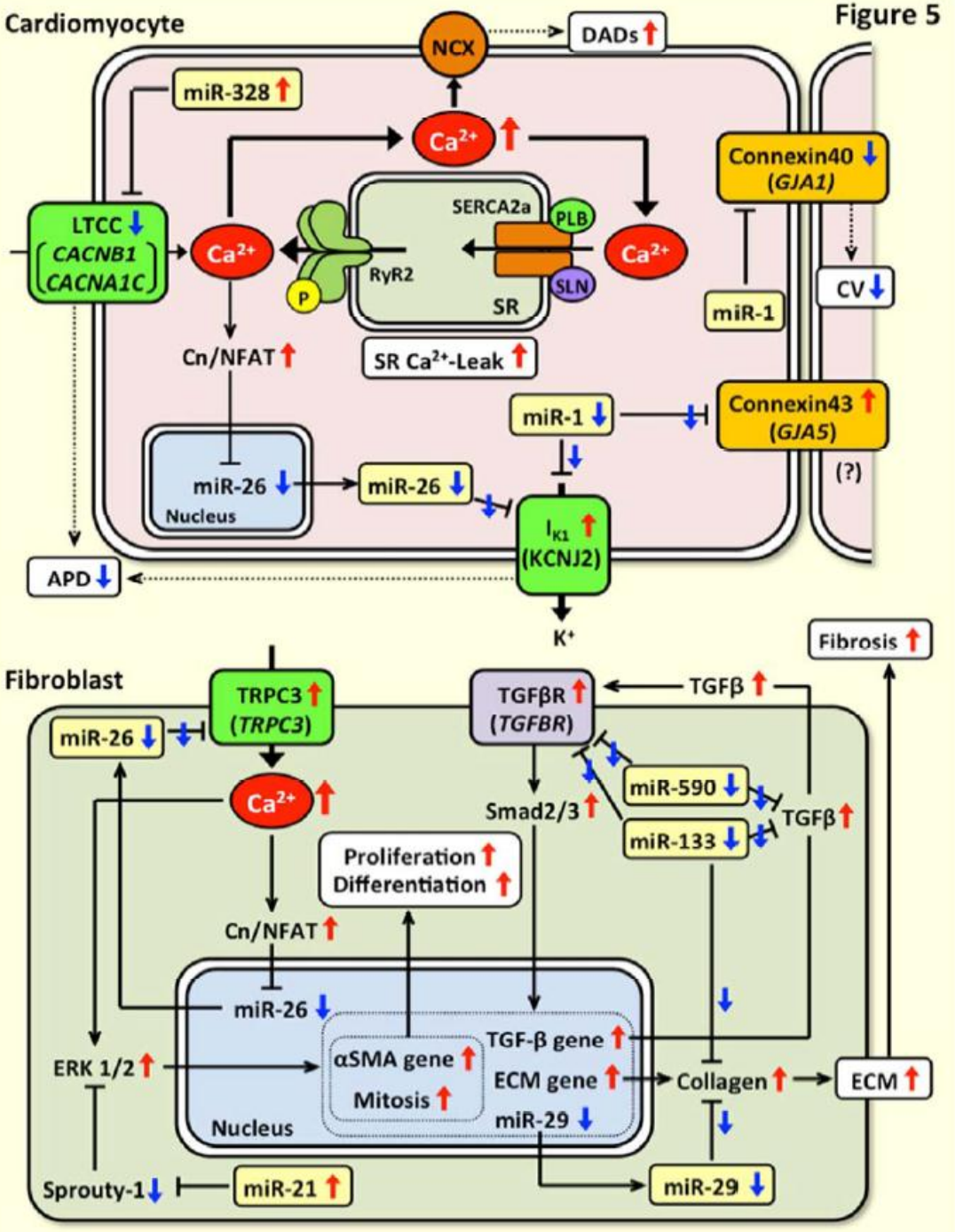


Figure 3

Figure 5



Fibrozisin belirlenmesi/ortaya konulması

- Lab «Belirleyiciler» ???

Table 1. Inflammatory biomarkers in atrial fibrillation: patient studies[a]

Biomarker	Patients (Number)	Duration	Design	Follow-up endpoint
CRP	19	5 days	Longitudinal	Interrelation of arrhythmia with CRP- and complement-plasma levels after CABG
	5806	6.9 ± 1.6 years	Longitudinal	Predictive value of CRP levels for AF occurrence
	77	2305 days	Longitudinal	CRP and IL-6 levels in patients with chronic AF
	90	–	Cross-sectional	Association of CRP and IL-6 levels with AF and left atrial size
	1011	4 years	Longitudinal	Prediction of risk of CRP levels for AF
	72	12.5 ± 5.7 months	Longitudinal	Association of AF recurrence after PVI with CRP levels
	5187	14 years	Longitudinal	Predictive value of CRP for incident AF
	3120	9.7 years	Longitudinal	Predictive value of CRP for incident AF
IL-6	77	2305 days	Longitudinal	CRP and IL-6 levels in patients with chronic AF
	90	–	Cross-sectional	Association of CRP and IL-6 levels with AF and left atrial size
	46	1 year	Longitudinal	IL-6 levels and prediction of sinus rhythm maintenance in patients with lone AF; association of TNF-α and IL-6 levels with lone AF
	84	180 days	Longitudinal	CRP and IL-6 levels predict AF recurrence after cardioversion
	374	–	Cross-sectional	Correlation of CRP and IL-6 levels with AF
TNF-α	46	1 year	Longitudinal	IL-6 levels and prediction of sinus rhythm maintenance in patients with lone AF; association of TNF-α and IL-6 levels with lone AF
Leukocytes	12	–	Cross-sectional	Atrial histology in biopsies of right atrial septum or ventricles from patients with lone AF
	253	5 days	Longitudinal	Correlation between postoperative leukocyte count and AF
	35	–	Cross-sectional	Leukocyte infiltration in atrial appendage tissue from patients with AF
	16	–	Cross-sectional	Leukocyte infiltration in atrial appendage tissue from patients with AF
MPO	42	3 months	Longitudinal	Correlation of AF burden with myeloperoxidase plasma levels
MMP2	50	14 months	Longitudinal	Recurrence of AF on ablation

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Novel fibro-inflammation markers in assessing left atrial remodeling in non-valvular atrial fibrillation

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
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Source of support: The abstract of this manuscript has been accepted and presented as an oral presentation in The 29th National Cardiology Congress, October 26-29/2013, Antalya, Turkey

Background: Structural remodeling is associated with the fibroinflammatory process in the atrial extracellular matrix. In the present study we aimed to investigate whether serum levels of new circulating remodeling markers differ in patients with atrial fibrillation (AF) compared to patients with sinus rhythm.

Material/Methods: The study population included 52 patients diagnosed with non-valvular AF and 33 age-matched patients with sinus rhythm. Serum levels of Galectin-3, matrix metalloproteinase-9 (MMP-9), lipocalin-2 (Lcn2/NGAL), N-terminal propeptide of type III procollagen (PIIINP), Hs-Crp, and neutrophil-to-lymphocyte ratio (NLR) were measured. The left atrial volume (LAV) was calculated by echocardiographic method and LAV index was calculated.

Results: Galectin-3, MMP-9, and PIIINP levels were significantly higher in AF patients except NGAL levels (1166 pg/ml (1126–1204) and 1204 pg/ml (1166–1362) p=0.001, 104 (81–179) pg/ml and 404 (162–564) pg/ml p<0.0001, and 1101 (500–1960) pg/ml and 6710 (2370–9950) pg/ml p<0.0001, respectively). The NLR and Hs-CRP levels were also higher in AF (2.1±1.0 and 2.7±1.1 p=0.02 and 4.2±1.9 mg/L and 6.0±4.7 mg/L p=0.04, respectively). In correlation analyses, NLR showed a strongly significant correlation with LAVi, but Hs-CRP did not (p=0.007 r=0.247, Pearson test and p=0.808 r=0.025, Pearson test, respectively). Moreover, Galectin-3, MMP-9, and PIIINP had a strong positive correlation with LAVi (p=0.021 r=640, Spearman test and p=0.004 r=0.319 Pearson test, and p=0.004 r=0.325 Pearson test, respectively).

Conclusions: Novel fibrosis and inflammation markers in AF are correlated with atrial remodeling. Several unexplained mechanisms of atrial remodeling remain, but the present study has taken the first step in elucidating the mechanisms involving fibrosis and inflammation markers.

Electrophysiology

Circulating fibrosis biomarkers and risk of atrial fibrillation: The Cardiovascular Health Study (CHS)

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Background Cardiac fibrosis is thought to play a central role in the pathogenesis of atrial fibrillation (AF). Retrospective studies have suggested that circulating fibrosis biomarkers are associated with AF, but prospective studies are limited.

Methods We measured circulating levels of 2 fibrosis biomarkers, procollagen type III, N-terminal propeptide (PIIINP) and transforming growth factor β1 among participants of the CHS, a population-based study of older Americans. We used Cox proportional hazards and competing risks models to examine adjusted risk of incident AF over a median follow-up of 8.8 years.

Results Levels of PIIINP were assessed in 2,935 participants, of whom 767 developed AF. Compared with the median PIIINP level (4.45 μg/L), adjusted hazard ratios (95% CIs) were 0.85 (0.72-1.00) at the 10th percentile, 0.93 (0.88-0.99) at the 25th percentile, 1.04 (0.95-1.04) at the 75th percentile, and 1.07 (0.90-1.26) at the 90th. Transforming growth factor β1 levels, assessed in 1,538 participants with 408 cases of incident AF, were not associated with AF risk.

Conclusion In older adults, PIIINP levels were associated with risk of incident AF in a complex manner, with an association that appeared to be positive up to median levels but with little relationship beyond that. Further studies are required to confirm and possibly delineate the mechanism for this relationship. (Am Heart J 2014;167:723-728.e2.)

Galectin 3 and incident atrial fibrillation in the community

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Background Galectin 3 (Gal-3) is a potential mediator of cardiac fibrosis, and Gal-3 concentrations predict incident heart failure. The same mechanisms that lead to cardiac fibrosis in heart failure may influence development of atrial fibrosis and atrial fibrillation (AF). We examined the association of Gal-3 and incident AF in the community.

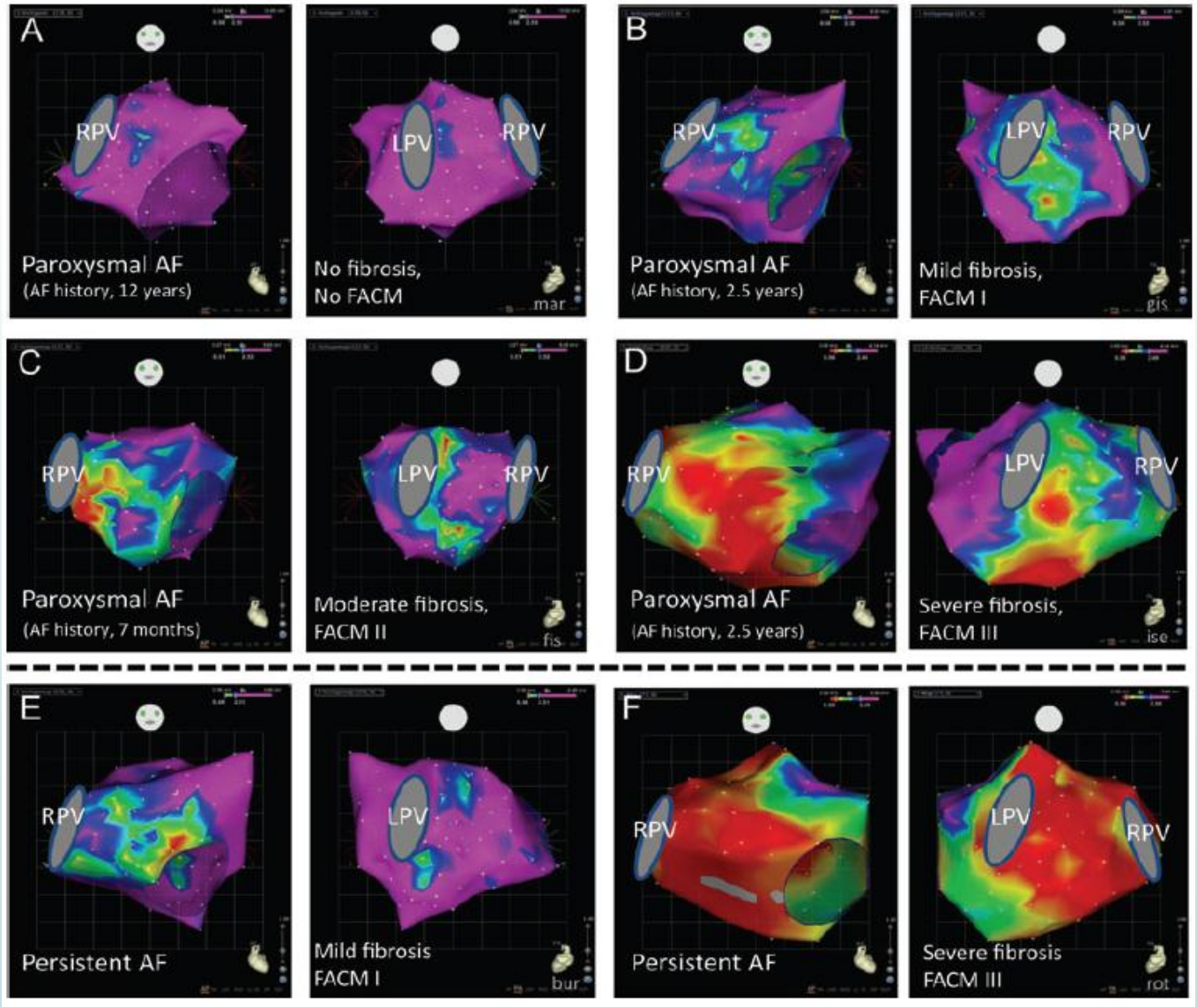
Methods Plasma Gal-3 concentrations were measured in 3,306 participants of the Framingham Offspring cohort who attended the sixth examination cycle (1995-1998, mean age 58 years, 54% women). Cox proportional hazards regression models were used to assess the association of baseline Gal-3 concentrations and incident AF.

Results Over a median follow-up period of 10 years, 250 participants developed incident AF. Crude incidence rates of AF by increasing sex-specific Gal-3 quartiles were 3.7%, 5.9%, 9.1%, and 11.5% (log-rank test $P < .0001$). In age- and sex-adjusted analyses, each 1-SD increase in $\log_e$-Gal-3 was associated with a 19% increased hazard of incident AF (hazard ratio 1.19, 95% CI 1.05-1.36, $P = .009$). This association was not significant after adjustment for traditional clinical AF risk factors (hazard ratio 1.12, 95% CI 0.98-1.28, $P = .10$).

Conclusion Higher circulating Gal-3 concentrations were associated with increased risk of developing AF over the subsequent 10 years in age- and sex-adjusted analyses but not after accounting for other traditional clinical AF risk factors. Our results do not support a role for Gal-3 in AF risk prediction. Further studies are needed to evaluate whether Gal-3 plays a role in the development of AF substrate similar to HF. (Am Heart J 2014;167:729-734.e1.)

Fibrozisin belirlenmesi/ortaya konulması

- Görüntüleme
  - Elektroanatomik voltaj haritalama !



Kottkamp H. Heart Rhythm 2012;9:481–482
Kottkamp H. European Heart Journal (2013) 34, 2731–2738

Fibrozisin belirlenmesi/ortaya konulması

- Görüntüleme
  - «Delayed enhancement» DE- MR !!

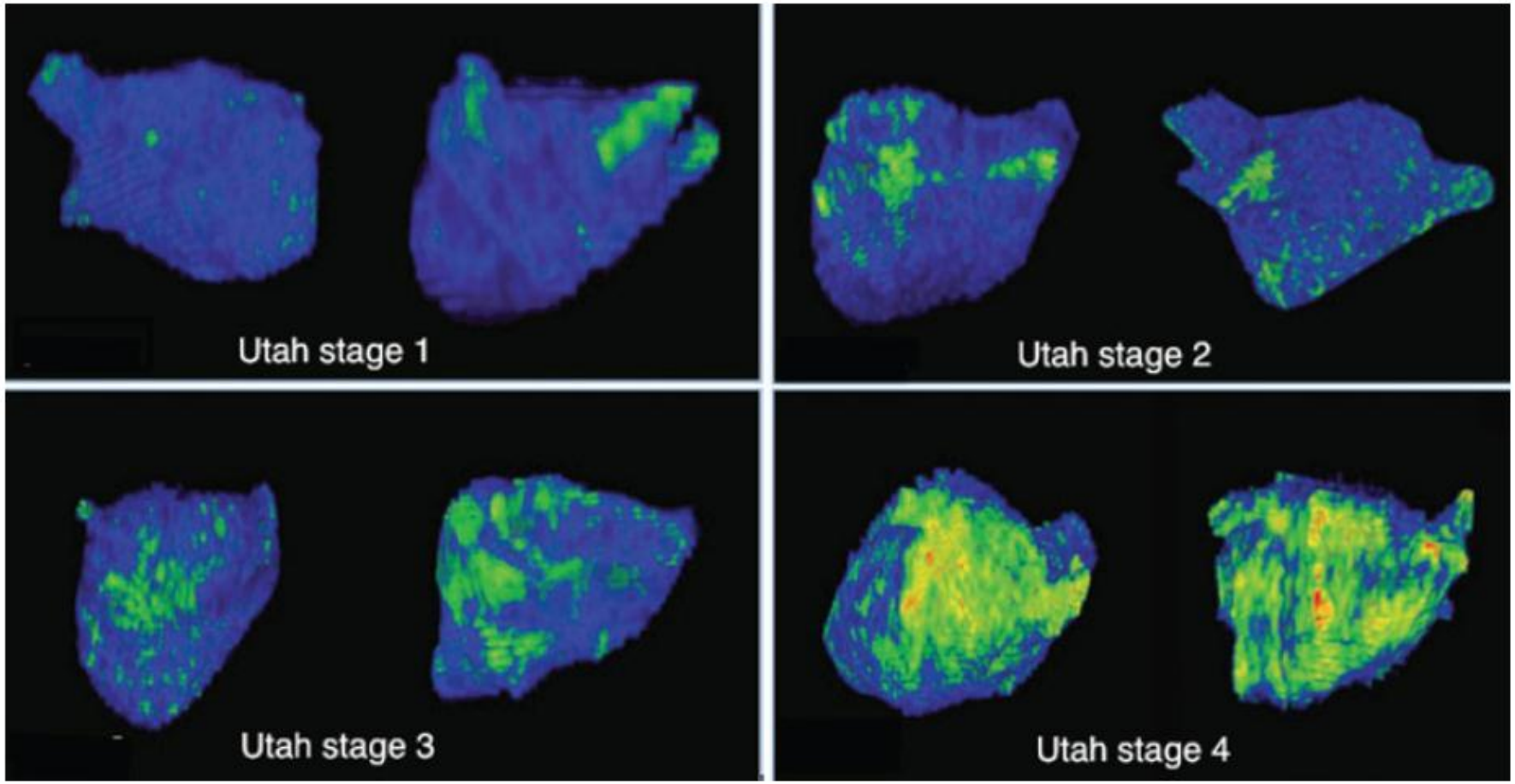


Figure 1. *A series of left atrial MRI 3D reconstructions displayed in the RAO and PA projections illustrating areas of fibrosis (bright green) across the 4 stages of fibrosis. Utah stage 1: <5% fibrosis, Utah stage 2: 5–20% fibrosis, Utah stage 3: 20–25% fibrosis, Utah stage 4: >35% fibrosis.*

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TABLE 1

Characteristics of 120 Patients with Preablation Quantification of Left Atrial Fibrosis

	Utah Stage 1 (<5%) (N = 10)	Utah Stage 2 (5–20%) (N = 71)	Utah Stage 3 (20–35%) (N = 23)	Utah Stage 4 (>35%) (N = 16)	P-value
Age (years)	58 ± 14	62 ± 13	67 ± 13	68 ± 8	ns
HTN (%)	50.0	53.5	56.5	43.8	ns
Diabetes (%)	10	7.0	21.7	6.3	ns
Coronary disease (%)	30	12.7	13.0	18.8	ns
CHF (%)	10	5.6	4.3	12.5	ns
LV EF (%)	57.2 ± 3.5	51.8 ± 9.5	49.7 ± 11.4	44.8 ± 13.2	ns
Paroxysmal/persistent AF (%)	60/40	45/55	35/65	25/75	ns

ns = nonsignificant.

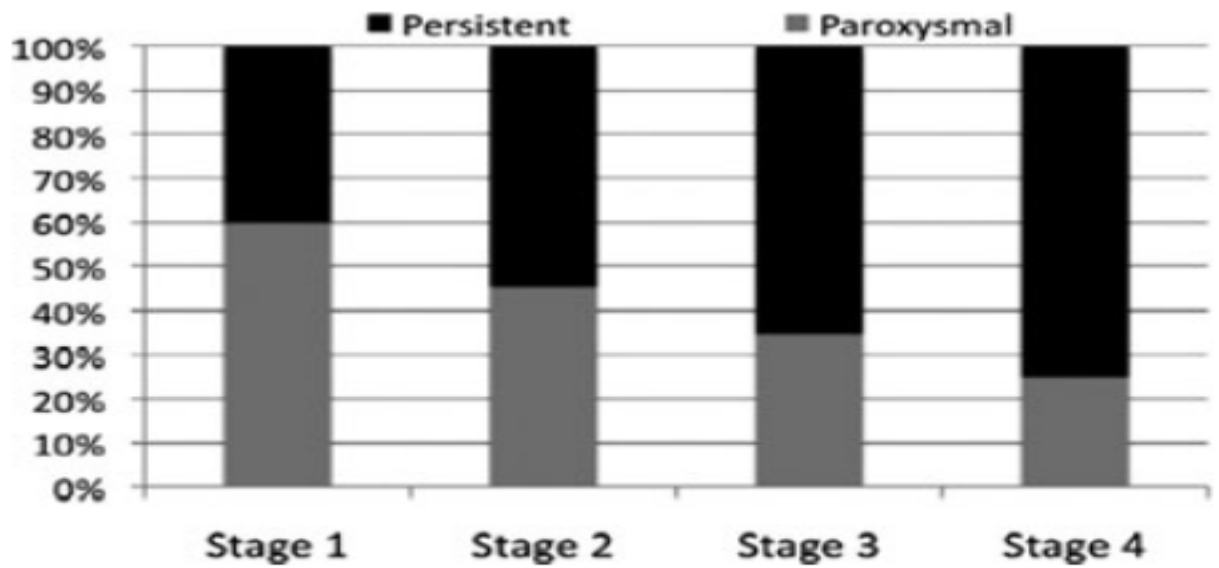

Figure 2. *Distribution of paroxysmal and persistent atrial fibrillation across the 4 stages of fibrosis. Note that each stage is a heterogeneous mix of both AF phenotypes with more predominant persistent AF in advanced stages.*

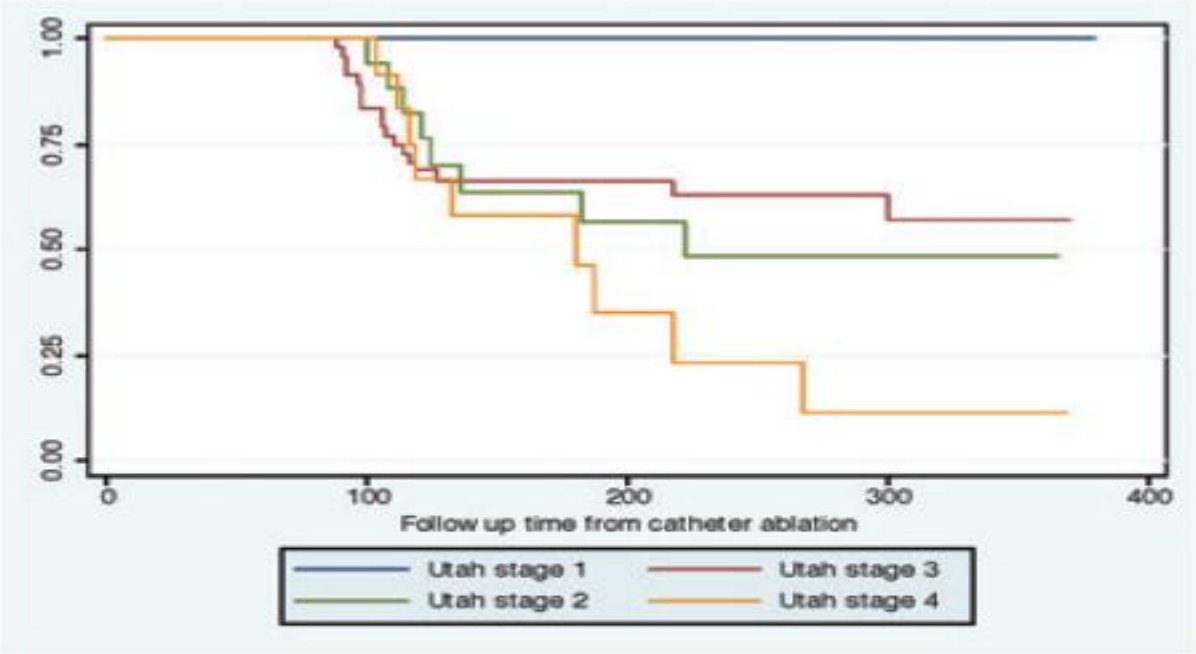

Figure 5. *Kaplan–Meier depicting AF recurrence stratified over the different stages of structural remodeling. Utah stage 1: <5% fibrosis, Utah stage 2: 5–20% fibrosis, Utah stage 3: 20–35% fibrosis, Utah stage 4: >35% fibrosis.*

Is lone AF lonely yet? What about the atrial fibrosis in lone AF and implications on the cryoablation success?

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- Purpose: Structural (atrial fibrosis), electrical and contractile remodelling play major role in the development of a vulnerable atrial substrate for AF. Serum transforming growth factor (TGF)-β1 is the key mediator and related to the degree of atrial fibrosis. Although pulmonary vein isolation (PVI) is an effective therapetic method to eliminate triggers in the pathogenesis, the impact of atrial substrate on the PVI success remains unclear. In this study, we aimed to investigate the relation of serum TGF-β1 level and degree of left atrium (LA) fibrosis using delayed enhanced magnetic resonance imaging (DE-MRI) and effects on the success of PVI in patients with lone paroxysmal AF.
- Methods: A total of 41 symptomatic lone paroxysmal AF patients (24 male, 58.5%; mean age: 49.2±7.6 years) underwent cryoballoon based catheter ablation. Cardiac DE-MRI to quantify atrial fibrosis, serum TGF- β1 levels, clinical and echocardiographic data were collected before cryoballoon ablation. Postablation blanking period was observed for 3 months. Results: Duration of the AF symptoms was median 60 months and mean EHRA score was 3.0±0.55. Mean LA anteroposterior diameter was 37.4±3.3 mm in all patients. DE-MRI revealed left atrial fibrosis in 27 (65.9%) patients [13 (31.7%) mild, 9 (22%) moderate and 5 (12.2%) severe fibrosis] with the median enhancement of 5% of the LA. At a median follow-up time of 18 months, 32 patients (78.1%) remained free of AF recurrence. **While only serum TGF-β1 level (p=0.008) found as the predictor of the presence of LA fibrosis; both serum TGFβ1 level (p=0.001) and duration of AF episode (p=0.001) were found as the predictors of the extent of LA fibrosis.** In multivariate cox regression analysis, **extent of the LA fibrosis (p= 0.007) and early AF recurrence (p= 0.011) were found as the independent predictors of AF recurrence**. Serum **TGFβ-1 level of >15.894 pg/mL predicted the presence of LA fibrosis with a sensitivity of 70.37% and specificity of 100%**. Also **LA fibrosis extent of >20% predicted the development of AF recurrence with sensitivity of 100% and specificity of 93.75%**
- Conclusion: LA fibrosis determined by DE-MRI and increased serum TGFβ-1 level play major role in LA structural remodelling and has an impact on the success of PVI. Presence and extent of LA fibrosis using DE-MRI may help select appropriate patients for catheter based AF ablation and improve procedural outcome.

Fibrozisi hedefleyen yaklaşımlar

- *İlaçlar ?*
  - *«Upstream» ilaçlar*
  - *İnflamasyon önleyici*
  - *Fibrozis önleyici*
- *Fibrozise dayanan stratejiler*
  - *Ablasyon ?*