"La cardiomiopatia atriale: riconsiderare il rapporto fra ictus tromboembolico e fibrillazione atriale"

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2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation

A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines and the Heart Rhythm Society

Developed in Collaboration With the Society of Thoracic Surgeons

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Modello classico FA-IS embolico

- Ipotesi vecchia di oltre 100 aa (triade di Virkow:FA→ Stasi→ Disfunzione parete→Trombosi→IS
- Anche in presenza di fattori di rischio in grado di giocare un ruolo importante , FA era considerata la causa primaria di IS.
- La documentazione di FA, comunque ottenuta, era il punto centrale su cui basare la prevenzione primaria e secondaria, di IS-TE e criptogenico (considerato in genere di natura TE). La FA era il solo marker di disfunzione LA utilizzato per indicazione alla TAO.
- Ottenuta la diagnosi di FA, l'utilizzo di score di rischio (CHADS2VASc), essenzialmente basati su parametri clinici consentiva di valutare la entità annuale del rischio, con indicazione a TAO se >1% anno (in pratica TAO indicata se score≥ 1 negli uomini e ≥2 nelle donne).

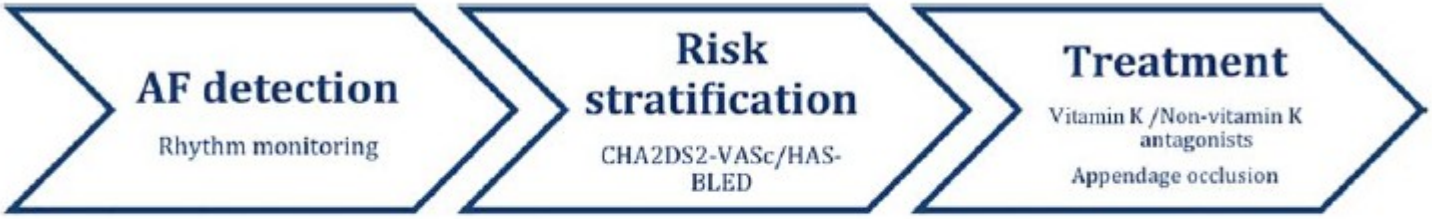

Figure 1 The current paradigm for prevention of AF-related thromboembolic events. AF, atrial fibrillation.

Accepted Manuscript

The multiple causes of stroke in atrial fibrillation: Thinking broadly

Atlantic D'Souza, MD, MRCP(UK), Kenneth S. Butcher, MD, PhD, FRCPC, Brian H. Buck, MD, FRCPC

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A. Souza "The multiple causes of Stroke in AF: thinking broadly"

Canad J Cardiol 2018 Nov. 2018
10.1016/J. CJCA.2018.08.036

- AF principale fattore di rischio per IS; OAC riduce rischio di 2/3, ma attribuire con precisione il meccanismo di IS nel singolo pz con AF è complicato
- Rispetto alla sindrome coronarica acuta, IS è malattia molto più eterogenea, con eziologie potenziali multiple che spesso coesistono ed interagiscono
- Ci sono IS lacunari di origine TE in pz con AF (3-18%), mentre il 30-40% di IS in pz con AF non sono di natura TE
- In pz >85aa con IS lacunare nel 30% è presente anche AF
- In pz con AF si evidenzia un IS silente in circa il 90% dei casi (possibili microemboli)
- Elevata incidenza di SCAF (SAF, AHRE) in pz con ESUS (reperto aspecifico!?)
- AF: uno dei molti markers di CMPA emboligena, indipendentemente da AF

Incongruenze del modello classico (1)

- Lavori recenti, sempre più numerosi, hanno evidenziato che l'approccio classico, pratico ed ampiamente usato, presenta numerose limitazioni ed incongruenze, suggerendo un modello alternativo in grado di correlare in maniera più razionale e convincente, IS, FA e fattori di rischio CV (FRCV) al processo patologico di rimodellamento atriale e quindi alla Cardiomiopatia Atriale fibrotica (CMPAF)

Incongruenze del modello classico (2)

- Nello IS-TE, la FA è diagnosticata nel 25-30% dei casi.
- Con vari sistemi, interni ed esterni, di monitoraggio prolungato nei pz con IS criptogenici, FA si rileva tanto più spesso quanto più si prolunga il monitoraggio (ad es. 30% a 3 aa nel CRISTAL), ma nella maggioranza dei casi la causa resta non definita (c.d. ESUS!)
- Analogamente il monitoraggio continuo del ritmo atriale nei pz portatori di device impiantati (PM o Def) con IS-TE evidenzia spesso episodi parossistici, solitamente asintomatici, più o meno brevi o comunque episodi di aritmia atriali ad alta frequenza, statisticamente associati con IS e con MACCE (con rischio crescente al crescere di CHADS-Vasc), ma senza che si sia riusciti a definire un "burden aritmico" di rischio!! In questi pz. **non** c'e rapporto temporale tra presenza di aritmie atriali e IS.
- Ad una meta-analisi di RCT, la strategia "rhythm control" **non** ha avuto alcun effetto sul rischi di IS-TE rispetto alla strategia "rate control"
- Questi dati suggeriscono che la presenza di FA può non essere un componente necessario nella genesi dell'IS-TE!

Freedman B "Screening for AF: A report of AF-Screen international collaboration" Circulation 2017; 135:1851

ESC European Society of Cardiology

Europace (2017) 19, 1556–1578
doi:10.1093/europace/eux163

EHRA CONSENSUS DOCUMENT

Device-detected subclinical atrial tachyarrhythmias: definition, implications and management—an European Heart Rhythm Association (EHRA) consensus document, endorsed by Heart Rhythm Society (HRS), Asia Pacific Heart Rhythm Society (APHRS) and Sociedad Latinoamericana de Estimulación Cardíaca y Electrofisiología (SOLEACE)

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Aritmie atriali subcliniche: definizione

- AHRE (atrial high rate event): episodi di aritmie atriali a fc> 190/min con device impiantati
- SCAF (subclinical AF): aritmie atriali ad alta fc, variabile durata (>6 min e n<24h), non correlate a sintomi, in pz. con device impiantati, rilevata col monitoraggio ECG intracardiaco continuo o in assenza di precedente diagnosi ECG di AF
- SAF (silent/asyntomatic AF): AF documentata in assenza di sintomi o di precedente diagnosi, spesso in coincidenza con una compilicanza (IS, HF..)
- ESVEA (excessive sopraventricolar ecotpic activity): almeno 30 extra/h o 729/24 h o run >20 battiti.

Embolic Stroke Undetermined Source (ESUS) Definizione

- IS non lacunare
- Assenza di stenosi>50% o di occlusione di arterie maggiori
- Assenza delle maggiori fonti cardiache di eventi embolici
- Assenza di altre cause di TE

Numerose cause potenziali: valutazione completa. Comunque il fenotipo di ESUS simile a IS da AF!!

Hart R: " ESUS: a systematic review and clinical update " Stroke, 2017;40:00

Takangi J "Detection of LA thrombus by CMR in ESUS" Stroke 2017; 49:00

JACC: CLINICAL ELECTROPHYSIOLOGY
VOL. ■, NO. ■, 2018

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STATE-OF-THE-ART REVIEW

Current and Future Use of Insertable Cardiac Monitors

Shaun Giancaterino, MD, Florentino Lupercio, MD, Marin Nishimura, MD, Jonathan C. Hsu, MD, MAS

TABLE 3 Guideline Recommendations on ECG Monitoring for AF After Cryptogenic Stroke

Year, Organization, and Reference	Recommendation	Class	Level of Evidence
2017 ISHNE/HRS expert consensus statement on AECG monitoring (29)	"A strategy of AECG monitoring is recommended in patients with cryptogenic stroke to detect undiagnosed AF"	I	B-R
2016 ESC/EHRA/ESO guidelines for the management of AF (36)	"Additional ECG monitoring by long-term non-invasive ECG monitors or implanted loop recorders should be considered to document silent atrial fibrillation"	IIa	C
2014 AHA/ASA guidelines for the prevention of stroke in patients with stroke and TIA (10)	"Prolonged rhythm monitoring (~30 days) for AF is reasonable within 6 months of the index event"	IIa	C
2014 Canadian stroke best practice recommendations: secondary prevention of stroke (37)	"Prolonged ECG monitoring is recommended in selected patients for the detection of paroxysmal atrial fibrillation"	N/A	B
2014 CCS guidelines for the management of atrial fibrillation (38)	"We suggest additional ambulatory monitoring (beyond 24 hours) for AF detection, where available, if it is likely that OAC therapy would be prescribed if prolonged AF is detected"	Conditional recommendation.	Moderate quality

AECG = ambulatory electrocardiogram; AF = atrial fibrillation; CCS = Canadian Cardiovascular Society; ECG = electrocardiogram; ISHNE/HRS = International Society for Noninvasive and Holter Electrocardiology/Heart Rhythm Society; OAC = oral anticoagulant agent; TIA = transient ischemic attack; other abbreviations as in Table 1.

TABLE 4 Detection of AF With ICMs in Cryptogenic Stroke

Study (yr), Reference	Number of Patients	AF Definition	Monitoring Duration Mean (SD)	Time to AF Detection	AF Detection Yield	Patients With AF Prescribed OAC
Dion et al. (2010) (43)	24	30 s	14.5 months	N/A	0	N/A
Cotter et al. (2013) (44)	51	2 min	229 (116) days	48 days (median)	25.5%	N/A
Ritter et al. (2013) (45)	60	2 min	1 yr	64 days (mean)	16.7%	N/A
Etgen et al. (2013) (46)	22	6 min	1 yr	153 days (mean)	27.3%	N/A
Rojo-Martinez et al. (2013) (47)	101	2 min	281 (212) days	102 days (median)	33.7%	N/A
SURPRISE (2014) (48)	85	2 min	569 (310) days	109 days (mean)	16.1%	N/A
CRYSTAL-AF (2014) (13,49)	221	0.25 min (30 s)	3 yr	84 days in original study 8.4 months in the 3-year follow-up (median)	8.9% at 6 months 12.4% at 12 months 21.1% at 24 months 30.0% at 36 months	90.5% at 36 months
Ziegler et al. (2017) (50)	1,247	2 min	2 yr	112 days (median)	4.6% at 1 month 12.2% at 6 months 16.3% at 12 months 21.5% at 24 months	N/A

CRYSTAL-AF = Cryptogenic Stroke and Underlying Atrial Fibrillation; SURPRISE = Stroke Prior to Diagnosis of Atrial Fibrillation Using Long-term Observation with Implantable Cardiac Monitoring Apparatus Reveal; other abbreviations as in Tables 1 and 3.

TABLE 5 Detection of AF With ICMs in Patients at High Risk for Stroke

Study (yr), Reference	Number of Patients	AF Definition	Monitoring Duration [Mean (SD)]	Time to AF Detection	AF Detection Yield	Patients With AF Prescribed OAC
PREDATE-AF (2017) (51)	245	6 min	18 months	141 days (mean)	22.4% at 18 months	76.4%
ASSERT-II (2017) (52)	256	5 min	16.3 (3.8) months	5.1(5.5) months	34.4% at 12 months	74%*
REVEAL AF (2017) (53)	385	6 min	30 months	123 days (median)	6.2% at 1 month 20.4% at 6 months 27.1% at 12 months 29.3% at 18 months 33.6% at 24 months 40.0% at 36 months	56.3%

*OAC started in 7 patients for indications other than AF.

ASSERT- II = Prevalence of Sub-Clinical Atrial Fibrillation Using an Implantable Cardiac Monitor; PREDATE-AF = Predicting Determinants of Atrial Fibrillation or Flutter for Therapy Elucidation in Patients at Risk for Thromboembolic Events; REVEAL AF = Incidence of Atrial Fibrillation in High Risk Patients; other abbreviations as in Tables 1 and 3.

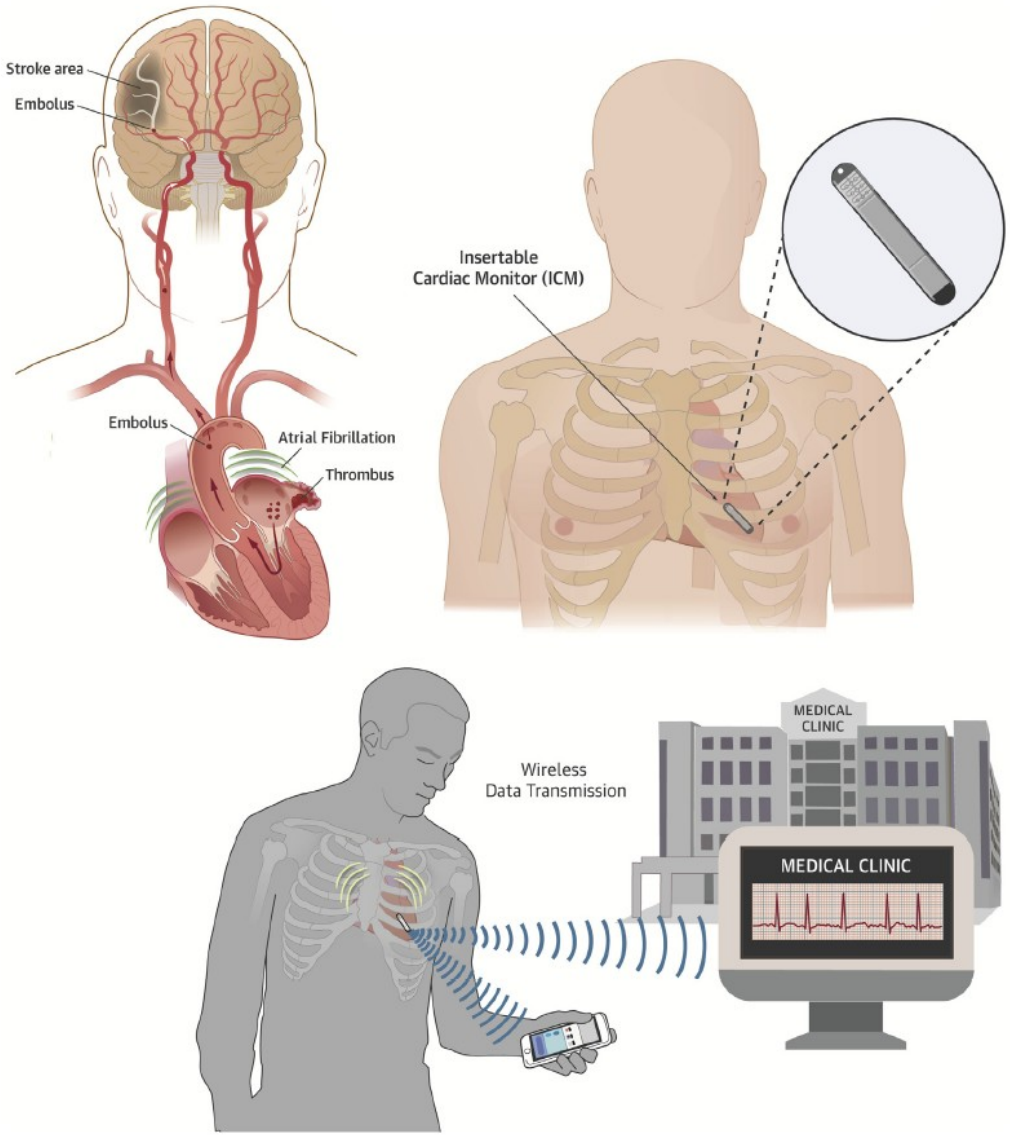
TABLE 6 Future Randomized Controlled Trials Involving ICMs for Detection of Subclinical AF

Study Acronym	Target Enrollment	Study Group	Treatment Arms	Primary Endpoint
ARTESiA	4,000	Subclinical AF detected by ICM, pacemaker, or ICD	1. Apixaban 2. Aspirin	Primary prevention of stroke, TIA, or SE
LOOP	6,000	High stroke risk*	1. ICM and subsequent OAC if new AF 2. Standard of care	Time to stroke or SE episode
NOAH	3,400	AHRE and 2+ stroke risk factors without AF diagnosis	1. Edoxaban 2. Standard of care	Primary prevention of stroke or SE
STROKE AF	500	Ischemic stroke secondary to large- or small-vessel disease	1. ICM 2. Standard of care	Incidence rate of AF through 12 months†

*Defined as age >70 years and at least 1 of: the following diabetes; hypertension; heart failure; or previous stroke. †Defined as any AF event lasting more than 30 s.

AHRE = atrial high rate event; ARTESiA = Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Sub-Clinical Atrial Fibrillation; ICD = implantable cardioverter-defibrillator; LOOP = Atrial Fibrillation Detected by Continuous ECG Monitoring; NOAH = Non-vitamin K antagonist Oral anticoagulants in patients with Atrial High rate episodes; SE = systemic embolism; STROKE AF = Rate of Atrial Fibrillation Through 12 Months in Patients With Recent Ischemic Stroke of Presumed Known Origin; other abbreviations as in Tables 1 and 3.

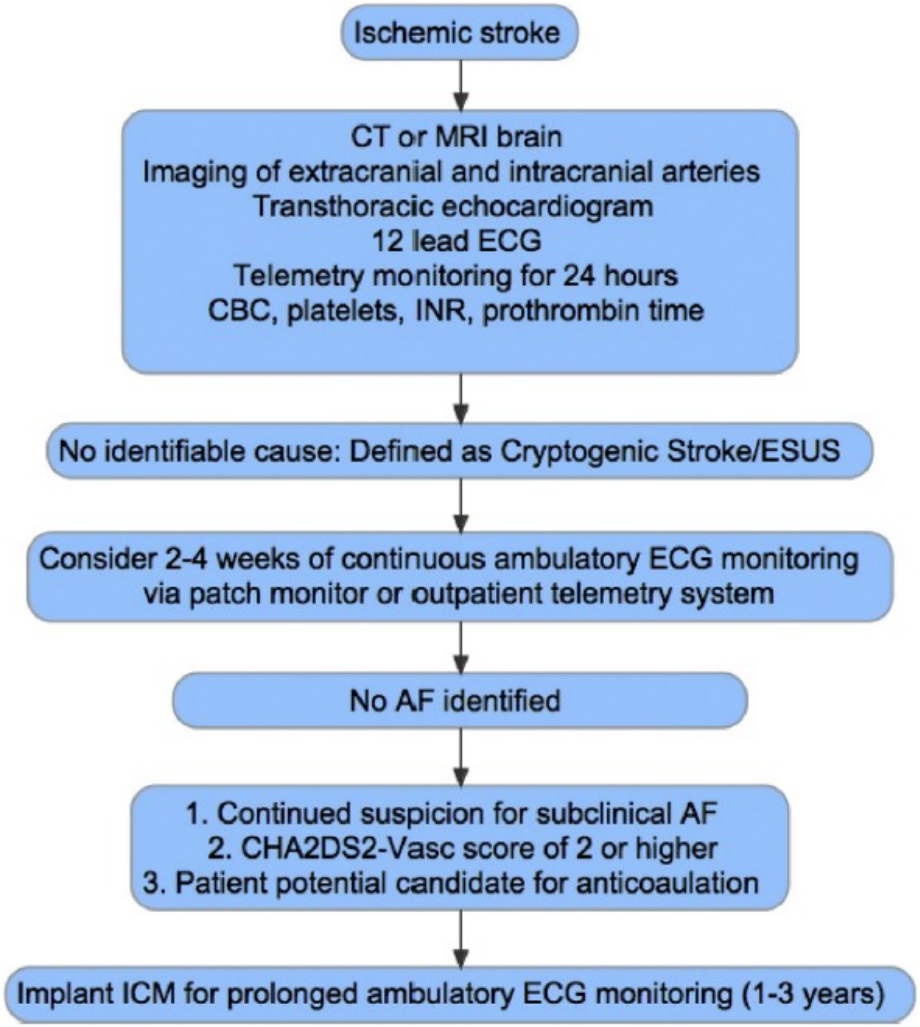
CENTRAL ILLUSTRATION An Insertable Cardiac Monitor Detects Subclinical Atrial Fibrillation Following Cryogenic Stroke



Giancaterino, S. et al. J Am Coll Cardiol EP. 2018;■(■):■-■.

This diagram illustrates 1) Subclinical atrial fibrillation leading to development of left atrial appendage thrombus formation and cardioembolic stroke; 2) Subcutaneous placement of an insertable cardiac monitor (ICM) near the left 4th intercostal space; and 3) ICM detection of subclinical atrial fibrillation and wireless cellular transmission of arrhythmia alert.

FIGURE 3 Proposed Flow Diagram for ICM Device Implantation in Select Patients with Cryptogenic Stroke



AF = atrial fibrillation; CBC = complete blood count; CHA_2DS_2-Vasc = congestive heart failure, hypertension, age, diabetes, stroke, vascular disease, sex CT = computed tomography; ECG = electrocardiogram; ESUS = embolic stroke of undetermined source; ICM = insertable cardiac monitor; INR = international normalized ratio; MRI = magnetic resonance imaging.

Device-detected subclinical atrial tachyarrhytmic: definition, implications and management
EHRA consensus document, endorsed by HRS, APHRS and SOLEACE
Europace 2017, 19: 1556

- Incidenza di AT/AF subclinica varia in rapporto alle caratteristiche cliniche della popolazione studiata
- Maggioranza di episodi di AF è asintomatica
- Probabilità di rilevare AT/AF subclinica aumenta con il prolungamento del monitoraggio, con una varietà di tecnologie invasive e non invasive.
- Comparsa di AT/AF subclinica predispone ad eventi TE, ma durata e burden aritmico (da min a h) che aumenta il rischio TE non è ben definito e non c'è una soglia precisa sopra o sotto cui aumenta o si riduce il rischio.
- Non c'è, nella maggior parte di pz con AHRE, relazione temporale tra aritmia e IS
- ESVEA va considerato come marker surrogato di PAF.

"Integrating new approaches to AF management: the 6th AFNET/EHRA Consensus Conference"

Europace 2018, 20:395

- Ancora irrisolta è la questione se differenti modi di rilevazione di AF con conseguenti pattern di AF e di burden di AF si collegano al rischio di IS e quindi a necessità di TAO
- Non chiarito se il il rilevamento di ATs (specie AHRE) usando vari metodi hanno stessa implicazione che AF clinica e comunque rilevata con ECG. Necessitano RCT per comprendere il significato di AT/AF riscontrata con i nuovi, avanzati metodi di rilevamento

GOLD MR "Treatment of Subclinical AF. Does one plus one always equal two?" (1)

Circulation 2018, 10,1161/Circulation AHA. 117.030096

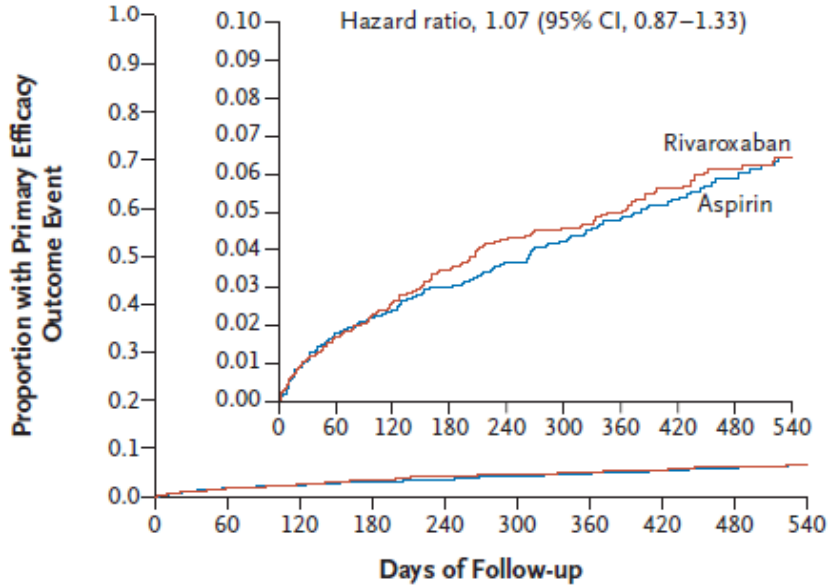
- In pz con PM-ICD è possibile la registrazione automatica di tachiaritmie atriali solitamente asintomatiche, definite SCAF, frequenti in pz. anziani
- Numerosi studi multicentrici riguardanti SCAF hanno portato ad un cambiamento sostanziale, nella pratica clinica, riguardo a TAO
- Nel TREND: SCAF>5,5 h/day associata a raddoppio del rischio di IS rispetto a pz. senza SCAF o con minore burden aritmico
- Nel ASSERT in pz anziani e ipertesi, in 3 mesi di FU, ogni episodio di SCAF> 6' si associava a 2,5 aumento di rischio di IS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

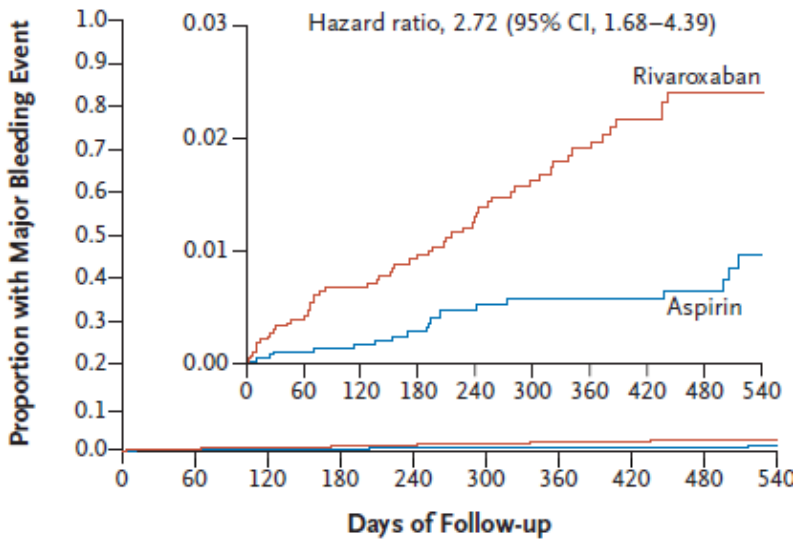
Rivaroxaban for Stroke Prevention after Embolic Stroke of Undetermined Source

A Kaplan–Meier Curves for Time to Event in the Primary Efficacy Outcome



No. at Risk										
Rivaroxaban	3609	3211	2854	2525	2156	1874	1584	1306	1046	786
Aspirin	3604	3205	2858	2531	2166	1880	1579	1319	1036	779

B Kaplan–Meier Curves for Time to Major Bleeding Event



No. at Risk										
Rivaroxaban	3609	3249	2906	2582	2206	1911	1615	1342	1071	807
Aspirin	3604	3254	2918	2597	2231	1939	1637	1371	1083	822

Hart RG " Rivaroxaban for stroke prevention after ESUS. NAVIGATE ESUS investigatators"

NEJM 2018; 378:2191 (1)

- Stoppato precocemente perché recidiva di IS uguale in pz in Rivar ed in pz in ASA (4,7%), ma con maggior rischio emorragico in pz in Rivar-
- La presenza di SCAF (o SAF o HRAE) non è quindi la causa principale di recidive di IS in pz con ESUS?
- Ma al recente World Stroke Congress 2018, analizzando il sottogruppo di pz (N° 361) che avevano LA significativamente dilatato, si evidenziava una significativa riduzione di IS nei pz in Rivar rispetto a quelli in ASA (1,1% vs 6,5%). Una AF era rilevata solo nel 6,4% dei pz, a conferma della ipotesi di CMPA emboligena, indipendentemente da AF
- Certo sono risultati che vanno confermati con RCT e in pz identificati da più precisi parametri di atriopatia!

Hart RG " Rivaroxaban for stroke prevention after ESUS investigatators"

NEJM 2018; 378:2191 (2)

- RCT in corso stanno direttamente testando questa ipotesi che certamente ha una chiara plausibilità biologica
- ARCADIA (Atrial Cardiophathy and Antithrombotic Drugs in Prevention after Cryptogenic Stroke): testa efficacia di Apixaban vs ASA in 1100 pz con ESUS e vari gradi di severità di atriopatia. Risultati attesi nel 2022
- DIENER D "Design of randomized double-blind evaluation of secondary stroke prevention comparing the efficacy of Dabigatran vs ASA in pts with ESUS" Intern J of Stroke 2017; 12:985

Kasner SE " Rivaroxaban or ASA for PFO and ESUS: a prespecified subgroup analysis from the NAVIGATE-ESUS investigatators"

Lancet Neurol 2018; 17: 1053

- Rivar riduce rischio di recidive di IS del 50% rispetto ad ASA (a conferma anche di precedenti RCT)
- Nei pz con Devices impiantati, i cateteri possono essere nidi di microemboli, oltrechè polmonari, anche cerebrali, specie se vicini ad eventuale PFO. Quindi nei pz con device impiantati ed ESUS, valutare anche questa possibilità

  (JACC Clinical Electrophys Nov. 2018)

GOLD MR "Treatment of Subclinical AF. Does one plus one always equal two?" (2)

Circulation 2018, 10,1161/Circulation AHA. 117.030096

- Aumentato uso di TAO ha una base razionale, ma in assenza di RCT evidenzianti beneficio della terapia, ha portato ad un "overtreatment" e talora rischio aumentato (CAST!)
- Nessuna associazione temporale tra SCAF e IS! Forse SCAF è solo marker di pz ad alto rischio?
- Mentre la soglia di 30", 6' o 5,5h … era stata predefinita nei vari studi, una successiva analisi di ASSERT suggeriva che rischio di IS aumentava solo per episodi di SCAF di almeno 24h
- Totale confusione su diagnosi e trattamento (accurato dialogo con il pz!). Ulteriore esempio di progressi tecnologici che causano più domande che risposte
- Attesa per risultati di ARTESIA e NOAH-AFFNET

White RD "Smartphone-based arrhythmia detection:should we encourage patients to use the ECG in their pocket?"

J Atrial Fibr 9; April-May 2017


AliveECG
60
© 2015 AliveCor, Inc.


Kardia
10:09
63
BPM
27
I'm feeling...

7.12. Device Detection of AF and Atrial Flutter (New)

Recommendations for Device Detection of AF and Atrial Flutter Referenced studies that support new recommendations are summarized in Online Data Supplement 9.		
COR	**LOE**	**Recommendations**
I	B-NR	1. In patients with cardiac implantable electronic devices (pacemakers or implanted cardioverter-defibrillators), the presence of recorded atrial high-rate episodes (AHREs) should prompt further evaluation to document clinically relevant AF to guide treatment decisions (S7.12-1–S7.12-5).
IIa	B-R	2. In patients with cryptogenic stroke (i.e., stroke of unknown cause) in whom external ambulatory monitoring is inconclusive, implantation of a cardiac monitor (loop recorder) is reasonable to optimize detection of silent AF (S7.12-6).

Recommendation-Specific Supportive Text (New)

1. Patients with AHREs detected by implanted devices are at increased risk of stroke and abundant data now link device-detected atrial tachycardia or AF (or AHREs) with the development of thromboembolic events (S7.12-1–S7.12-5). Remote monitoring with AHRE alerts increases the likelihood of detecting silent AF. However, it is unclear whether patients with AHREs benefit from oral anticoagulation. Careful review of stored electrograms may confirm the presence of AF and rule out false positive events. Occasionally, the addition of extended external electrocardiographic monitoring may be needed if data from the implanted device are uncertain. Prospective clinical trials of prophylactic anticoagulation based on device-detected AF are under way but have not been completed. Although increased duration of AHREs is associated with increased stroke risk, the threshold duration of AHREs that warrants anticoagulation is unclear. Current approaches factor in the duration of device-detected AF and the patient's stroke risk profile, bleeding risk, and preferences to determine whether to initiate long-term anticoagulation.
2. The cause of ischemic stroke remains unknown in 20% to 40% of patients, leading to a diagnosis of cryptogenic stroke. Prolonged electrocardiogram monitoring with an implantable cardiac monitor in these patients (age >40 years) has the advantage of increasing the likelihood of detecting silent AF that would escape detection with short-term monitoring. A recent RCT established the superiority of an implantable cardiac monitor over conventional monitoring for detecting silent AF, a finding with major clinical ramifications for these patients (S7.12-6). A role in screening for silent AF may also exist for remote electrocardiographic acquisition and transmission with a "smart" worn or handheld WiFi-enabled device with remote interpretation (S7.12-7, S7.12-8).

Waldo AL" Atrial Fibrillation: Atrial High-Rate Events (AHRES): Look and you will find: than what?"

Circulation 20017;136:1795

- Editoriale relativo allo studio REHEARSE-AF che, utilizzava ALIVE KARDIA Monitor (monitoraggio 2 volte la settimana) in pz. anziani per 1 anno. Rilevata AF con frequenza 4 volte maggiore che nei controlli, ma solo CHADS-Vasc score $\geq$4 era un fattore di rischio indipendente di AF
- E' ovvio l'interesse a identificare il prima possibile AF, ma questo è vero solo se abbiamo strategie terapeutiche che possono prevenire le gravi complicanze di AF
- La maggior parte degli studi di monitoraggio dei pz per evidenziare AHRE o SCAF evidenziava che il rischio assoluto di IS è molto più basso di quanto atteso: in ASSERT (FU di 3 aa) IS in 1,20%. Simulazioni di rischio evidenziano che solo una frequenza di IS $\geq$ 0,9% anno giustifica TAO
- In attesa di ARTESIA e NOAH

Ip J "Wearable devices for cardiac rhythm dagnosis and management"

JAMA 2019;321:337

- Numerosi device indossabili, attivati o meno dal pz, sono in grado di registrare un ECG, e quindi di rilevare episodi di AF, più o meno prolungati, più o meno frequenti, sintomatici o asintomatici, altrimenti non rilevabili
- Possibili errate interpretazioni e risultati inappropriati che possono portare anche a ricadute negative, specie se utilizzati in popolazione con bassa prevalenza di malattia e comunque a basso rischio
- Rimane ancora da chiarire come meglio integrare questi device per migliorare le cure dei pz
- In effetti anche recentemente la TASK Force per i Servizi di Prevenzione in USA ha evidenziato scetticismo sulla utilità di questo tipo di monitoraggio

US Prevention Services Task Force (USPSTF). Reccomandation Statement " Screening for AF with ECG"

JAMA 2018; 5: 478

- The USPSTF conclude che la attuale evidenza non è sufficiente per bilanciare R/B dello screening per AF con ECG negli adulti>65aa asintomatici, in assenza di precedente AF, mentre documentato è il rischio lieve-moderato, di diagnosi errate, esami, anche invasivi, non appropriati e rischio emorragico in assenza di documentati benefici di OAC.
- Numerosi RCT in corso per valutare la superiore capacità diagnostica rispetto ai metodi tradizionali (compresa palpazione del polso) ed altri RCT per valutare rischio di IS associato a brevi episodi di AF ed efficacia di OAC vs ASA nella prevenzione di IS in pz con AF rilevata durante screening

Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study

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Background Smartwatch and fitness band wearable consumer electronics can passively measure pulse rate from the wrist using photoplethysmography (PPG). Identification of pulse irregularity or variability from these data has the potential to identify atrial fibrillation or atrial flutter (AF, collectively). The rapidly expanding consumer base of these devices allows for detection of undiagnosed AF at scale.

Methods The Apple Heart Study is a prospective, single arm pragmatic study that has enrolled 419,093 participants (NCT03335800). The primary objective is to measure the proportion of participants with an irregular pulse detected by the Apple Watch (Apple Inc, Cupertino, CA) with AF on subsequent ambulatory ECG patch monitoring. The secondary objectives are to: 1) characterize the concordance of pulse irregularity notification episodes from the Apple Watch with simultaneously recorded ambulatory ECGs; 2) estimate the rate of initial contact with a health care provider within 3 months after notification of pulse irregularity. The study is conducted virtually, with screening, consent and data collection performed electronically from within an accompanying smartphone app. Study visits are performed by telehealth study physicians via video chat through the app, and ambulatory ECG patches are mailed to the participants.

Conclusions The results of this trial will provide initial evidence for the ability of a smartwatch algorithm to identify pulse irregularity and variability which may reflect previously unknown AF. The Apple Heart Study will help provide a foundation for how wearable technology can inform the clinical approach to AF identification and screening. (Am Heart J 2019;207:66-75.)

American Heart Journal
Volume 207

Table I. Inclusion and exclusion criteria

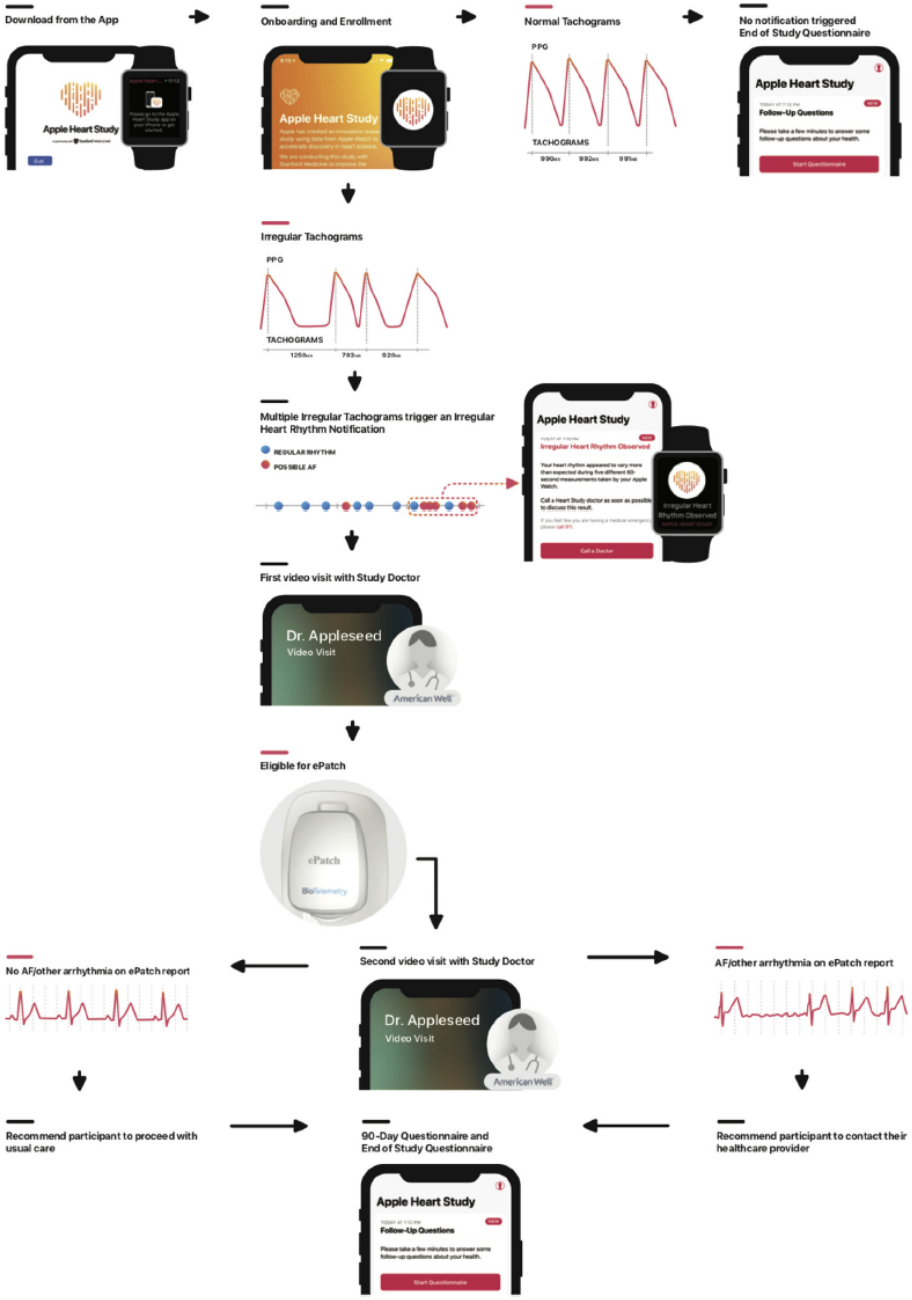
Inclusion criteria

1. iPhone (5 s or later) with iOS version 11.0 or later
2. Apple Watch (Series 1 or later) with watchOS version 4.0 or later
3. Age ≥22 years at time of eligibility screening
4. US resident (50 states or D.C.)
5. Proficient in written and spoken English, defined by self-report
6. Valid phone number associated with iPhone, ascertained from self-report.
7. Valid email address, ascertained from self-report.

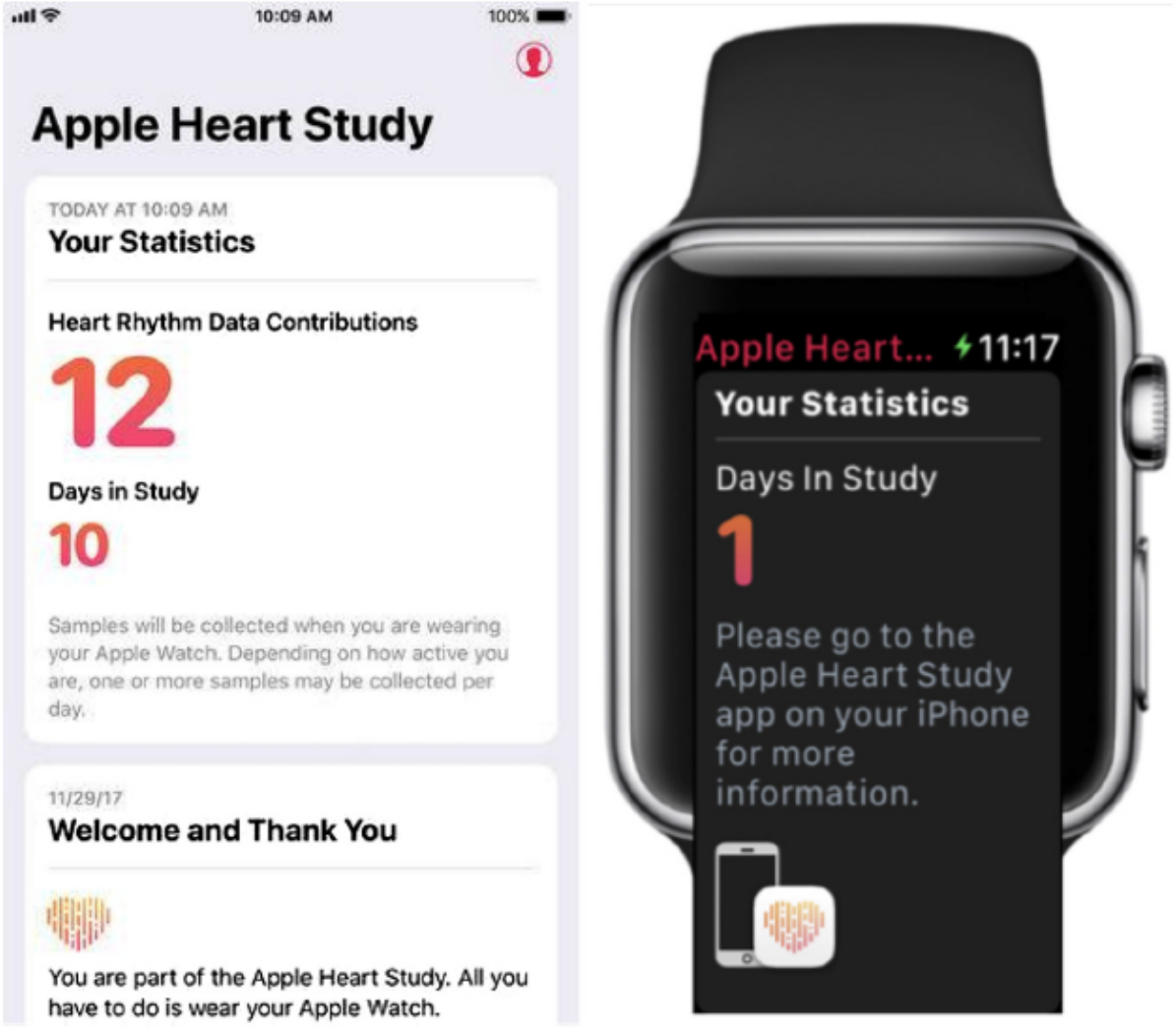
Exclusion criteria

1. Self-reported diagnosis or history of Atrial Fibrillation at the time of consent.
2. Self-reported diagnosis or history of Atrial Flutter at the time of consent.
3. Currently on anticoagulation therapy, as self-reported at the time of consent.

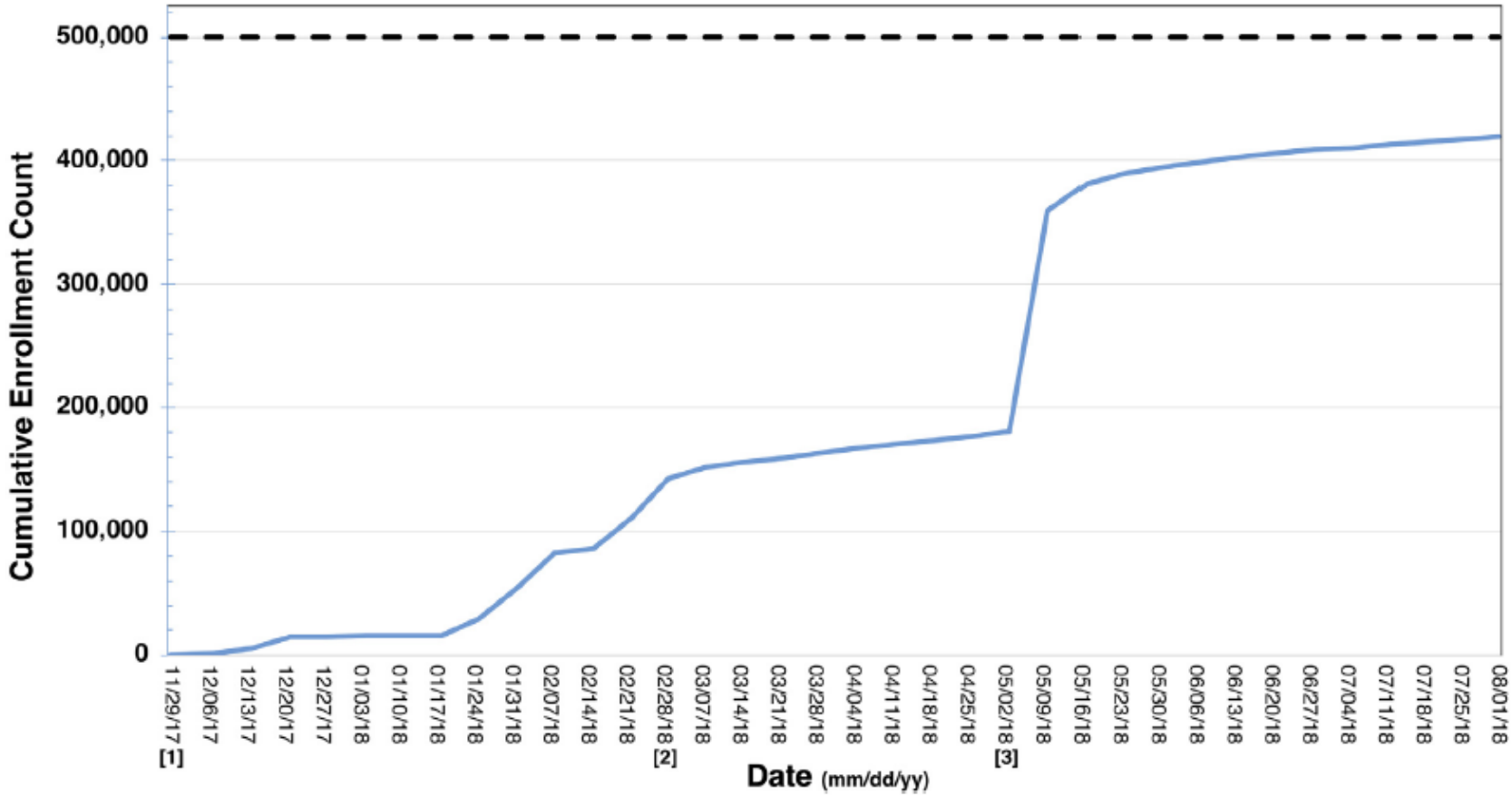
Figure 1



Study design. Overview of study flow with example tachograms and screenshots. The tachograms are not visualized or provided to the participant, and analyses are run in the background.



Participant study engagement screenshots. Number of days the participant has been in the study and total number of tachograms recorded for that participant as seen within the app on the phone (left) and watch (right).



Cumulative participant enrollment per week based on operational metrics. [1] Study launch with media promotion (Apple press release, App store feature). [2] Waiting room eliminated. All individuals that had been in the waiting room were invited into the study. Enrollment metering ceased. [3] Single recruitment email sent.

Table II. Primary, secondary and tertiary endpoints

Primary

1. Atrial fibrillation or atrial flutter of greater than 30 seconds duration detected on subsequent ambulatory ECG monitoring for a participant who received an irregular pulse watch notification.
2. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with atrial fibrillation or atrial flutter during time intervals when the spot tachogram is positive for an irregular pulse among those who received a notification.

Secondary

1. Simultaneous ambulatory ECG monitoring indicating an irregular rhythm consistent with atrial fibrillation or atrial flutter when the Irregular Pulse Notification Algorithm based on multiple tachograms is positive for an irregular pulse among those who received a notification
2. Self-reported contact with a health care provider within 3 months following an irregular pulse watch notification

Tertiary

1. Other arrhythmias detected on cardiac patch monitoring.
2. Different durations of atrial fibrillation (6 minutes, 1 hour, 6 hours, 24 hours)
3. Clinical Diagnosis of atrial fibrillation or atrial flutter
4. Therapies for atrial fibrillation or atrial flutter (anticoagulation, antiarrhythmics, rate-controlling meds)
5. Cardioversion by a health care provider.

Turakhia M: "Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smart watch: Apple Heart Study" Am Hearth J 2019; 207:66 (1)

- Il più ampio studio (circa 400 mila pz!) per identificare AF in un' ampia tipologia di pz utilizzando l' uso di fotopletismografia (con algoritmo dedicato) della Apple Watch, con successivo monitoraggo ecg ambulatoriale per 7 gg mediante patch, ma solo in pz che avevano ricevuto "allert", dal device , di irregolarità del ritmo
- Ottenere ed analizzare informazioni da device indossabili o impiantabili sembra fondamentale per realizzare una medicina di precisione
- Non chiaro se questo ci avvicina o ci allontana, al momento, dal concetto di medicina di precisione, considerando che la tecnologia sta avanzando troppo velocemente rispetto alla nostra capacità di analizzare correttamente e compiutamente i troppi dati disponibili e di tirare conclusioni significative per medici e pazienti

Turakhia M: "Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smart watch: Apple Heart Study" Am Hearth J 2019; 207:66 (2)

- Comunque Apple Watch è un prodotto di consumo e non è classificato come device autorizzato per diagnostica medica (e sta distruggendo l' industria del monitoraggio cardiaco!!), nonostante un dirigente Apple lo abbia definito "Il massimo guardiano della salute del paziente" in occasione del lancio di Apple Watch OS5 (dotato di accelerometro e giroscopio: in caso di caduta brusca se l' orologio avverte immobilità assoluta >60 sec, automaticamente chiama il numero dell' emergenza, dando anche la localizzazione)
- Problemi di falsi negativi e soprattutto di falsi positivi con ricadute anche gravi

Zanad E " Rivaroxaban in patients with HF, sinus rhythm and CAD. COMMANDER HF investigatators"

NEJM 2018; 379: 1332

- In pz con recente riacutizzazione di HF, bassa Fe e CAD (oltre 50% in classe NYHA III-IV), Rivaroxaban a basse dosi non riduceva GM, IMA o IS (come in precedenti RCT: WASH, WATCH, WARCEF) con esiti negativi largamente dovuti a progressione di HF
- Una sotto-analisi (2018 AHA session) evidenzia riduzione del 17% di eventi TE, specie IS anche AMI, soprattutto in pz con BNP meno alterato con HF meno grave. Necessari RCT per identificare i pz con HF e ritmo sinusale cui limitare OAC! (dati positivi di COMPASS-Trial e ATLAS ACS-TIMI 51 in pz con sindrome coronarica acuta e HF)
- HF è comunque di per se, indipendentemente da AF, fattore di rischio per IS-TE

10.1161/CIRCULATIONAHA.118.035864

Stroke Outcomes in the Cardiovascular OutcoMes for People using Anticoagulation StrategieS (COMPASS) Trial

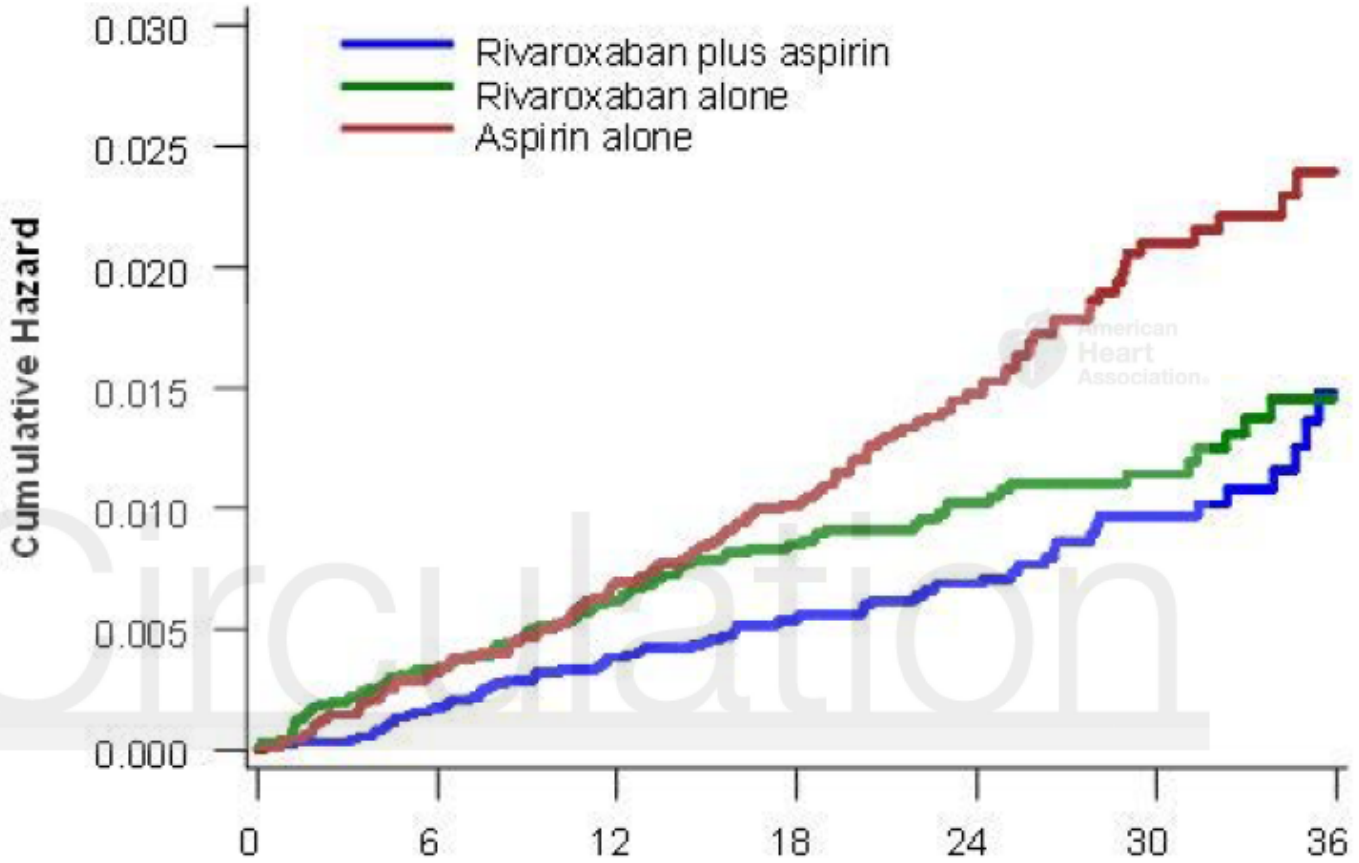
Running Title: *Sharma et al.; Stroke Outcomes in the COMPASS Trial*

Mukul Sharma, et al.

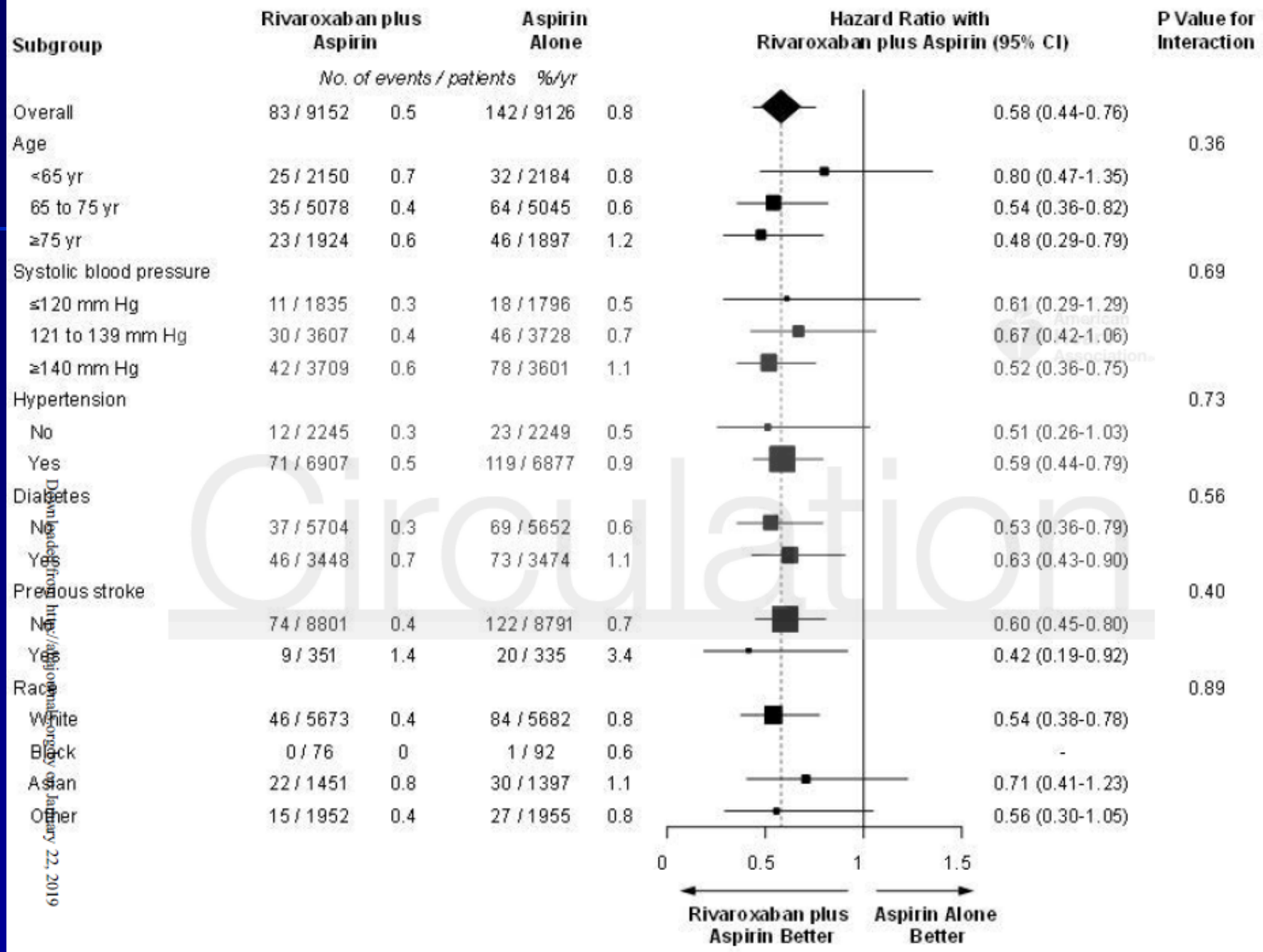
The full author list is available on page 19.

Circulation 2019; 139:1134

A Ischemic or uncertain stroke



No. at Risk							
Rivaroxaban plus aspirin	9152	9069	7973	6374	3975	2259	673
Rivaroxaban alone	9117	9016	7898	6291	3943	2228	691
Aspirin alone	9126	9022	7874	6251	3951	2231	693



Stroke Risk Stratification of AF Patients: The $CHADS_2$ VASC Score

Risk factor	Points
Congestive heart failure	1
Hypertension	1
Age >75	2
Diabetes mellitus	1
Stroke/TIA	2
Vascular disease	1
Age 65–74	1
Female sex	1
Maximum score	**9**

	Annual stroke risk %
O	0.78
1	2.0
2	3.7
3	5.9
4	9.2
5	15.2
6	19.7
7	21.5
8	22.3

- Koteche D et al "ESC: smartphone and tablet applications for pts with AF and their health care providers" *Europace 2018,20:225*
- White R D " Smartphone-based arrhhythmic detection: should we encourage pts to use the ECG in their pocket?" *Jafib 2017, 9:6*
- Healey JS "What do ICMs Reveal about AF?" *JAMA Cardiol online August 26, 2017*
- Hess PL "The role of CIEDs in the detection and treatmment of SCAF. A *review online Janauary 11,2017*
- Puerta RC "AF and cryptogenic stroke. What is the current evidence? Role of ECG monitoring" *J of Arrhytmia 2018,34:1*
- Belkin M N £ Incidence and clinical significance of newonset Device Detected Atrial Tachyarrhythmia. A meta-analysis" *Circ Arrhythm Electrophysiol 2018, 11, 1005393*
- Passman Rod "AF and stroke: the more we learn, the less we understand" *Amer Heart J online April 2018*
- Mahajan R " Subclinical device-detected AF and stroke risk: a systematic review and meta-analysis" *EuropHeart Journal 2018, 0:1*

Table 5 | **Comparison of ARTESiA and NOAH studies**

Feature	ARTESiA[66]	NOAH[67]
Proposed number of patients	4,000	3,400
Double-blind, randomized, controlled trial	Yes	Yes
Cardiac implanted electronic device-detected atrial high-rate event ≥6 min	Yes	Yes
Exclude single episode >24 h	Yes	No
Censored if single episode >24 h	Yes	No
Atrial fibrillation on implantable cardiac monitor ≥6 min included	Yes	No
CHA_2DS_2-VASc score	≥4	≥2
Active drug	Apixaban 5.0 mg or 2.5 mg twice daily	Edoxaban 60 mg or 30 mg daily
Comparator	Aspirin 80 mg daily	Aspirin 100 mg daily
Primary end points	Stroke or systemic embolism, bleeding	Composite of stroke, systemic embolism, and cardiovascular death
Secondary end points	Ischaemic stroke, myocardial infarction, cardiovascular and all-cause mortality, composites	Components of composite, all-cause death, and others
Estimated study completion date	July 2019	Event-driven

Il rimodellamento atriale: **CMPAF** (1)

- La assenza di FA nella maggior parte di IS-TE e la non correlazione di eventi TE e FA porta a valorizzare il concetto di "Cardiomiopatia Atriale Fibrotica (CMPAF), potenzialmente emboligena, essenzialmente dovuta ad una fibrosi atriale progressiva, con conseguente disfunzione elettro-meccanica, che può direttamente mediare il TE indipendentemente dal ritmo atriale, che rappresenterebbe un aggravante del rimodellamento elettro-meccanico
- Molti e complessi processi patologici interessati a partire dai comuni FRCV.
- Le alterazioni strutturali si riferiscono essenzialmente ad alterazioni tissutali di tipo fibrotico, che possono condurre a cambiamenti irreversibili

- Frustaci A, Bellocci F… Maseri A "Hystological substrate of atrial biopsies in patients with lone AF"

Circulation 1997; 96:1180

Il rimodellamento atriale: **CMPAF** (2)

- Le alterazioni elettriche sono strettamente correlate alle precedenti (cambiamenti di funzione dei canali ionici, modificazioni di Ca intracellulare, attività automatica, conduzione elettrica intercellulare….)
- Ambedue i processi, strettamente correlati, presentano complessi meccanismi, spesso sovrapponentisi.
- FA, se e quando compare, impatta ulteriormente, in un circolo vizioso, sulla progressione di CMPAF
- Comunque è più importante la valutazione del substrato atriale "statico" indipendentemente dal substrato "variabile" (non sempre presente o identificabile) del ritmo

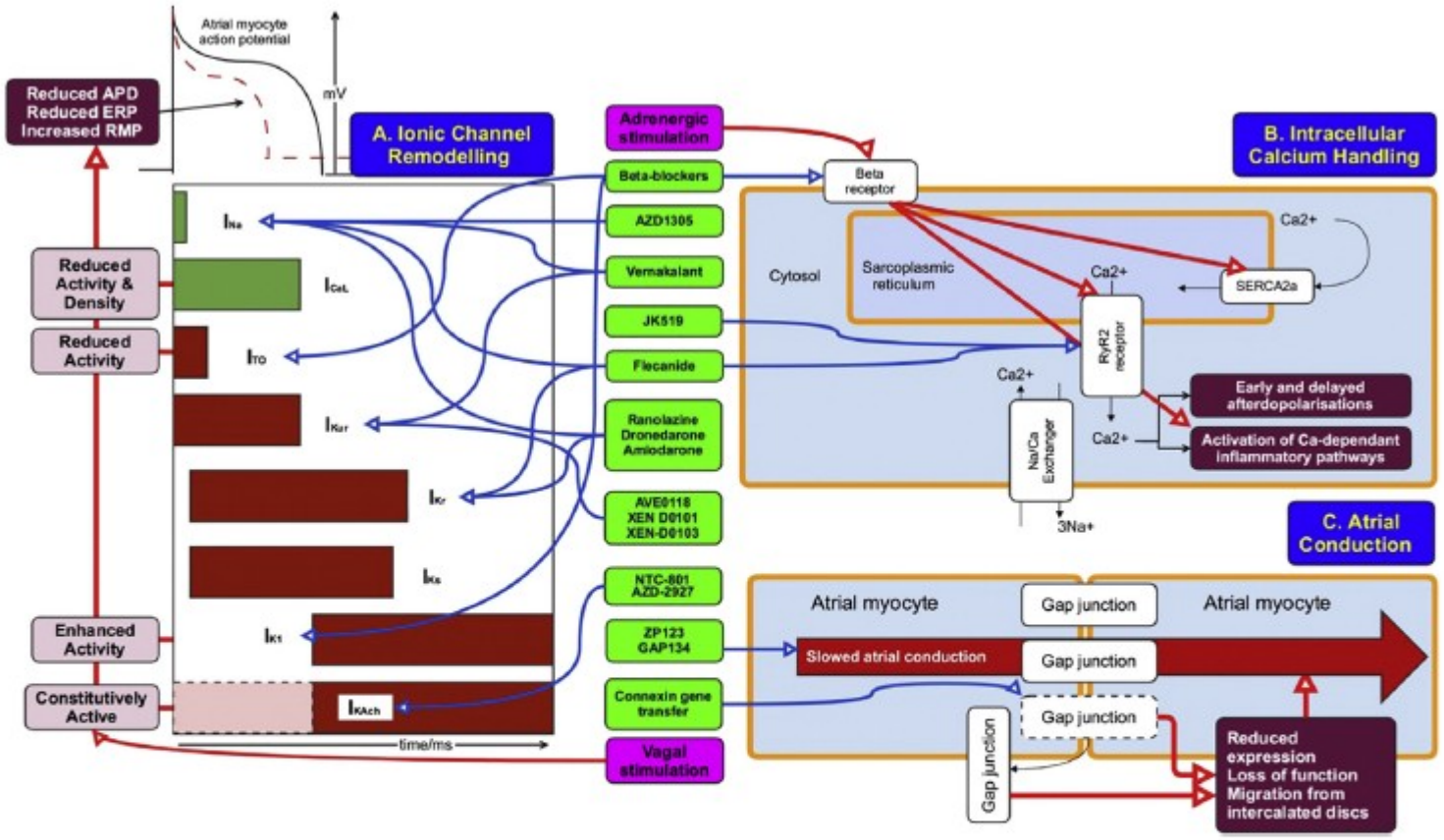


Fig 1 – The interplay of processes contributing to electrical remodelling in AF. Panel A: Ionic remodelling. The bar graph indicates the ionic currents active during the atrial myocyte action potential. Green bars indicate inward current, red bars outward current. Panels B and C highlight the processes in calcium processing and inter-cell electrical coupling respectively. The green boxes highlight the various pharmacological strategies and their site of action against electrical remodelling. *Abbreviations*: APD = action potential duration, ERP = effective refractory period, RMP = resting membrane potential, TO = transient outward, I_{Kur} = ultra-rapid delayed rectifier current, I_{CaL} = L-type Ca^{2+} current, I_{Kr} = rapid delayed rectifier current, I_{Ks} = slow delayed rectifier current, I_{K1} = inward rectifier current, I_{KAch} = acetylcholine-activated inward rectifier current, RyR2 = ryanadine receptor 2, SERCA = sarcoplasmic reticulum clacium-ATP-ase.

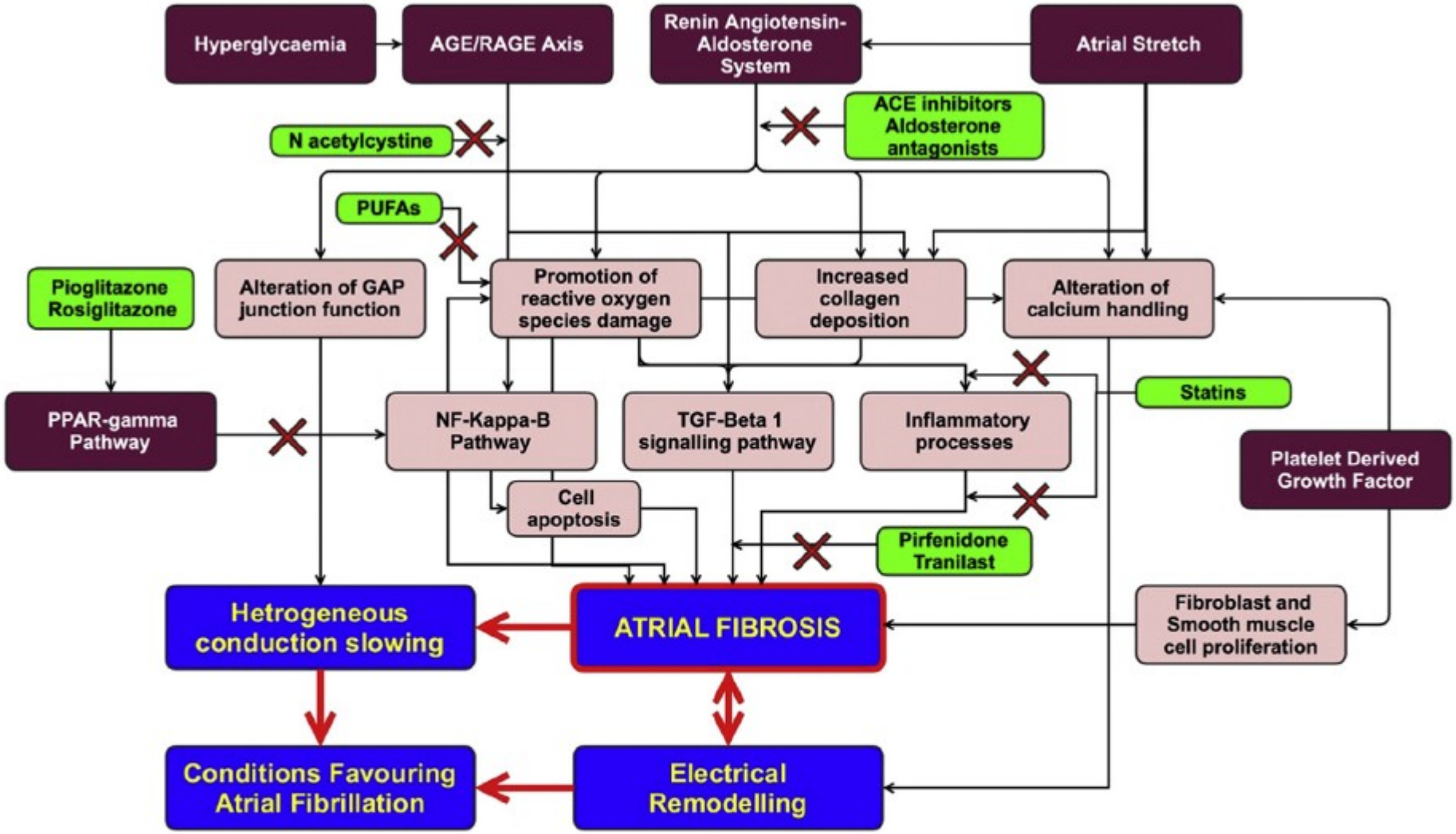


Fig 3 – The complex interplay of physiological processed involved in structural remodelling in AF. *Abbreviations*: ACE = angiotensi converting enzyme, PUFA = poly-unsaturated fatty acids, (R)AGE = (Receptor) for advanced glycalation end-products, PPAR = peroxisome proliferator-activated receptor, TGF = transforming growth factor, NF-Kappa-B = nuclear factor kappa light-chain-enhancer of activated B cells.

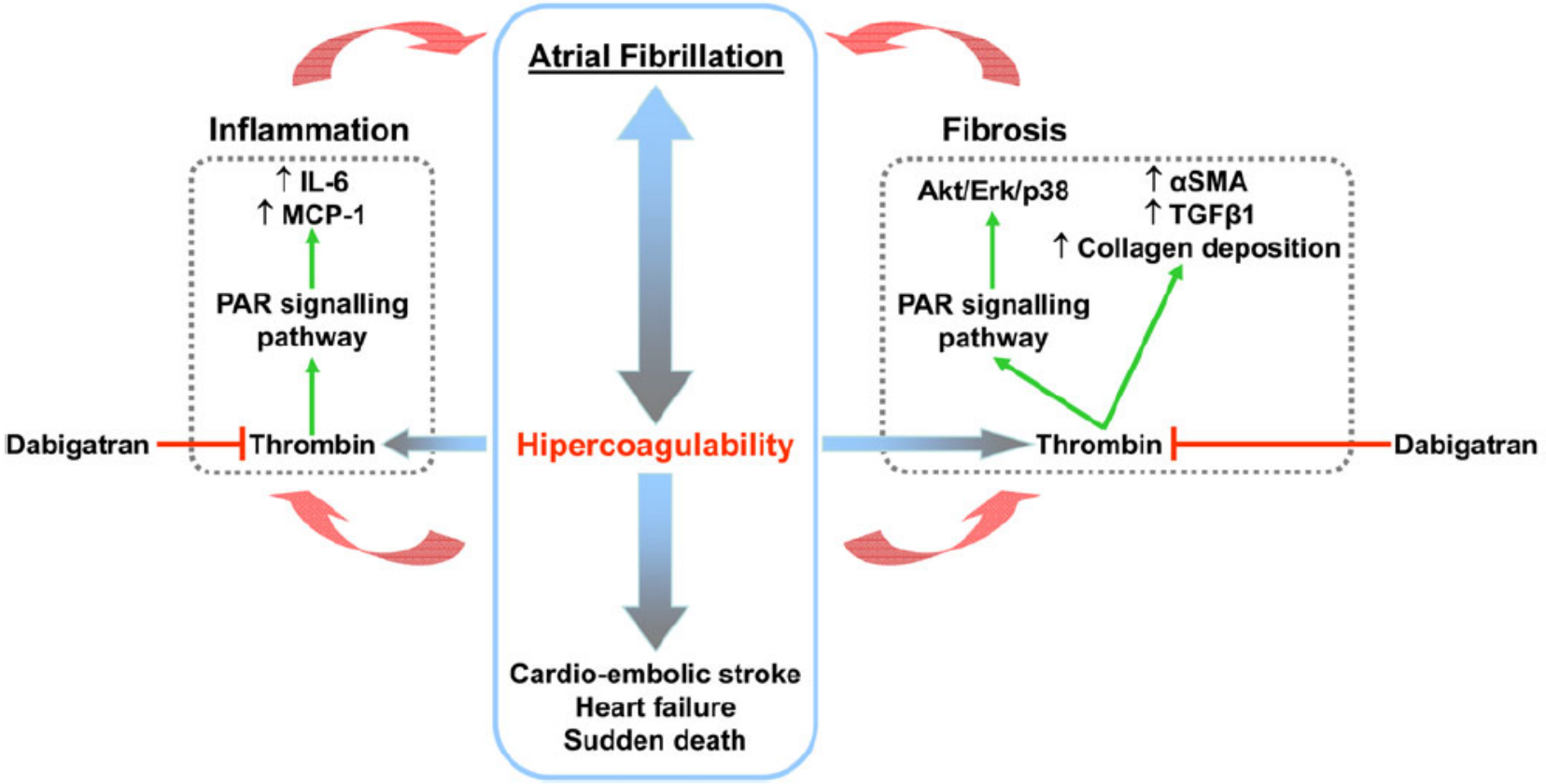


Figure 1 Schematic diagram showing the potential association between hypercoagulability and atrial fibrillation (AF). On the one hand, AF promotes a hypercoagulable state which is directly associated with the presence of thrombo-embolic complications. On the other, hypercoagulability induces atrial fibrosis further enhancing AF, mainly through the activation of the protease-activated receptor (PAR) signalling pathway. IL-6, interleukin-6; MCP-1, monocyte chemoattractant protein-1; α SMA, α smooth muscle actin; TGFβ1, transforming growth factor β1.

Il rimodellamento atriale: **CMPAF** (3)

- I meccanismi della trombogenesi nella CMPAF non sono del tutto noti.
- Certo importante la stasi (specie in LAA), alterazioni di parete, trombogenicità ematica, infiammazione… tutti fattori aggravanti, in un circolo vizioso, la FA
- Questa nuova ipotesi molto plausibile (ma con alcuni dati contraddittori e che comunque attende conferma da numerosi RCT in corso) risolve in larga parte le incongruenza della associazione IS-FA e focalizza la attenzione, sia dal punto di vista diagnostico che terapeutico, sulla miopatia atriale piuttosto che sul ritmo atriale (AHARE, SCAF, FA, flutter atriale, tachicardia atriale, BPSV, SSS) che di essa è un epifenomeno.

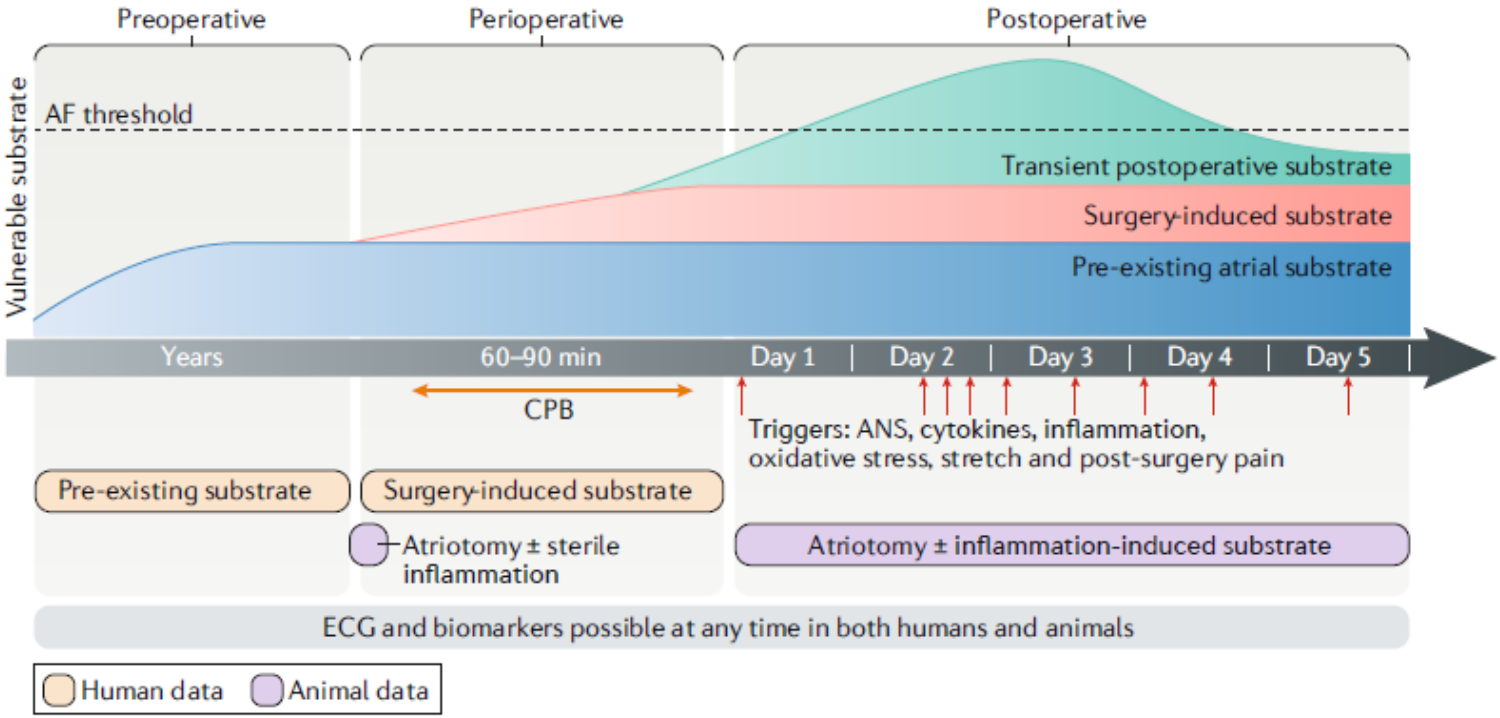


Fig. 2 | **Time course of the components of a vulnerable substrate for postoperative atrial fibrillation.** The transient atrial fibrillation (AF)-promoting changes resulting from surgery (postoperative substrate) combine with previous atrial remodelling (pre-existing substrate) to increase the vulnerability over a threshold so that triggers promoted by the autonomic nervous system (ANS), inflammation and oxidative stress can initiate postoperative AF (POAF). Human-tissue data from samples obtained intraoperatively provide information on the pre-existing and surgery-induced substrates present at the end of a surgical procedure (orange boxes) but cannot directly inform us about the changes present several days postoperatively, when POAF occurs. Animal models enable extensive investigation of the effects of atriotomy with or without an inflammation-induced substrate (purple boxes) but do not fully reproduce clinical cardiac surgery. CPB, cardiopulmonary bypass; ECG, electrocardiogram.

- Al momento molto dibattuta la fisiopatologia di IS in pz con AF
- AF marker di rischio per IS?
- AF fattore di rischio per IS?

HF come rischio di IS indipendentemente da AF (1)

- MELGAARD Let al "Assesment of CHA_2DS_2VASc score in predicting IS, TE and death in pts with AF with and without AF" *JAMA 2015, 314:1030*
- PARSONS C et al "CHA_2DS_2VASc score: a predictor of TE events and mortality in pts with IMD without AF" *MayoClin Proced 2017,92:360*
- Kim Wetal "FF as a risk factor for IS. A review" *Journal of Stroke, 2018;7:727*

HF come rischio di IS indipendentemente da AF (2)

- Il rischio di IS e TE aumenta nettamente in pz. con HF (con Fe ridotta o conservata), in ritmo sinusale, fino ad uguagliare (o superare) il rischio dei pz con AF, specie in presenza di CVRF

  A 5aa IS e TE presenti nel 16,5% di pz con CHF senza AF e nell' 11,9% di pz con AF

- IS in HF è soprattutto di origine TE, indipendentemente da AF (dilatazione/disfunzione LA e LV, stato protrombotico, disfunzione endoteliale)
- WASH, WATCH e WARCEF: ad una meta-analisi warfarin riduce IS del 41% rispetto ad ASA (ma raddoppiato rischio emorragico). NOAC!!

HF come rischio di IS indipendentemente da AF (3)

- CHA_2DS_2VASc stratifica rischio in pz con HF e SR. Per score ≥ 4, non differenza tra pz con o senza AF. Differente valore dei singoli componenti, con età al primo posto. Comunque moderato VPP
- Necessari RCT per cambiare attuale approccio terapeutico
- COMPASS e COMMANDER: basse dosi di Rivaroxaban riducono IS in pts con HF in SR?

Amiloidosi cardiaca ed IS indipendentemente da AF

- In assenza di AF, pt con CA sviluppano spesso trombosi parietale in LA e LV (26% in una serie autoptica e 27% con TEE)
- Valutazione morfo-funzionale (specie LALS) utile metodica per identificare pz ad alto rischio di TE da sottoporre a TAO, al di là di CHA_2DS_2VASc score
- Circa 25-30% di p. anziani con HfpEF ha amiloidosi cardiaca al riscontro autoptico!

NoKioka K..Rapezzi C et al " LA structure and function in cardiac amyloidosis" Europ Heart J Cardiovasc Imaging" 2017, 18:1128

Shah S "Targeted therapeutics for TTR-CA": Circulation 2019; 139:144
Anderson Kp "Cardiac Amyloidosis and the risks of cardioversion" JACC 2019; 73:598

- CMP infiltrativa da TTR-CA, identificata sempre più spesso come causa, poco riconosciuta, di HfpEF (25-30%) negli anziani
- Sospettare la diagnosi (ECG, ecocardio, RMC, Scintigrafia ossea: non più EMB)
- Elevata incidenza di trombosi di LA: CMPA infiltrativo-fibrotica, elevato rischio di IS-TE, anche indipendentemente da AF (peraltro frequente): TAO anche oltre AF e CHADS-VASC
- Cardioversione guidata da TEE, anche indipendemente da durata di AF<48 h (almeno il 25% dei pz presenta trombi in LA anche se durata di AF <48h)
- Necessari RCT per modificare GL riguardo a cardioversione in pz (specie ad alto rischio)con AF insorta <48 h (attuali GL di scarso valore scientifico basate su presupposti non validati in RCT)

6. Rhythm Control

6.1. Electrical and Pharmacological Cardioversion of AF and Atrial Flutter

6.1.1. Prevention of Thromboembolism

Recommendations for Prevention of Thromboembolism Referenced studies that support modified recommendations are summarized in Online Data Supplement 6.		
COR	**LOE**	**Recommendations**
I	B-R	1. For patients with AF or atrial flutter of 48 hours' duration or longer, or when the duration of AF is unknown, anticoagulation with warfarin (INR 2.0 to 3.0), a factor Xa inhibitor, or direct thrombin inhibitor is recommended for at least 3 weeks before and at least 4 weeks after cardioversion, regardless of the CHA_2DS_2-VASc score or the method (electrical or pharmacological) used to restore sinus rhythm (S6.1.1-1–S6.1.1-12). MODIFIED: The 2014 AF Guideline recommendation for use of warfarin around the time of cardioversion was combined with the 2014 AF Guideline recommendation for NOACs to create a single recommendation. This combined recommendation was updated to COR I/LOE B-R from COR IIa/LOE C for NOACs in the 2014 AF Guideline on the basis of additional trials that have evaluated the use of NOACs with cardioversion.
I	C	2. For patients with AF or atrial flutter of more than 48 hours' duration or unknown duration that requires immediate cardioversion for hemodynamic instability, anticoagulation should be initiated as soon as possible and continued for at least 4 weeks after cardioversion unless contraindicated.
I	C-EO	3. After cardioversion for AF of any duration, the decision about long-term anticoagulation therapy should be based on the thromboembolic risk profile and bleeding risk profile. MODIFIED: The 2014 AF Guideline recommendation was strengthened with the addition of bleeding risk profile to the long-term anticoagulation decision-making process.
IIa	B-NR	4. For patients with AF or atrial flutter of less than 48 hours' duration with a CHA_2DS_2-VASc score of 2 or greater in men and 3 or greater in women, administration of heparin, a factor Xa inhibitor, or a direct thrombin inhibitor is reasonable as soon as possible before cardioversion, followed by long-term anticoagulation therapy (S6.1.1-13, S6.1.1-14). MODIFIED: Recommendation COR was changed from I in the 2014 AF Guideline to IIa, and LOE was changed from C in the 2014 AF Guideline to B-NR. In addition, a specific CHA_2DS_2-VASc score is now specified.
IIa	B	5. For patients with AF or atrial flutter of 48 hours' duration or longer or of unknown duration who have not been anticoagulated for the preceding 3 weeks, it is reasonable to perform transesophageal echocardiography before cardioversion and proceed with cardioversion if no left atrial thrombus is identified, including in the LAA, provided that anticoagulation is achieved before transesophageal echocardiography and maintained

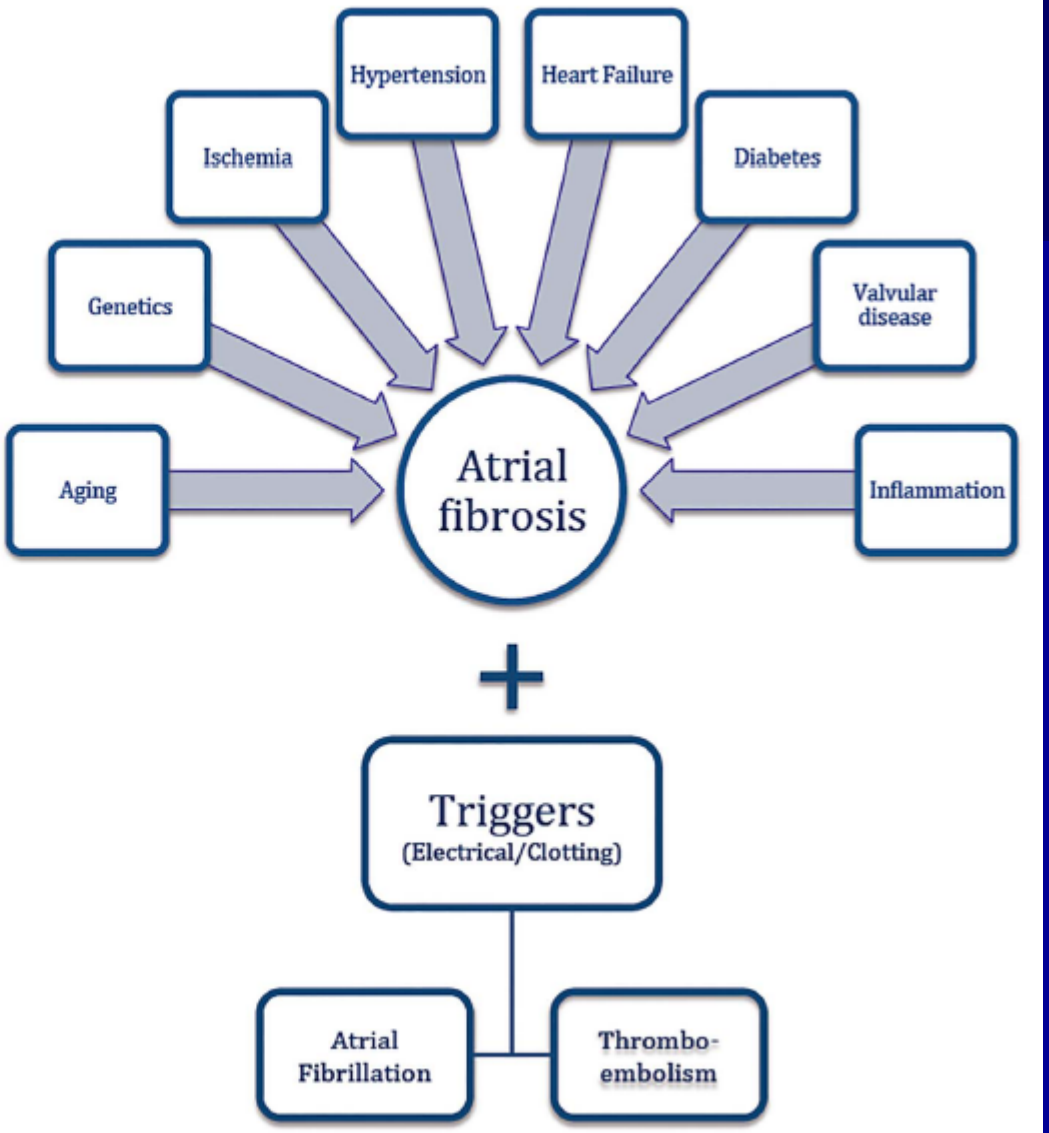


Figure 5 Diagram depicting proposed association between risk factors leading to atrial fibrosis and clinical outcomes of atrial fibrillation and thromboembolism. Risk factors contribute to formation and progression of atrial fibrosis. Once fibrosis is present, arrhythmic triggers together with the fibrotic substrate initiate and maintain the arrhythmia; thrombogenic triggers together with mechanical dysfunction associated with fibrosis lead to thromboembolisation.

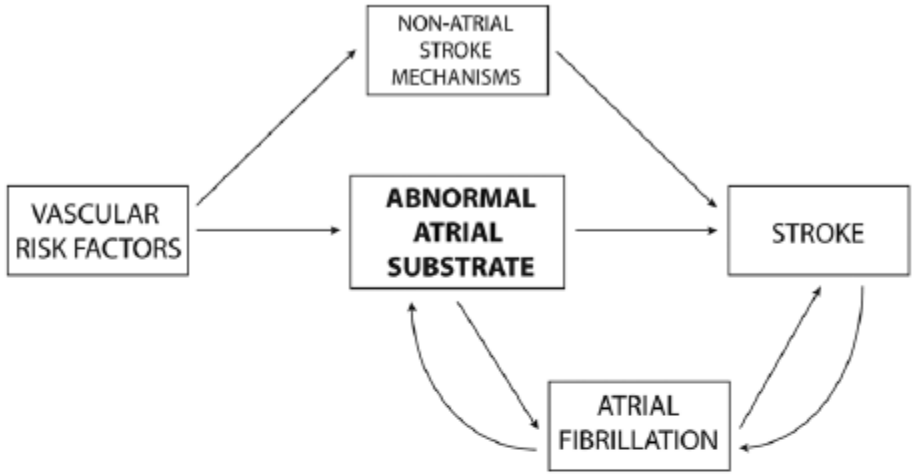


Figure. Updated model of thromboembolic stroke. This model emphasizes the importance of systemic and atrial substrate as well as rhythm in explaining the relationship between atrial fibrillation (AF) and stroke. In this model, aging and systemic vascular risk factors cause an abnormal atrial tissue substrate, or atrial cardiopathy, that can result in AF and thromboembolism. Once AF develops, the dysrhythmia causes contractile dysfunction and stasis, which further increases the risk of thromboembolism. In addition, over time, the dysrhythmia causes structural remodeling of the atrium, thereby worsening atrial cardiopathy and increasing the risk of thromboembolism even further. In parallel, systemic risk factors increase stroke risk via other mechanisms outside the atrium, such as large-artery atherosclerosis, ventricular systolic dysfunction, and in-situ cerebral small-vessel occlusion. Once stroke occurs, autonomic changes and post-stroke inflammation may transiently increase AF risk.

Diagnostica, diretta o indiretta, della CMPAF

- Il progresso tecnologico nel campo dell' imaging ha confermato come AF non sia semplicemente una aritmia, ma una sindrome associata con rimodellamento LA rappresentato da progressiva fibrosi.
- Varie modalità di imaging proposte per valutare la CMPAF, quindi il rimodellamento atriale, quindi la fibrosi atriale.
- ECG
- Ecocardiogramma
- Mappaggio elettro-anatomico
- MRI

ECG e CMPAF

- Numerosi parametri, indicativi di dilatazione LA, come intervallo PQ, morfologia e durata dell'onda P, soprattutto durata e ampiezza di forze terminali in V1 (PTFV1), correlano con rischio di FA e IS di tipo TE, non lacunare, indipendentemente da FA.

- Extra sopraventricolari e comunque aritmie sopraventricolari veloci non FA correlano con rischio di IS e di sviluppo di FA, ma rischio di TE indipendente da presenza di FA. Si comprende come sia difficile da definire la entità della durata e del burden aritmico correlato a rischio di IS (e anche di FA). Sono aritmie marker di CMPAF!

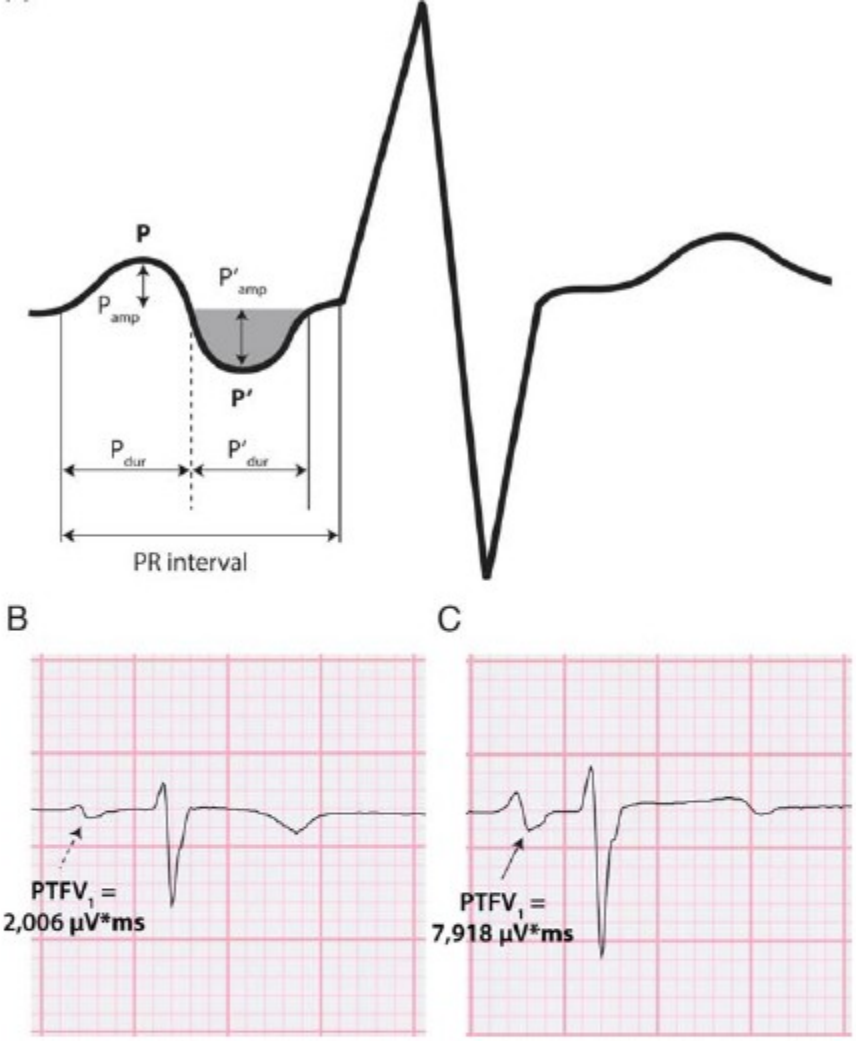


FIGURE 1: Schematic illustration and examples of normal and abnormal P-wave terminal force in electrocardiogram lead V_1 ($PTFV_1$). $PTFV_1$ was defined as the absolute value of the amplitude (P'_{amp}) multiplied by the duration (P'_{dur}) of the terminal portion of the P-wave (P′; shaded area) in lead V_1 of a standard 12-lead electrocardiogram (A). (B) shows an example of a P-wave with normal $PTFV_1$ (dashed arrow), whereas (C) shows an example of a P-wave with abnormally increased $PTFV_1$ (solid arrow). Note the wider and deeper downward deflection of the P-wave in (C) compared with (B).

Maheshwari A " Refining prediction of AF-related stroke using the P_2-CHA_2DS_2-VASC Score"

Circulation 2019;139:180 (1)

- Numerosi parametri ECG di alterazioni atriali direttamente correlati con danno LA e rimodellamento atriale e IS sia in pz con che senza AF
- Ipotizzato che l' aggiunta di parametri ECG di danno LA aumenti la predizione individuale di rischio TE in pz con AF (quando in ritmo sinusale) e senza AF
- Ipotesi testata in 2 ampi e prospettici studi di coorte (ARIC: Atherosclerotic Risk in Communities) e MESA (Multiethnic Study of Atherosclerosis)

Maheshwari A " Refining prediction of AF-related stroke using the P_2-CHA_2DS_2-VASC Score"

Circulation 2019;139:180 (2)

- In effetti specie PWA (asse della P), con valore di 2 punti aggiunta a CHADS-VASC score migliorava significativamente la stratificazione del rischio di IS (specie nei pz a basso rischio 0-1, che hanno ancora un rischio non del tutto trascurabile: 1-1,7% anno)
- Validati questi dati, sono indicati RCT per valutare se OAC riducono IS in pz con AF o senza AF con marker di CMPAF come PWA e altri marker di rimodellamento fibrotico LA

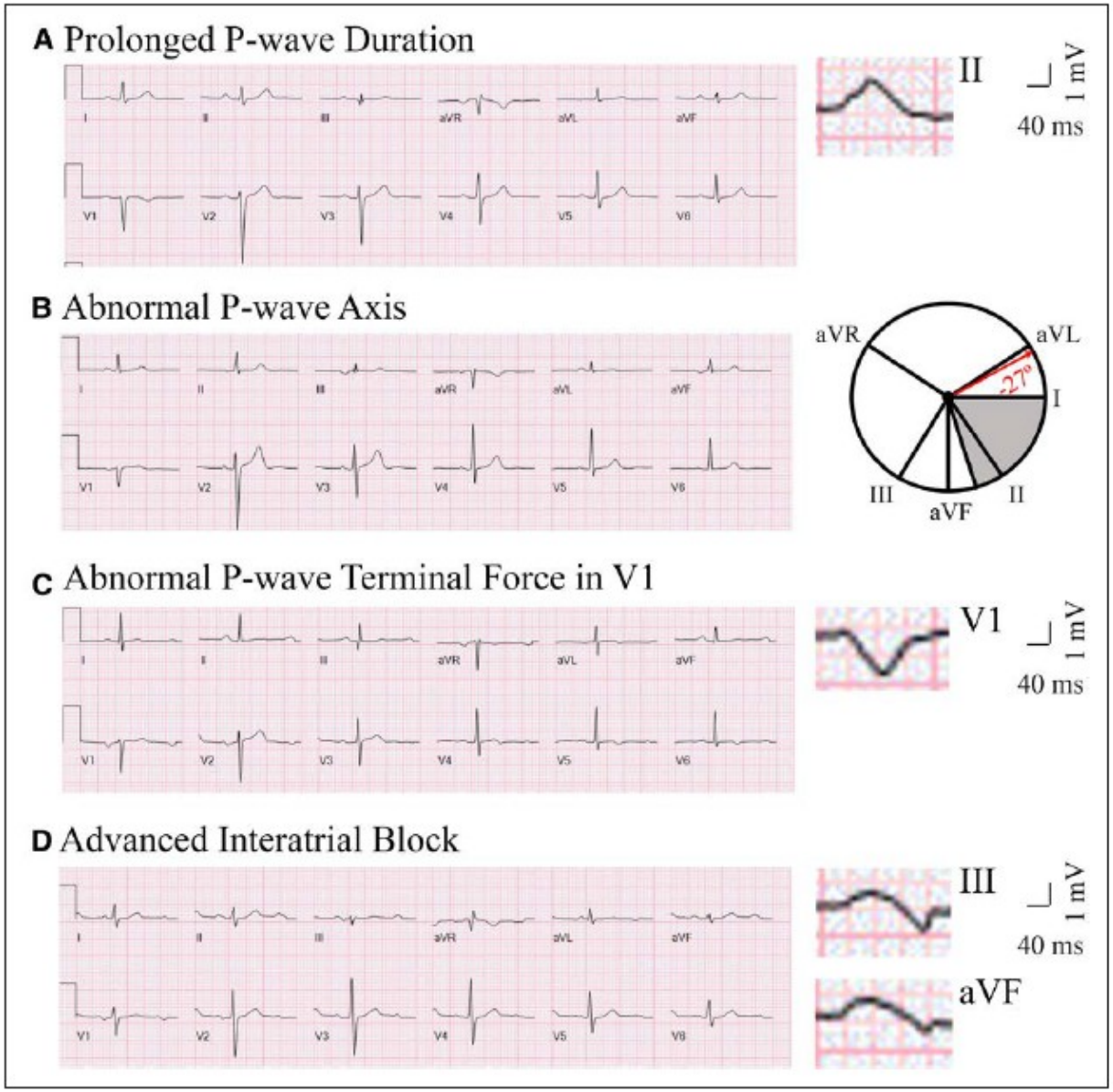


Figure 1. Representative ECG tracings of abnormal P-wave indices.
A through **D**, Prolonged P-wave duration (**A**), abnormal P-wave axis (**B**), abnormal P-wave terminal force in V1 (**C**), and advanced interatrial block (**D**). **A**, The maximal P-wave duration is seen in lead II (136 ms). The P-wave axis on **B** is –27°. **B**, The grey area on the hexaxial reference system (lead I 0°, lead II 60°, aVF 90°, aVR –150°, aVL –30°) represents normal P-wave axis (0–75°). **C**, The P-wave terminal force is –9632 μV*ms (amplitude –112 μV, duration 86 ms). **D**, The maximal P-wave duration is seen in lead III (136 ms). Biphasic P-waves can be seen in III and aVF.

Circulation

ORIGINAL RESEARCH ARTICLE

Refining Prediction of Atrial Fibrillation–Related Stroke Using the P_2-CHA_2DS_2-VASc Score

ARIC and MESA

Table 4. Performance of P_2-CHA_2DS_2VASc Score for 1-Year Ischemic Stroke Risk in Participants With Atrial Fibrillation in ARIC Study (Atherosclerosis Risk in Communities) and MESA (Multi-Ethic Study of Atherosclerosis)

Study	Score	C-Statistic (95% CI)	NRI (95% CI)*	Relative IDI (95% CI)
ARIC	CHA_2DS_2VASc†	0.60 (0.51–0.69)		
	P_2-CHA_2DS_2VASc‡	0.67 (0.60–0.75)	0.25 (0.13–0.39)	1.19 (0.96–1.44)
MESA	CHA_2DS_2VASc†	0.68 (0.52–0.84)		
	P_2-CHA_2DS_2VASc‡	0.75 (0.60–0.91)	0.51 (0.18–0.86)	0.82 (0.36–1.39)

IDI indicates integrated discrimination improvement; and NRI, net reclassification improvement.

*For categorical NRI, we used the following categories for stroke risk: <1%, 1% to <2%, and ≥2%.

†Age (1 point for >65, 2 points for >75 years), sex (1 point for female), heart failure (1 point), hypertension (1 point), diabetes mellitus (1 point), previous myocardial infarction/peripheral artery disease (1 point), and prevalent stroke/transient ischemic attack (2 points).

‡CHA_2DS_2VASc+abnormal P-wave axis (2 points).

Ecocardiogramma e CMPAF (1)

- Le dimensioni di LA, valutate con metodi grossolani (dimensioni di LA) o più attendibili (volume indicizzato di LA) correlano con FA, esiti di CV e ATC e con IS di tipo TE indipendentemente da FA.
- Ecotransesofageo: associazione fra dilatazione LA ed eco-contrasto spontaneo e ridotta velocità di flusso e trombi in LAA.
- Eco 3D: migliore correlazione delle dimensioni LA con fibrosi valutata con DE-MRI

Ecocardiogramma e CMPAF (2)

- Eco: valutazione funzionale mediante "spekle tracking" soprattutto il " LA global longitudinal strain" è il parametro che più strettamente correla con l'entità della fibrosi atriale valutata con DE-MRI, alterata ancora prima che compaia la dilatazione atriale e predittiva di eventi CV, specie IS di tipo TE, indipendentemente da FA. Proposto come integrazione di CHADS-VASC per aumentare VPP. Alterato precocemente nei pz. ipertesi, diabetici., obesi.....

- Quindi le anormalità morfo-funzionali atriali rappresentano un rischio più specifico per IS-TE (indipendentemente dalla presenza di FA) mentre i comuni fattori di rischio cardiovascolare rappresentano un fattore indipendente aspecifico di rischio.

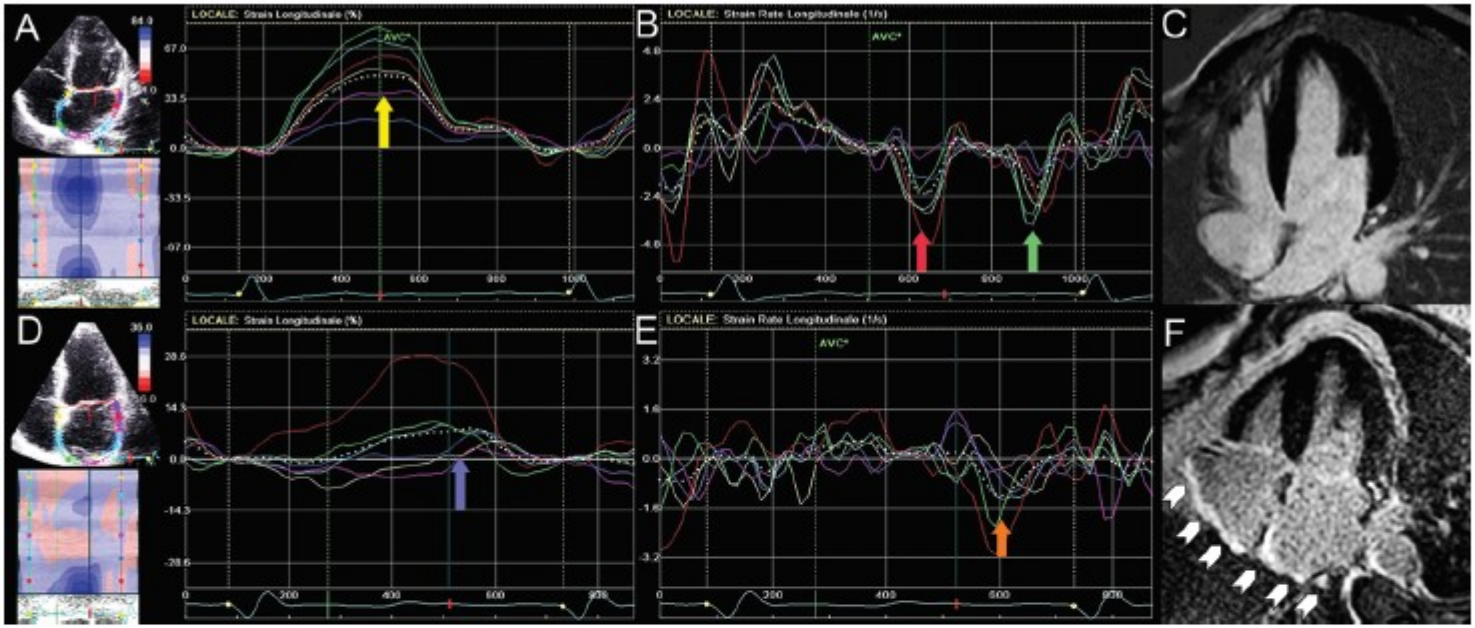


Figure 1 Transthoracic echocardiography in the four-chamber view showing global left atrial (LA) longitudinal strain in a normal subject. The positive peak (yellow arrow) represents an atrial preserved reservoir phase, which occurs during ventricular systole (*A*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain rate in a normal subject. During ventricular diastole it is possible to identify two negative peaks, the first corresponding to passive early LV filling (red arrow) and the second to atrial booster pump function (green arrow) (*B*). Cardiac magnetic resonance imaging in the four-chamber view showing a normal heart with no atrial delayed contrast enhancement and normal atrial volumes (*C*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain in a patient with permanent atrial fibrillation (AF). A reduction of positive curve during the reservoir phase (purple arrow) is expected in a patient with reduced LA compliance (*D*). Transthoracic echocardiography in the four-chamber view showing global LA longitudinal strain rate in the same patient. Loss of left atrial booster pump function occurs and a single negative deflection (orange arrow) can be observed during ventricular diastole, as the main pattern of AF (*E*). Cardiac magnetic resonance imaging in the four-chamber view showing delayed contrast enhancement in both atria (white arrow heads) and atrial dilatation in the same patient with permanent AF (*F*).

Circulation: Cardiovascular Imaging

ORIGINAL ARTICLE

Left Atrial Reservoir Function and Outcome in Heart Failure With Reduced Ejection Fraction

The Importance of Atrial Strain by Speckle Tracking Echocardiography

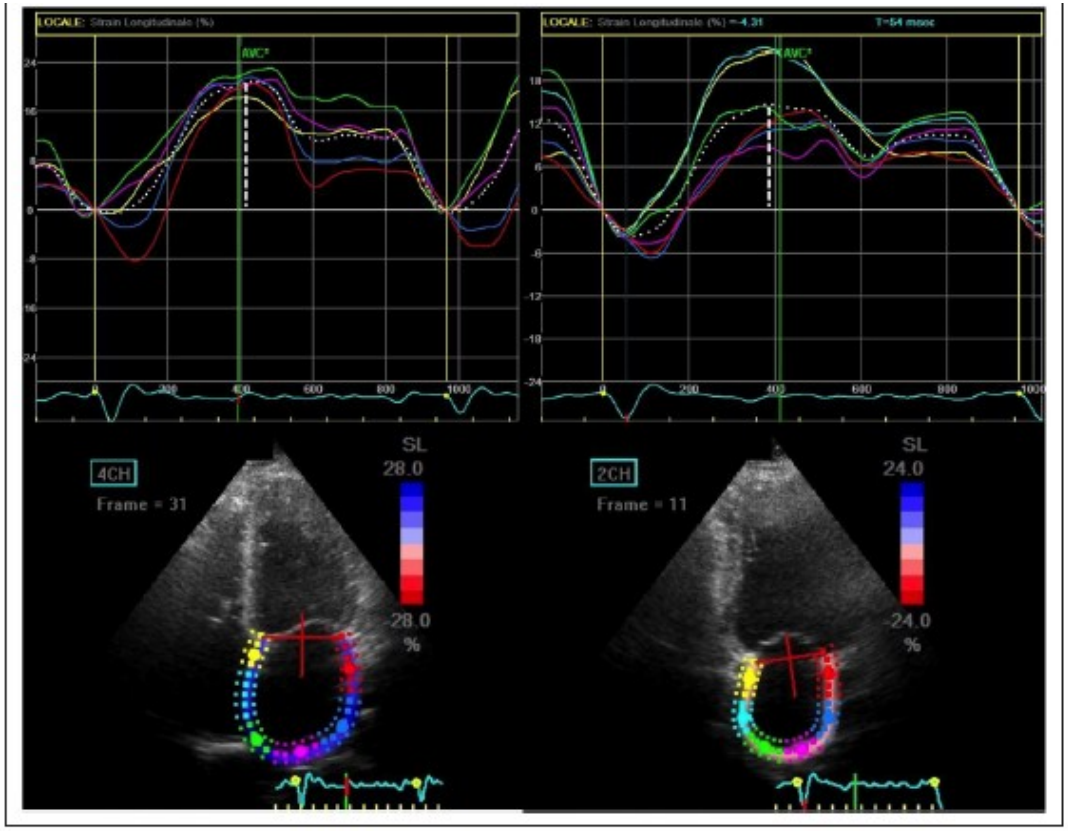


Figure 1. Measurement of peak atrial longitudinal strain (PALS) using speckle tracking echocardiography from apical 4-chamber (4CH; left) and 2-chamber (2CH; right) views in a representative patient with heart failure with reduced ejection fraction.

Lancellotti P, Galderisi M " Prediction of IS in non valvular AF if advanced echo plays a game"

Europace Heart J 2018,0:1

- Aggiungere parametri eco più sofisticati di funzionalità LA (LA strain) che, se alterati, esprimono più avanzate anormalità strutturali, al CHA_2DS_2VASc score, migliora la stratificazione del rischio TE e quindi la decisione di TAO specie nei pz a basso rischio

- In corso studio osservazionale policentrico (EACVI AFib Echo Europe Registry) per correlare dimensioni e funzioni di LA e geometria, dimensioni e funzioni di LV con sviluppo di FA e rischio TE.

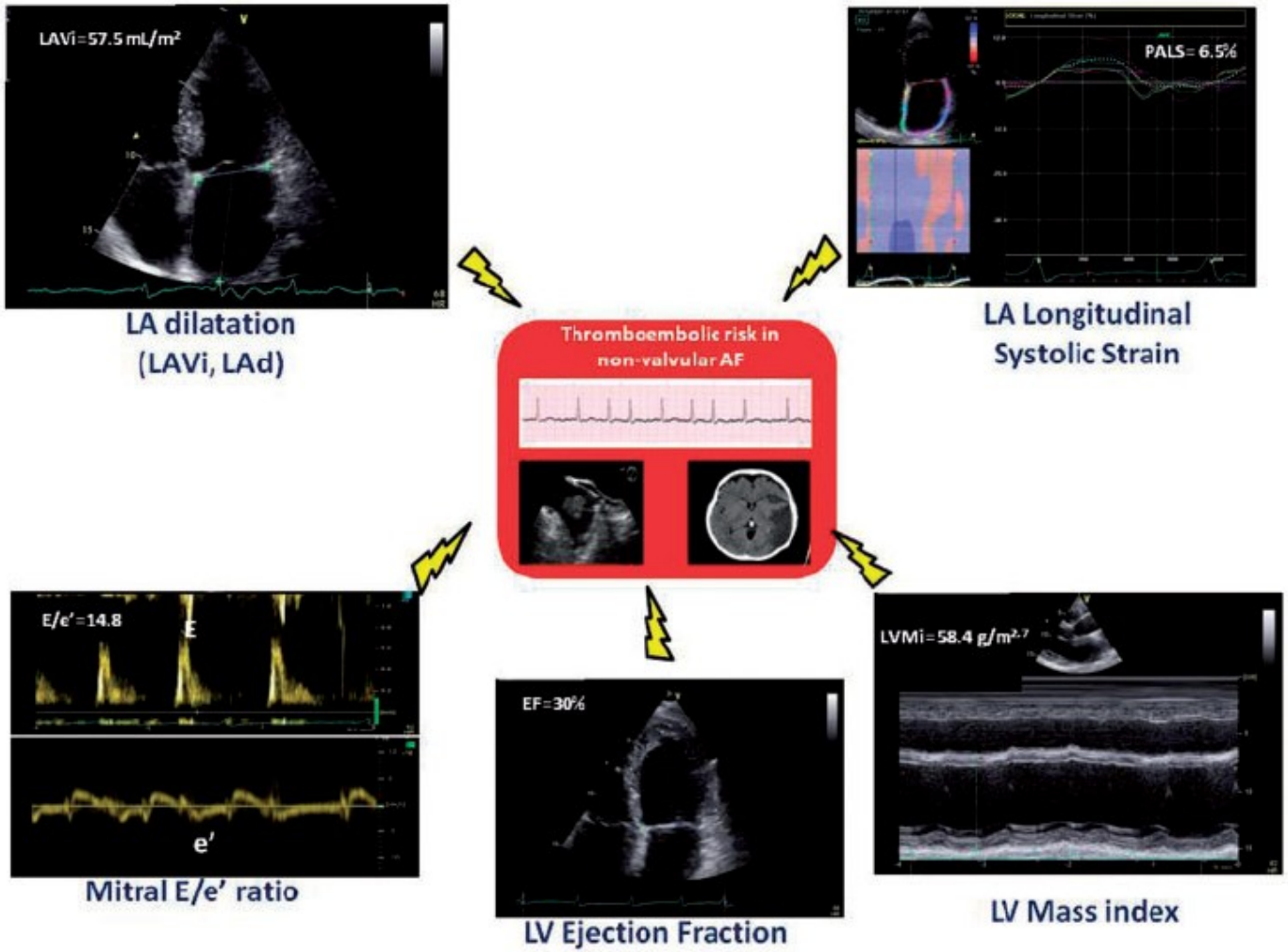


Figure 1 Key echo-Doppler parameters of potential additive value for thromboembolic risk prediction. LA, left atrial; LAd, left atrial diameter; LAVi, left atrial volume index; LV, left ventricular.

Zghaibt T "New insights into the use of CMR imaging to guide decision making in AF managment"

Canad J Cardiol 2018 Nov. 2018

10.1016/J. CJCA.2018.07.007 (1)

- CMR emersa come sviluppo tecnologico per visualizzare LA con alta risoluzione spazio-temporale
- Voltaggio elettro-anatomico bipolare correla punto-punto con LGE, con sensibilità per discriminare aree di basso voltaggio di 0,84, e specificità di 0,68 (però nel 20% circa di casi non possibile analisi di fibrosi di LA)
- Estensione di fibrosi LA ha importanti implicazioni predittive-prognostiche. Classificazione UTAH. ATC subottimale nel 50% dei casi!!

Zghaibt T "New insights into the use of CMR imaging to guide decision making in AF managment"

Canad J Cardiol 2018 Nov. 2018

10.1016/J. CJCA.2018.07.007 (2)

- Cine CMR: analisi funzionale di LA ha maggior valore predittivo per IS che analisi anatomica (almeno il 20% di pz con LA di dimensioni normali, ha alterazioni funzionali)
- Alterazioni strutturali e funzionali di LA (CMPAF) piuttosto che AF di per se possibili basi fisio-patologiche per IS-TE, anche in assenza di AF?

DE-MRI e CMPAF
(1)

- "Gold standard" nella valutazione non invasiva di presenza ed entità di fibrosi atriale.
- ECG, eco, TC… identificano le alterazioni atriali come marker indiretto di rimodellamento strutturale. I complessi cambiamenti fasici di LA (funzioni di reservoir, condotto e contrattile) non possono ovviamente valutare direttamente la presenza di fibrosi.
- La possibilità di quantificare con DE-MRI ha comportato significative ricadute diagnostiche e prognostiche.
- Il burden fibrotico (volume totale di tessuto fibroso calcolato come % di parete atriale) viene categorizzato in 4 stage UTAH:

  I : <10% di fibrosi

  II : fra 10 e 20% di fibrosi

  III : fra 20 e 30% di fibrosi

  IV : >30% di fibrosi
- Il grado di fibrosi valutato con DE-MRI, correla strettamente con CHADSVASC score, con MACCE (specie embolic stroke), esito di ATC.

DE-MRI e CMPAF
(2)

- Da notare che si evidenzia fibrosi anche in pz senza FA, specie se con numerosi fattori di rischio cardiovascolari, e con disfunzione VS, a conferma che essa precede la eventuale FA (e comunque prescinde da FA) ed è malattia progressiva, comunque a rischio di IS-TE per presenza di trombi, specie in LAA.

- Quindi si conferma che FA fa parte di una sindrome CMPAF-relata. Più avanzata è la fibrosi maggiore è il rischio di MACCE indipendentemente da AF

- Non è chiaro perché la maggior parte dei pz con CMPAF non sviluppi FA (analogamente a quanto accade nella disfunzione VS a bassa FE nei riguardi di FV).

King J "LA fibrosis and risk of cerebro-cardiovasolar events in pts with AF" Jacc 2017, 70:1311

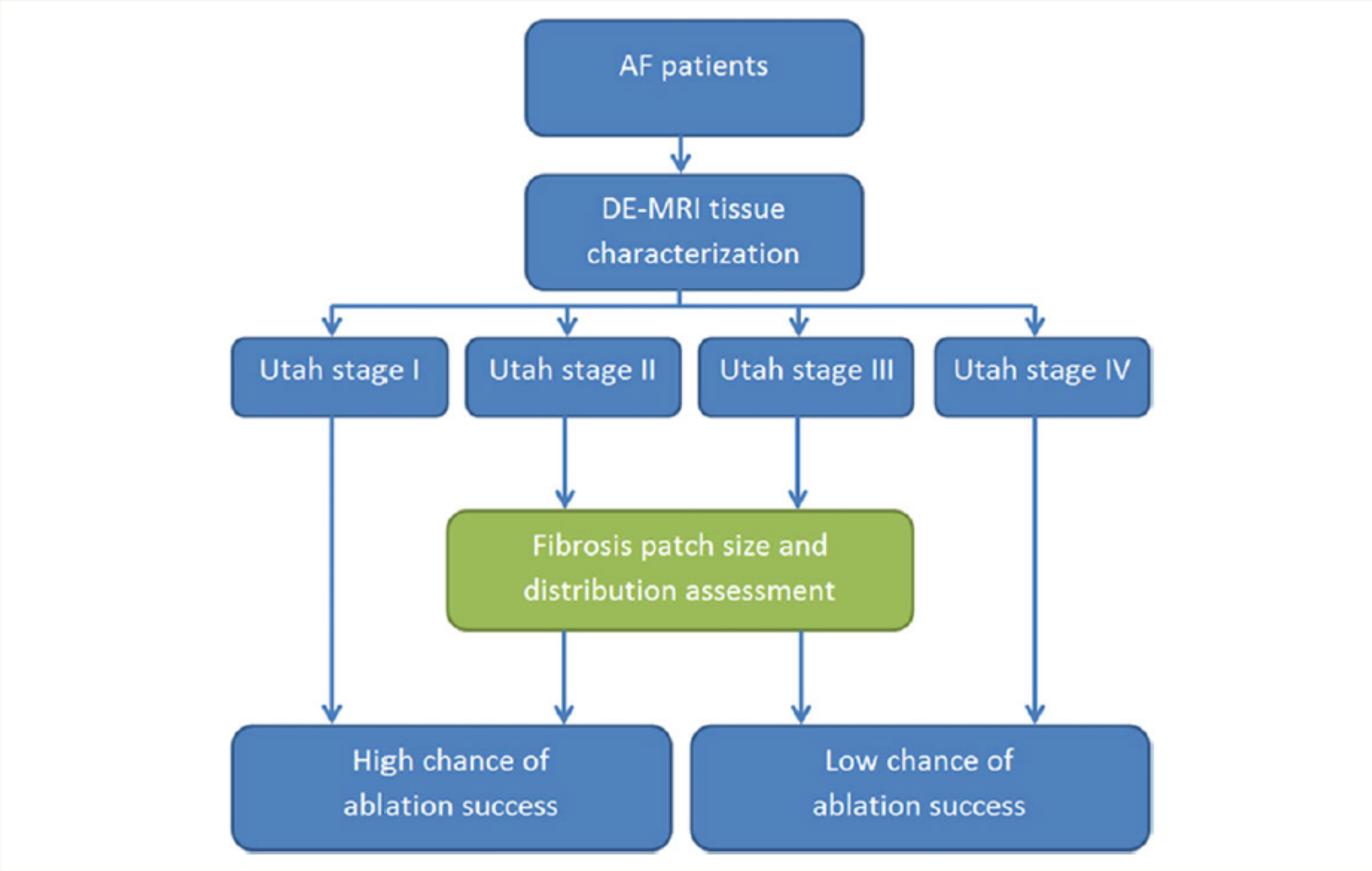


Figure 2 Fibrosis-guided treatment flow chart. Flowchart of delayed enhancement-magnetic resonance imaging-guided patient selection for atrial fibrillation trigger ablation. Utah stage I patients show a high chance of ablation success, as well as patients in Utah stages II and III with a limited fibrosis patch size. Conversely, patients with a larger patch size, as well as Utah stage IV patients, display a low chance of success. Potentially, these patients may be eligible for substrate ablation or no ablation at all. AF, atrial fibrillation; DE-MRI, delayed enhancement magnetic resonance imaging.

Mappaggio elettro-anatomico (EAVM) e CMPAF (1)

- EAVM utilizzato da aa nei laboratori di elettrofisiologia per descrivere anomalie del substrato, specie fibrosi
- Classificazione fibrosi LA in base a EAVM:
- CMPAF 0 : non rilevabili aree di V<1.5mV
- CMPAF 1: aree con limitate zone di severa fibrosi, ma rilevamento di zone confluenti di V moderatamente ridotto (tra 0.5 e 1.5 mV) con elettrogrammi frammentati
- CMPAF 2: aree non confluenti di severa fibrosi (<0.5mV)
- CMPAF 3: fibrosi marcata (<0.5 mV) in almeno 2 aeree, ma ancora confinate regionalmente
- CMPAF 4: "fragola": fibrosi severa e diffusa, con piccole zone moderatamente alterate, con V che raramente raggiungono 1.5
- "Scar" definita come V <0.005

Mappaggio elettro-anatomico (EAVM) e CMPAF (2)

- Analogamente alla fibrosi rilevata con DE-MRI, la fibrosi rilevata con EAVM correla nettamente con CHADS2-Vasc, MACCE (specie ES), risultato di ATC
- Ambedue le metodiche, permettendo una precisa localizzazione della fibrosi atriale, sono impiegate per una ATC mirata nei casi di AF più complesse utilizzando varie procedure più "individualizzate" ad es.
  - Omogenizzazione di aree di basso voltaggio
  - BIFA (box isolation of fibrotic areas): isolamento circonferenziale delle aree compromesse

Kottkamp H"Therapeutic approach to AF ablation targeting LA fibrosis" Jacc 2017; 3:643

Skanes A " AF and HF: untangling a modern gordian Knot"

Canad J Cardiol 2018 Nov. 10,1016/J. CJCA.2018.07.483 (1)

- AF e HF strettamente connessi, con comuni fattori di rischio CV. Oltre il 50% di pz con HF svilupperà AF, che a sua volta può determinare o aggravare HF (TCMP!)
- **Ablazione TC di AF in pz con HF:**

  CAMERA-MRI: risultati positivi (riduzione del burden aritmico, normalizzazione Fe nel 58% dei casi) ma non nei pz con significativo DE-MRI (substrato atriale marcatamente alterato! Più precoce ATC?)

  AATAC (Ablation vs Amio for treatment of persistent AF in CHF and an implanted device)

Skanes A " AF and HF: untangling a modern gordian Knot"

Canad J Cardiol 2018 Nov. 10,1016/J. CJCA.2018.07.483 (2)

CASTLE: simile, ma con risultati sorprendenti anche su GM (ma non su IS!), ma valutazioni controverse (analisi statistica, utilizzo di Amio, HF meno severo e 60% da patologia non ischemica, TCMP?…)

- Necessari RCT rigorosi che, negativi o positivi, vengano universalmente accettati. In attesa di RAFT-AF!

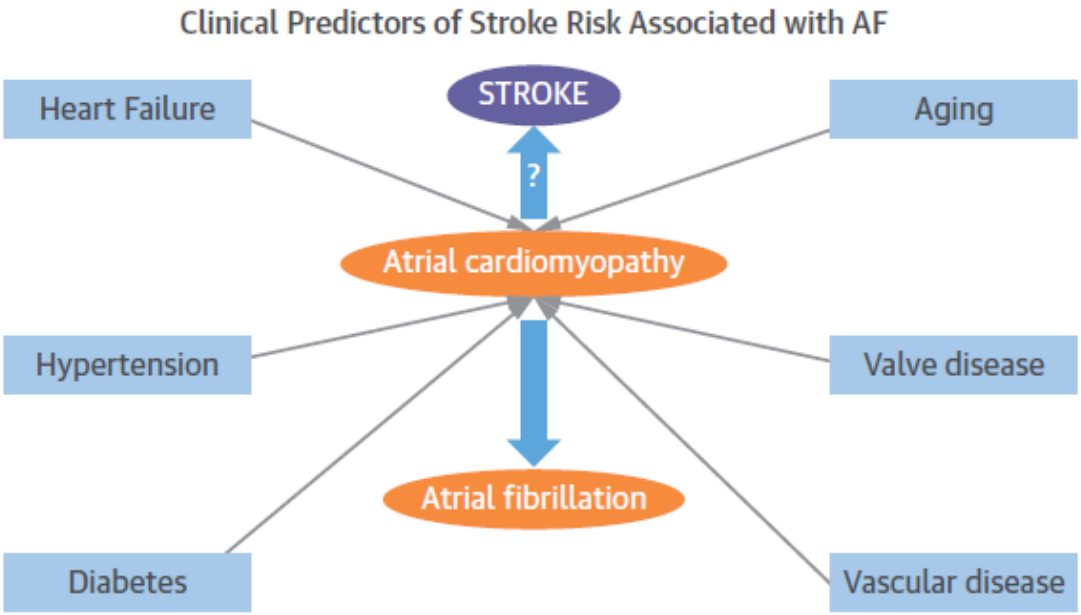
ATC di AF e CMPAF

- Ogni procedura di ATC crea nuove aree di fibrosi atriale (rilevate con DE-MRI o EAVM)
- Non chiarito l'impatto di lesioni-ATC correlate in funzione di LA
- La presenza di una CMPAF (pre-esistente), addirittura aggravata da una scar aggiuntiva post ATC, non riduce il rischio di TE
- In genere i pz. con forme più avanzate di AF hanno anche un "substrato" più avanzato e anche più fattori di rischio.
- Se e quando è indicata una ATC precoce per prevenireo ridurre la progressione delle alterazioni del substrato atriale?

CHADS-VASC: limitato valore predittivo

- Semplicemente e grossolanamente identifica, in pz. con FA, le comorbilità come fattori di rischio di IS.
- Recentemente sempre più utilizzato come score di rischio anche per FA, HF, CHD, mortalità CV anche in pz senza FA.
- Accuratezza predittiva comunque modesta, con "C statistic" di circa 0,6 (meta-analisi di otto studi clinici): buon VPN ma discreto VPP.
- In effetti vengono valutati solo FRCV e non direttamente i meccanismi di IS-TE correlati direttamente al substrato protrombotico di LA (con o senza AF)
- Quindi anche nei pz con FA, decisione di TAO collegata più al profilo di rischio CV che alla presenza di FA!

FIGURE 1 Clinical Predictors of Stroke Risk Incorporated in the $CHADS_2$ and CHA_2DS_2-VASc Schemes All-Cause Atrial Cardiomyopathy



This observation supports the idea that atrial cardiomyopathy may be a direct contributor to stroke risk. CHA_2DS_2-VASc = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism, vascular disease, age 65 to 74 years, sex category; $CHADS_2$ = congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack or thromboembolism.

Biomarker serici e CMPAF

- NP: sembrano aggiungere valore predittivo oltre le variabili cliniche di CHADS-VASC in quanto espressione di alterazioni dell'emodinamica cardiaca

- Troponine: anche esse sembrano aggiungere valore predittivo oltre le variabili cliniche di CHADS-VASC in quanto indicative di fibrosi sostitutiva da perdita di miociti.

Ruff C et all "Cardiovascular biomarker Score and clinical outcomes in patients with AF. A subanalysis of the ENGAGE AF-TIMI 48 RCT" (1)

JAMA Cardiology 2016;1:999

- Usando Biomarker Score da 0 a 11 (NT-proBNP + Troponina + D Dimero) rischio di IS e mortalità variava da 1,2% anno a 21% (nel solo CHADS-VASc da 2,2 a 9,9

- Il solo Biomarker Score aveva maggior valore prognostico di CHADS-VASc (C statistic di 0,7 vs 0,59)

Ruff C et all "Cardiovascular biomarker Score and clinical outcomes in patients with AF. A subanalysis of the ENGAGE AF-TIMI 48 RCT" (2)

JAMA Cardiology 2016;1:999

- Incompleta valutazione di danno strutturale e funzionale di LA e di comorbilità?!
- Possibilità di un più preciso profilo fenotipico ("Precision Medicine") ed una precoce identificazione e trattamento aggressivo dei principali FRCV prima di un irreversibile danno strutturale, salvaguardando semplicità e pragmatismo degli score di rischio.
- Validare questa impostazione con RCT!

CHADS-VASC: inserire altri marker?

LAS-CHADS-VASC?

Hylek EM "Biomarkers for prediction of stroke and bleeds in AF" Circulation 2019;139:772 (1)

- BM consentono di andare oltre la natura grossolamente dicotomica di molte variabili di CHADS-VASC (HF, DM, Hyp) che non consente di cogliere severità e durata di malattia in corso e di valutare la risposta biologica individuale ai vari insulti
- Profilo individuale basato su BM riflette meglio meccanismi fisiopatologici alla base di trombogenicità e suscettibilità ad AF nell' ambito di una atriopatia.
- Quindi Troponina hs e BNP riflettono meglio risposte individuali allo stress cardiaco (disfunzione contrattile, tensione di parete, disfunzione endoteliale, stasi…) e segnalano precocemente rimodellamento sfavorevole, magari ancora clinicamente silente, e quindi una CMPA fibrotica sottostante

Hylek EM "Biomarkers for prediction of stroke and bleeds in AF" Circulation 2019;139:772 (2)

- BM, associati anche ad altri fattori di rischio non compresi in CHADS-VASC (obesità, sedentarietà, OSAS, sindrome metabolica, IRC..) identificano meglio i pazienti a rischio di IS-TE e AF che eventualmente necessitano di TAO.

- Anche analizzando RCT con NOAC (ENGAGE AF Trial, Circulation 2019; 139:760 e RE-LY trial, J Am Heart Assoc 2019;8:107) se ne ricava che i BM sono i migliori predittori di IS-TE con C-index di 0,77 vs 0,59 di CHADS-VASC

CHADS-VASC: inserire altri marker?

BM-LAS-CHADS-VASC?

Valutazione di score di rischio di IS-TE

- CHA_2DS_2VASc
- Valutazione ECG
- Valutazione eco anatomo-funzionale di LA
- BNP e troponine
- Altre condizioni cliniche pro-fibrotiche (obesità, sedentarietà, SAS, BPCO, insufficienza renale…)
- Da chiarire definitivamente con RCT se una combinazione di parametri clinici, elettrici, strutturali, laboratoristici, identifichino pz ad alto rischio di ES anche prima che compaia AF (pz prefibrillatori?) o anche in assenza di AF, da sottoporre a TAO in relazione alla presenza di CMPAF!

7.13. Weight Loss (New)

Recommendation for Weight Loss in Patients with AF Referenced studies that support the new recommendation are summarized in Online Data Supplement 10.		
COR	**LOE**	**Recommendation**
I	B-R	1. **For overweight and obese patients with AF, weight loss, combined with risk factor modification, is recommended (S7.13-1–S7.13-3).** **NEW**: New data demonstrate the beneficial effects of weight loss and risk factor modification on controlling AF.

Recommendation-Specific Supportive Text (New)

1. Obesity is associated with atrial electrostructural remodeling (S7.13-4) and AF (S7.13-5–S7.13-7). One RCT demonstrated that a structured weight management program for obese patients (body mass index >27) with symptomatic AF reduced symptom burden and severity and reduced the number of AF episodes and their cumulative duration when compared with attempts to optimally manage risk factors alone (S7.13-1). Risk factor modification included assessment and treatment of underlying sleep apnea, hypertension, hyperlipidemia, glucose intolerance, and alcohol and tobacco use. A second nonrandomized observational study reported improved outcomes of AF catheter ablation among obese patients who enrolled in a weight loss program (S7.13-2). Observational studies have revealed that the degree of improvement in the AF type and symptoms were related to the degree of weight loss (S7.13-3, S7.13-8). Taken together, these studies support a treatment approach that addresses the risk factors for AF.

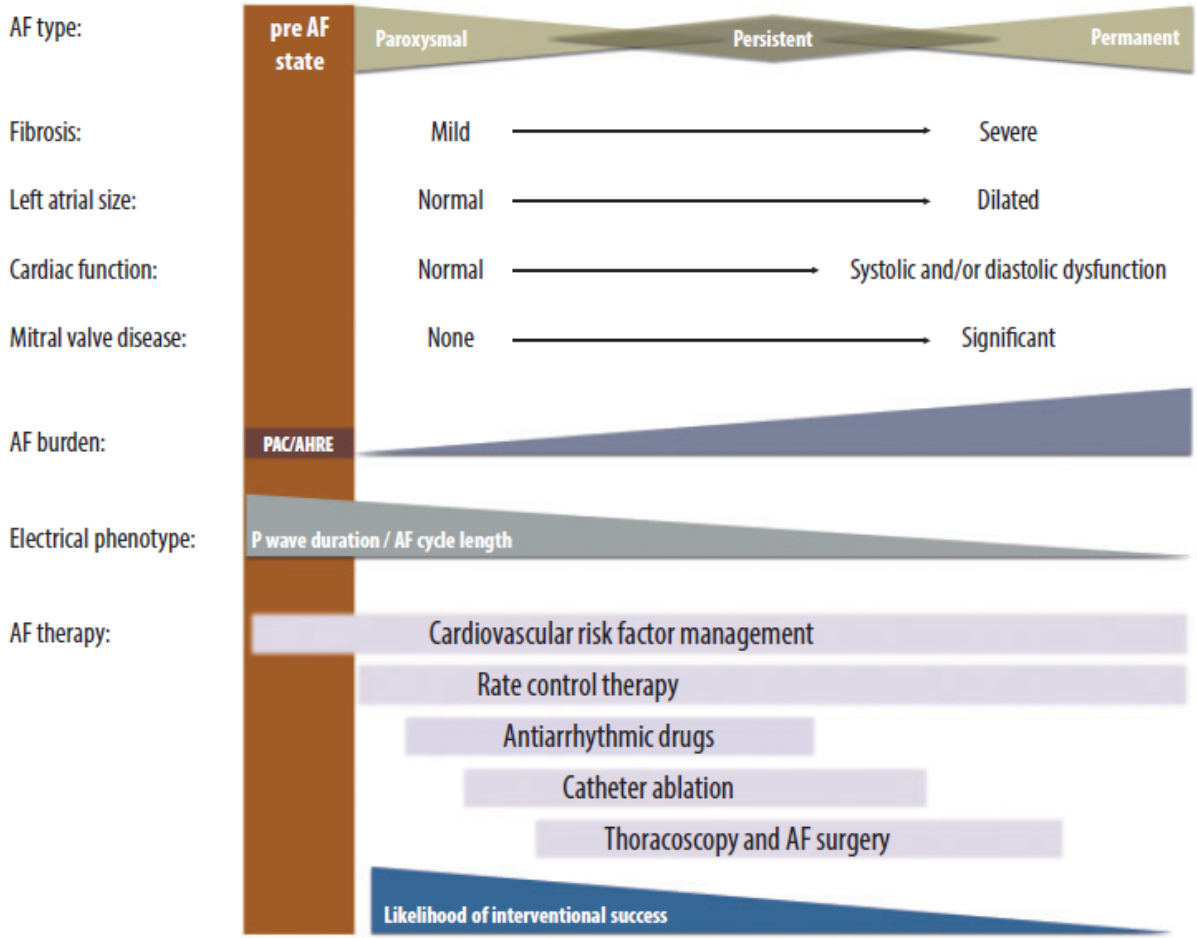


Figure 4 Pre-AF, atrial cardiomyopathy, and the spectrum of AF management. AHRE, atrial high rate episodes; PAC, premature atrial complex.

Accepted Manuscript

The importance and future of population screening for atrial fibrillation

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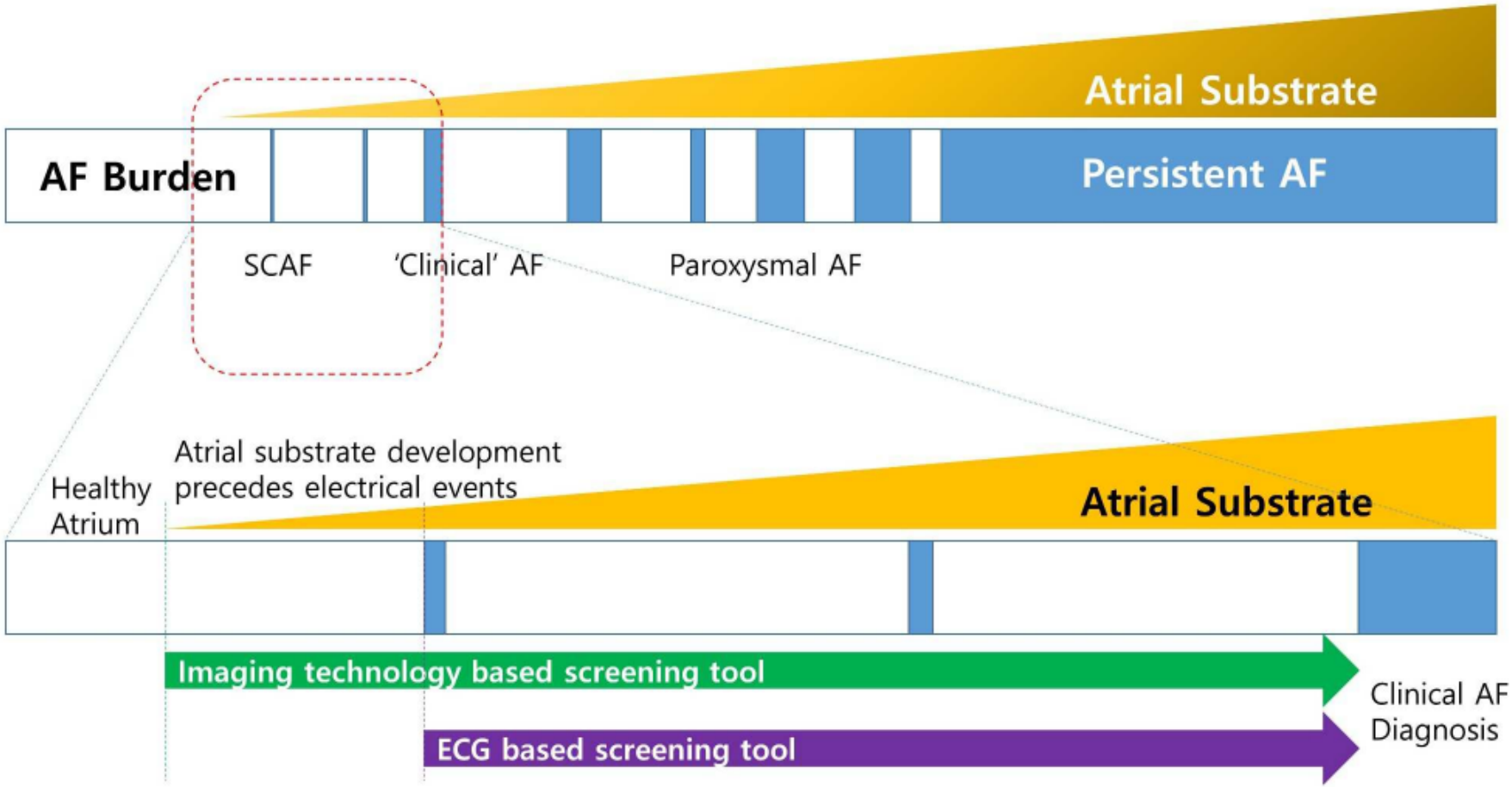
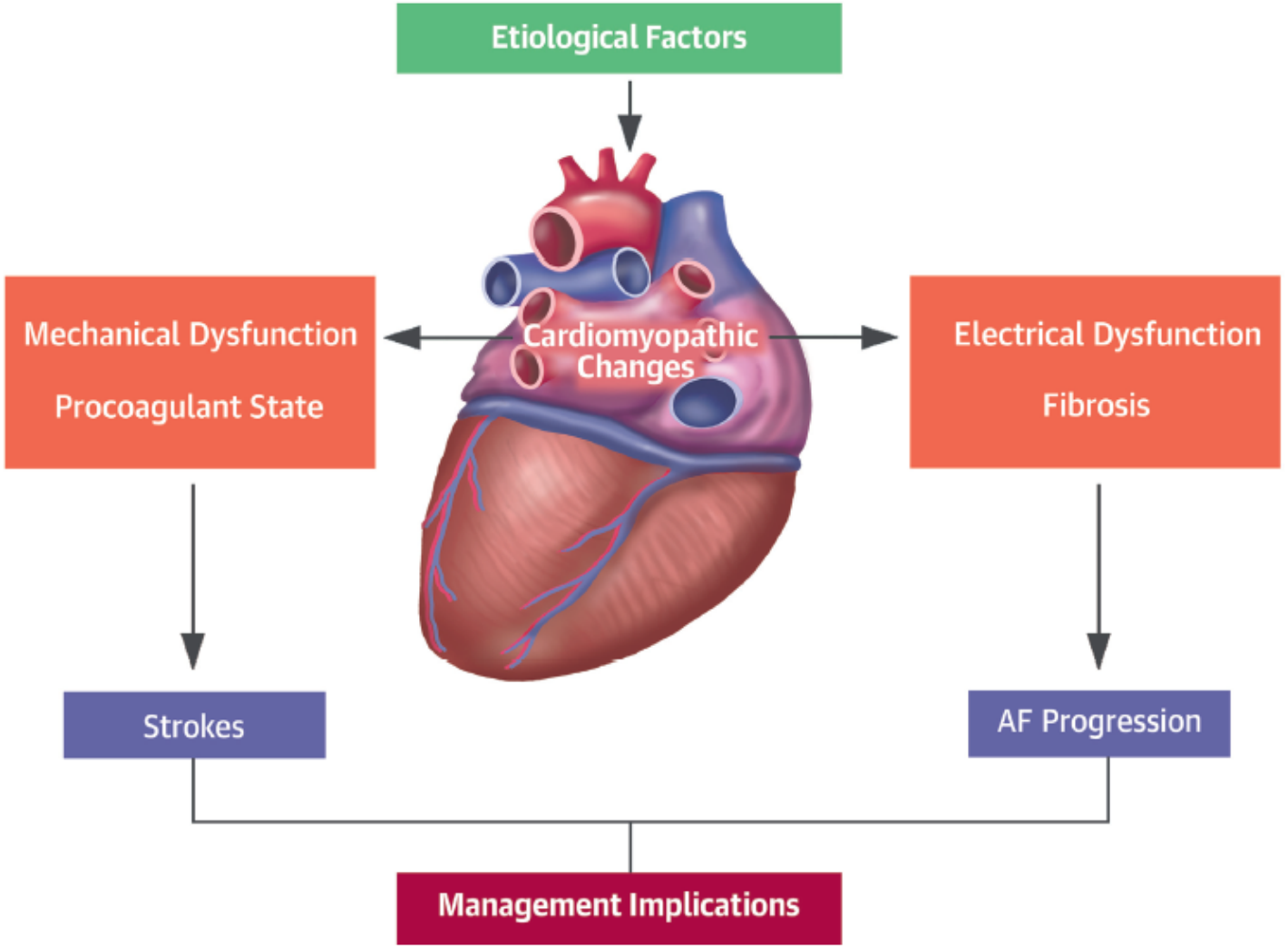
Accepted Date: 9 August 2018

Figure 1. Future of AF screening



AF: atrial fibrillation; SCAF: subclinical atrial fibrillation; ECG: electrocardiography.

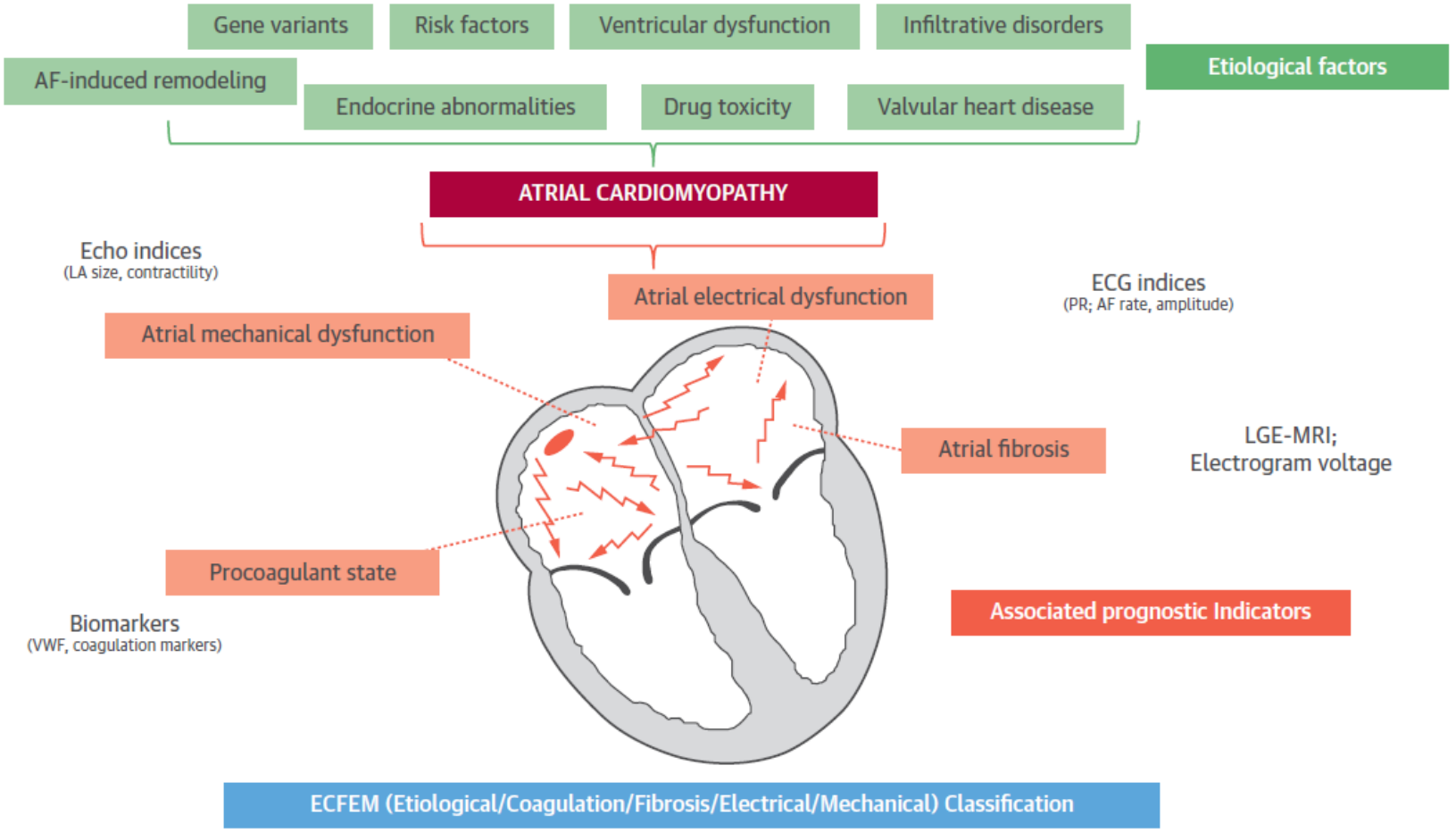
CENTRAL ILLUSTRATION Etiological Factors Lead to Atrial Cardiomyopathic Changes



Guichard, J.-B. et al. J Am Coll Cardiol. 2017;70(6):756–65.

These factors, in turn, cause electrical, mechanical, profibrotic, and procoagulant abnormalities, which lead to enhanced stroke risk and atrial fibrillation (AF) progression. Consideration of the causes and consequences of atrial cardiomyopathy has the potential for significant management implications that validate the relevance of the underlying concept.

FIGURE 4 Potential Components of a Clinically Relevant Classification of Atrial Cardiomyopathies



A schematic representation of the key determinants and components of atrial cardiomyopathy upon which a clinically relevant classification system could be built. Etiological factors should figure in the classification system, as they drive the cardiomyopathy and have specific therapeutic and prognostic implications. In addition, key cardiomyopathic consequences, such as atrial mechanical dysfunction, a procoagulant state, electrical dysfunction, and fibrosis, have implications for major complications, such as stroke and AF progression, and must be considered. The classification could be based on these factors, to which we have applied the mnemonic ECFEM (etiological, coagulation, fibrosis, electrical, or mechanical indexes). The key determinant of both the concept of atrial cardiomyopathy and any classification will be their utility in facilitating important management decisions. The value of the concept and classification will be determined based on outcome measures, such as stroke occurrence, cardiac dysfunction, and impaired quality of life (QOL), which their application should tangibly improve. AF = atrial fibrillation; CV = cardiovascular; ECG = electrocardiographic; Echo = echocardiographic; LA = left atrial; LGE-MRI = late gadolinium enhancement-magnetic resonance imaging; VWF = von Willebrand factor.

TABLE 1 EHRAS Classification of Atrial Cardiomyopathy

Class	Definition
I	Primarily cardiomyocyte dependent
II	Primarily fibroblast dependent
III	Mixed cardiomyocyte-fibroblast dependent
IV	Primarily noncollagen deposits

EHRAS = European Heart Rhythm Association score.

FIGURE 3 EHRAS Classes Corresponding to Each of the Atrial Cardiomyopathic Processes in the EHRA/HRA/APHRS/SOLEACE Consensus Document

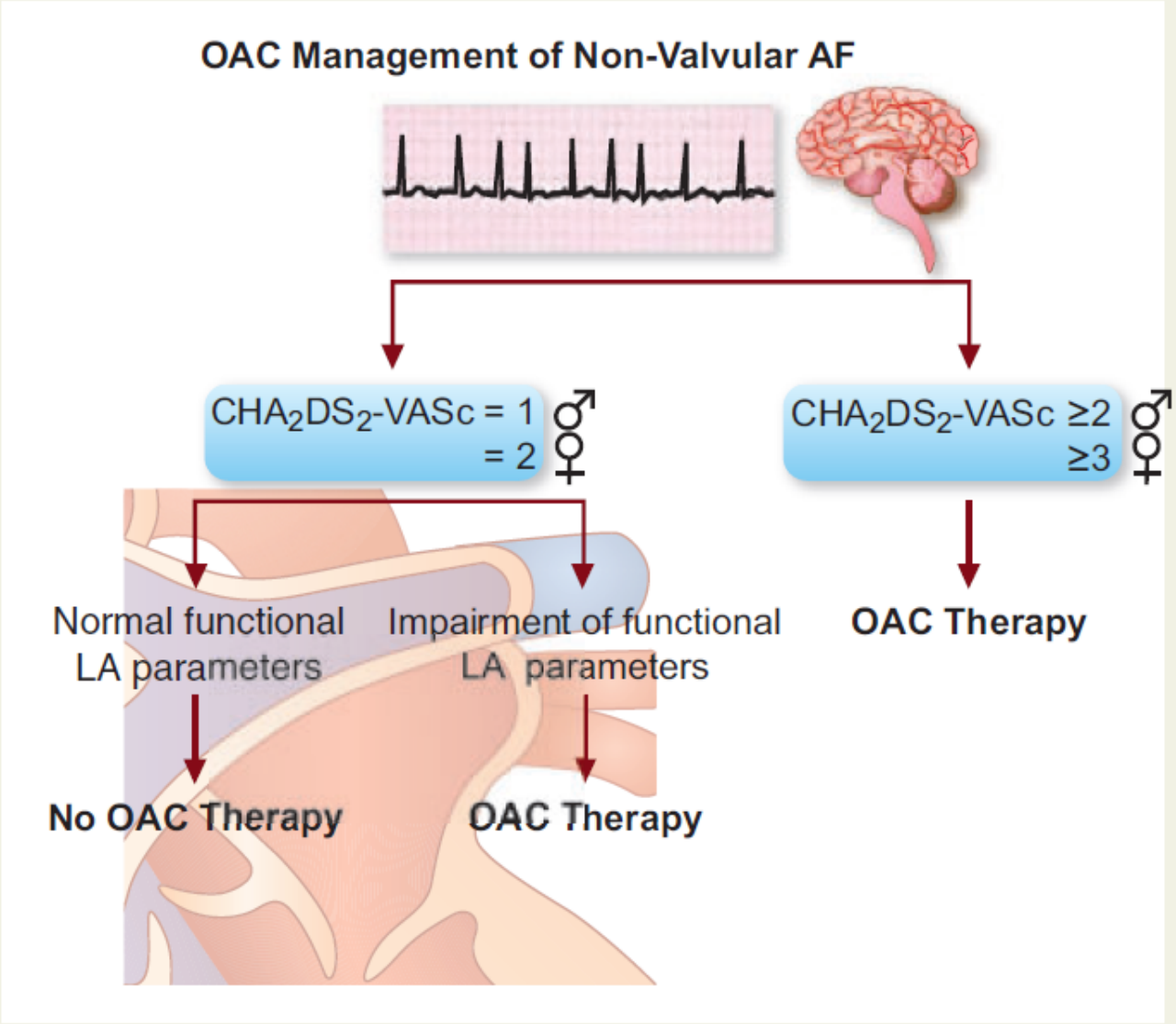
	EHRAS class			
	I	II	III	IV
Type of Atrial Cardiomyopathy	Cardiomyocyte	Fibrosis	Fibrosis + cardiomyocyte	Non collagen infiltrate
Lone AF		✔	✔	
Atrial amyloidosis				✔
Muscular dystrophies	✔	✔	✔	✔
Congestive heart failure		✔	✔	✔
Obstructive sleep apnea	✔		✔	
AF-induced remodeling	✔		✔	
Drug-induced	✔	✔	✔	✔
Myocarditis			✔	✔
Age		✔		
High blood pressure	✔	✔	✔	
Obesity			✔	✔
Diabetes mellitus	✔		✔	✔
Valvular heart disease	✔	✔	✔	✔

To obtain the information shown, we carefully reviewed the paper for European Heart Rhythm Association (EHRA), Heart Rhythm Society (HRS), Asia-Pacific Heart Rhythm Society (APHRS), and Sociedad Latinoamericana de Estimulación Cardiaca y Electrofisiología (SOLEACE) classes as described in the EHRA/HRS/APHRS/SOLEACE Consensus Document (6). Check marks indicate which EHRAS classes were associated with each type of atrial cardiomyopathy as discussed in the consensus document. AF = atrial fibrillation.

TABLE 2 Potential Practical Applications of the Atrial Cardiomyopathy Concept

1. Stroke prevention
   a. Identification of at-risk individuals, independent of AF
   b. More efficient identification of patients with AF who do not require anticoagulation
   c. Indicating when OAC can be stopped after ablation
   d. Therapeutic specification of anticoagulation (e.g., patients inadequately protected by OAC)
2. Rhythm therapy
   a. Identification of individuals for whom ablation therapy will fail
   b. Therapeutic specification of ablation approach
   c. Guiding and evaluating upstream therapy
   d. Guiding antiarrhythmic drug therapy
   e. Guiding ancillary therapy for rhythm maintenance
3. Rate control
   a. Defining patient-specific rate control targets
   b. Identifying individuals for whom rate control is likely to fail

AF = atrial fibrillation; OAC = oral anticoagulant.



Take home figure A futuristic echo-based algorithm for anti-coagulant therapy management of patients with non-valvular atrial fibrillation. OAC, oral anticoagulant therapy; LA, left atrial.

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  JACC 2017,6:756

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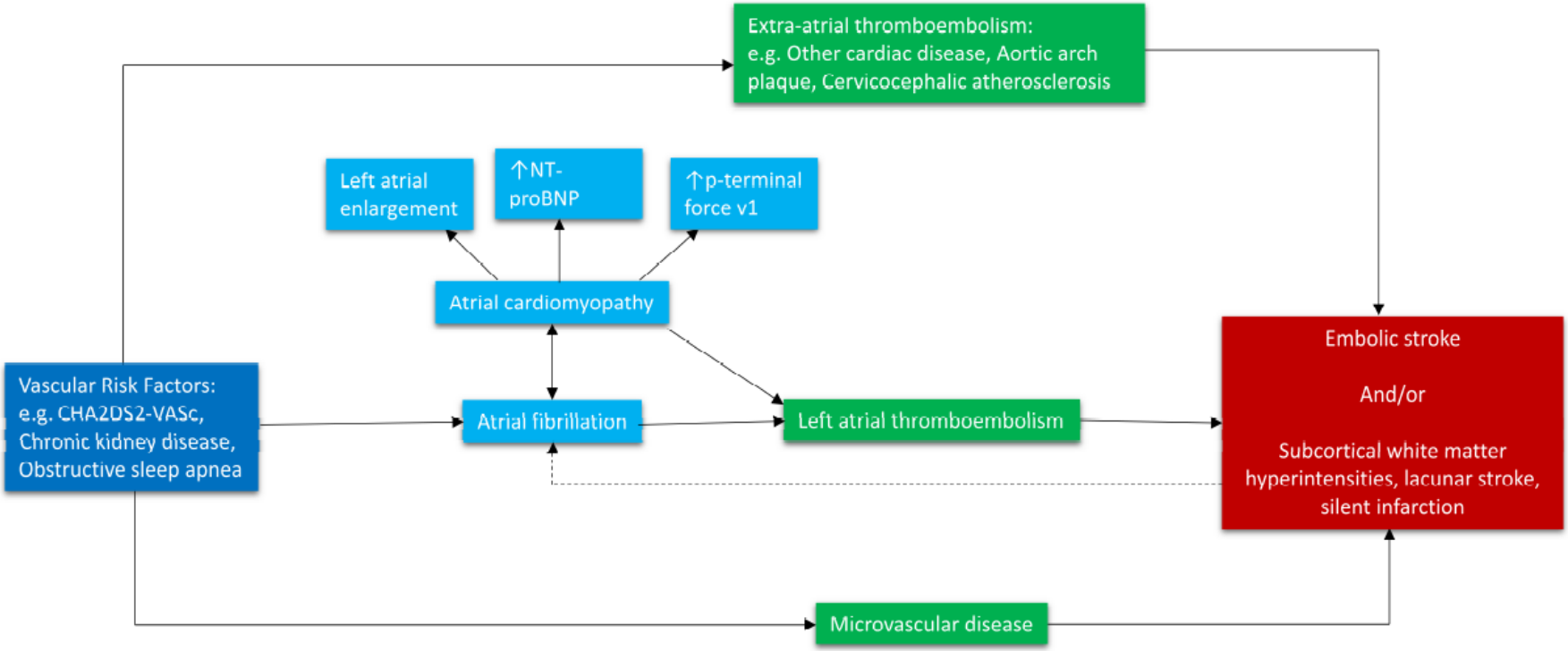

Extra-atrial thromboembolism:
e.g. Other cardiac disease, Aortic arch plaque, Cervicocephalic atherosclerosis
Left atrial enlargement
↑NT-proBNP
↑p-terminal force v1
Atrial cardiomyopathy
Vascular Risk Factors:
e.g. CHA2DS2-VASc, Chronic kidney disease, Obstructive sleep apnea
Atrial fibrillation
Left atrial thromboembolism
Embolic stroke
And/or
Subcortical white matter hyperintensities, lacunar stroke, silent infarction
Microvascular disease

Conclusioni (1)

- CMPAF è un processo patologico secondario a fibrosi progressiva che è alla base di IS-TE, a prescindere da FA.
- Attuali score di rischio inadeguati predittori di IS

- Nuovi fattori clinici di rischio, ma soprattutto biomarcatori umorali e reperti di imaging sembrano fondamentali per una ottimale stratificazione di rischio di IS e quindi di una TAO mirata, anche prescindendo da FA

Conclusioni (2)

- Rimane decisivo e obbligatorio, come primo step terapeutico , un trattamento globale di tutti i fattori di rischio, coinvolti direttamente o indirettamente, in IS sia TE che non TE.

- Obiettivo futuro è il rimodellamento inverso di un LA fibrotico: al momento non esistono dati clinici conclusivi che dimostrino questa possibilità!!

Conclusioni

- La suscettibilità atriale alla trombosi e la capacità di mantenere integrità tissutale e vascolare coinvolge una complessa situazione biologica correlata ad una molteplicità di percorsi biochimici, modulati da fattori intrinseci ed estrinseci
- Data questa complessità, la perfezione nella predizione del rischio TE (con o senza AF) rimane un obiettivo certamente lodevole ma, al momento, sfuggente, pur se in fase di lenta, ma progressiva chiarificazione
- Nella speranza di aggiungere, la prossima volta, altri tasselli a questo "puzzle" in perenne attesa di essere completato

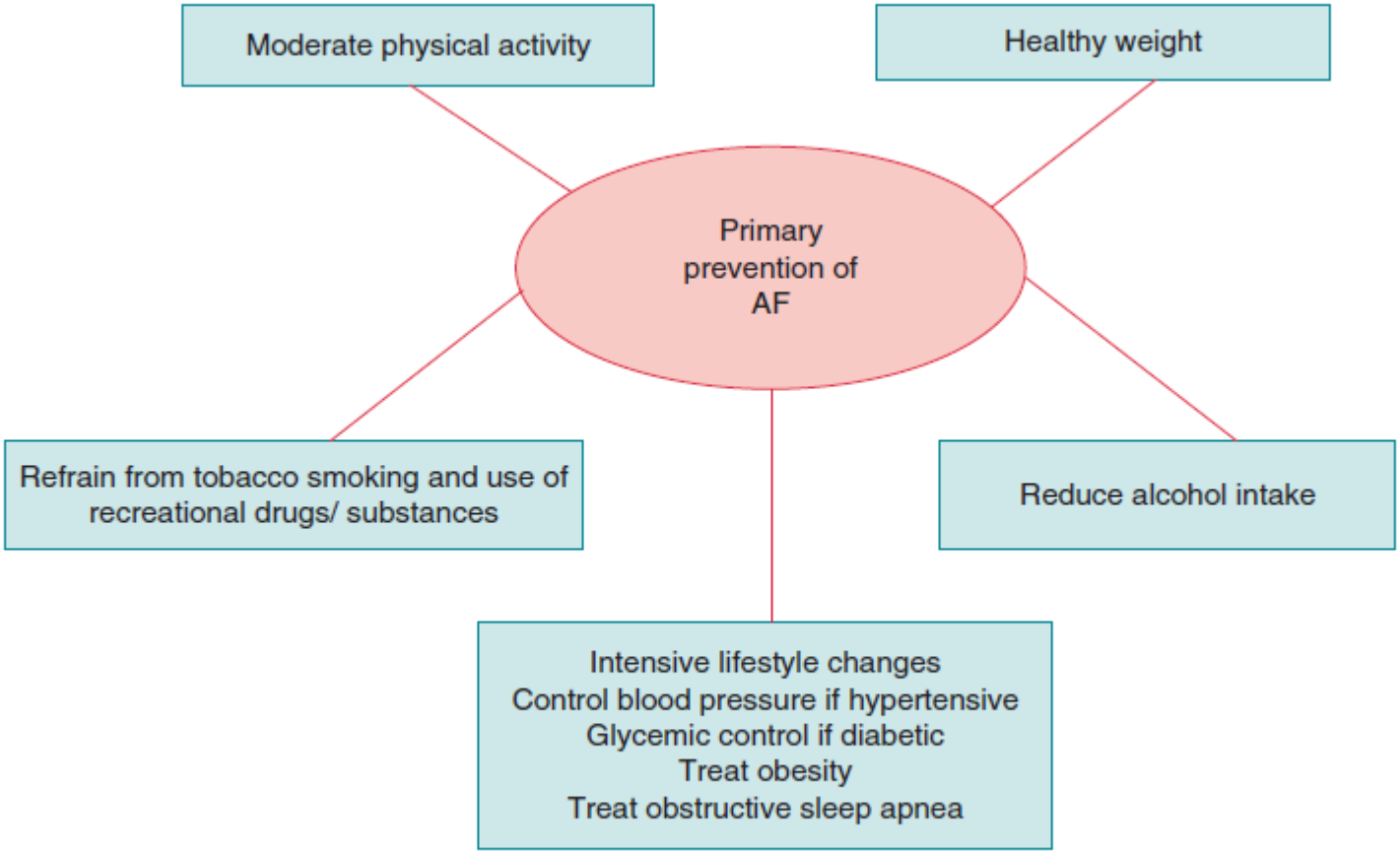
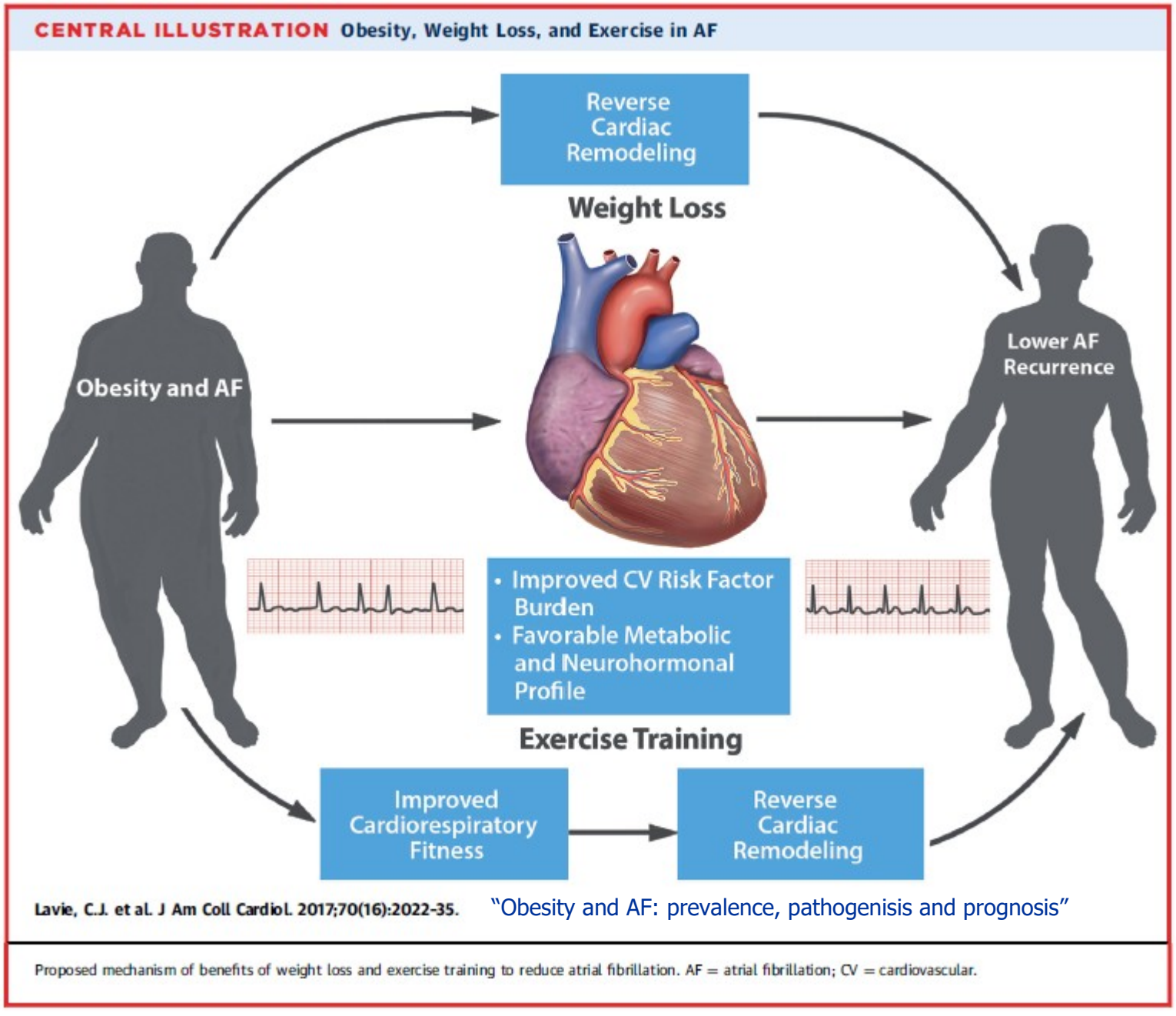
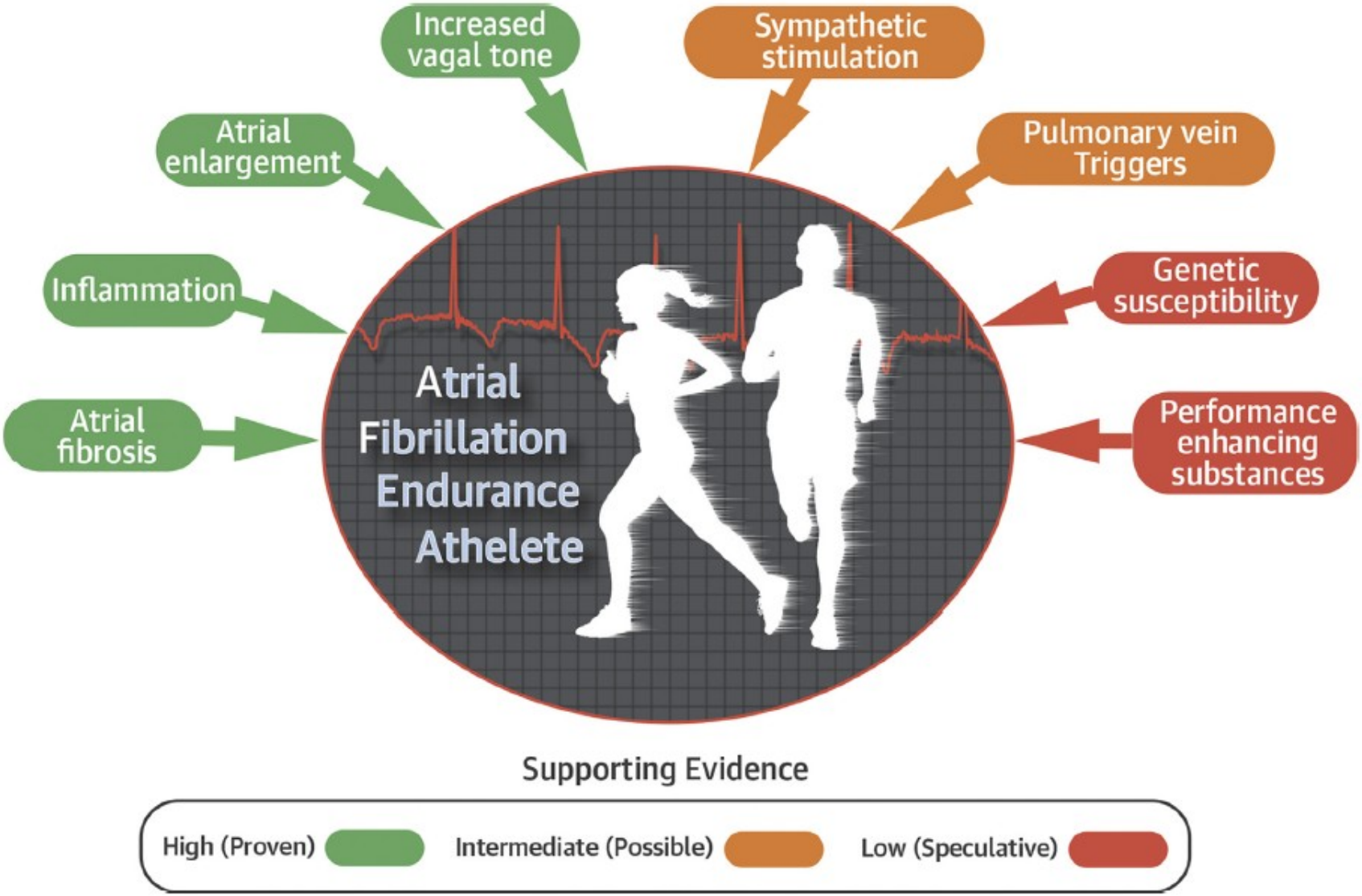


Figure 3 Lifetime approach to primary prevention of AF. AF, atrial fibrillation.


CENTRAL ILLUSTRATION Obesity, Weight Loss, and Exercise in AF
Reverse Cardiac Remodeling
Weight Loss
Obesity and AF
Lower AF Recurrence
• Improved CV Risk Factor Burden
• Favorable Metabolic and Neurohormonal Profile
Exercise Training
Improved Cardiorespiratory Fitness
Reverse Cardiac Remodeling
Lavie, C.J. et al. J Am Coll Cardiol. 2017;70(16):2022-35.
"Obesity and AF: prevalence, pathogenisis and prognosis"
Proposed mechanism of benefits of weight loss and exercise training to reduce atrial fibrillation. AF = atrial fibrillation; CV = cardiovascular.

CENTRAL ILLUSTRATION Proposed Pathophysiologic Mechanisms of AF in the Endurance Athlete



Estes, N.A.M. et al. J Am Coll Cardiol EP. 2017;■(■):■-■.

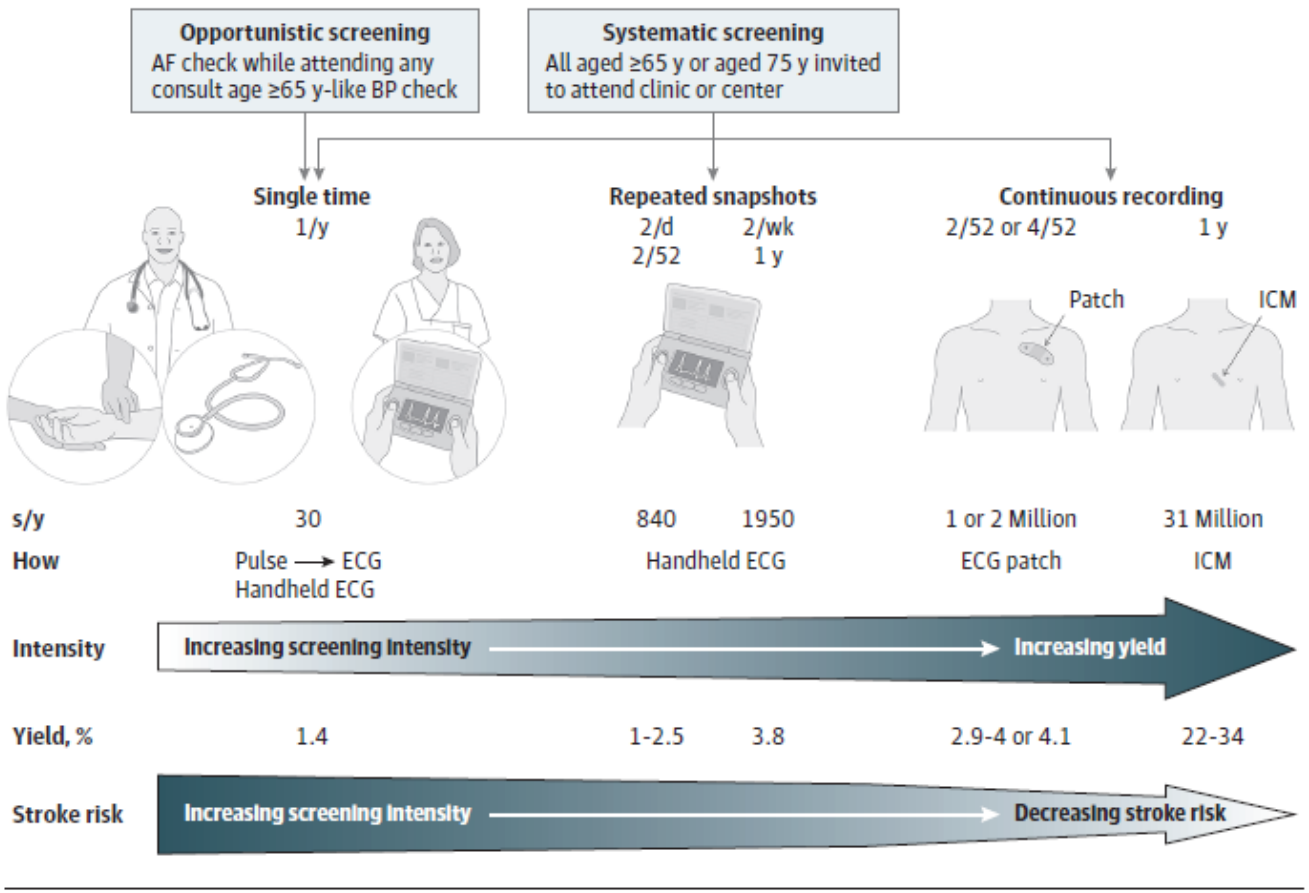
Multiple factors contributing to AF with intense endurance exercise are shown with color coding according to the strength of the supporting evidence. PV = pulmonary vein; other abbreviation as in Figure 1.

Grazie per l'attenzione

VIEWPOINT

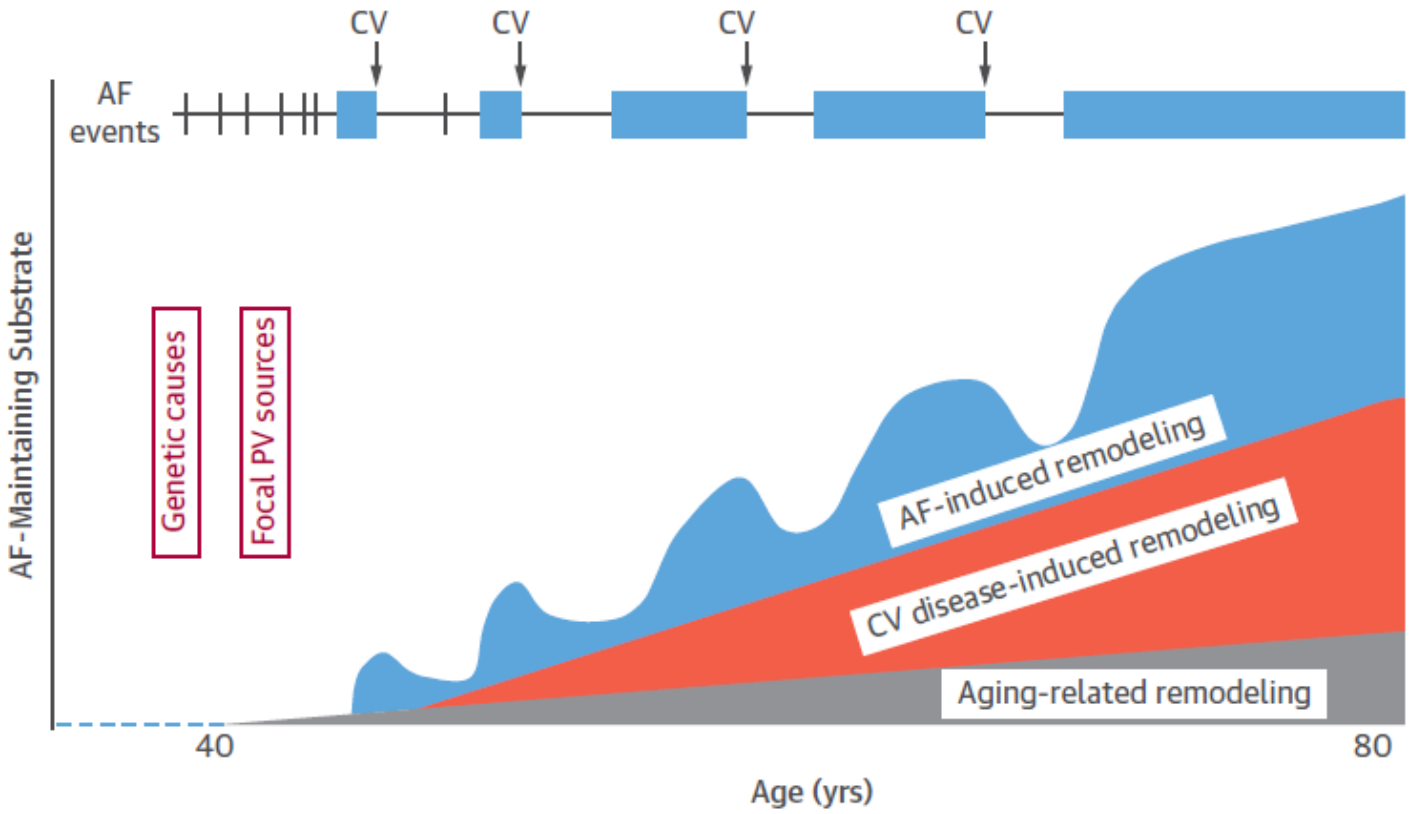
Opportunistic Electrocardiogram Screening for Atrial Fibrillation to Prevent Stroke

Figure. Opportunistic and Systematic Screening for Atrial Fibrillation (AF)



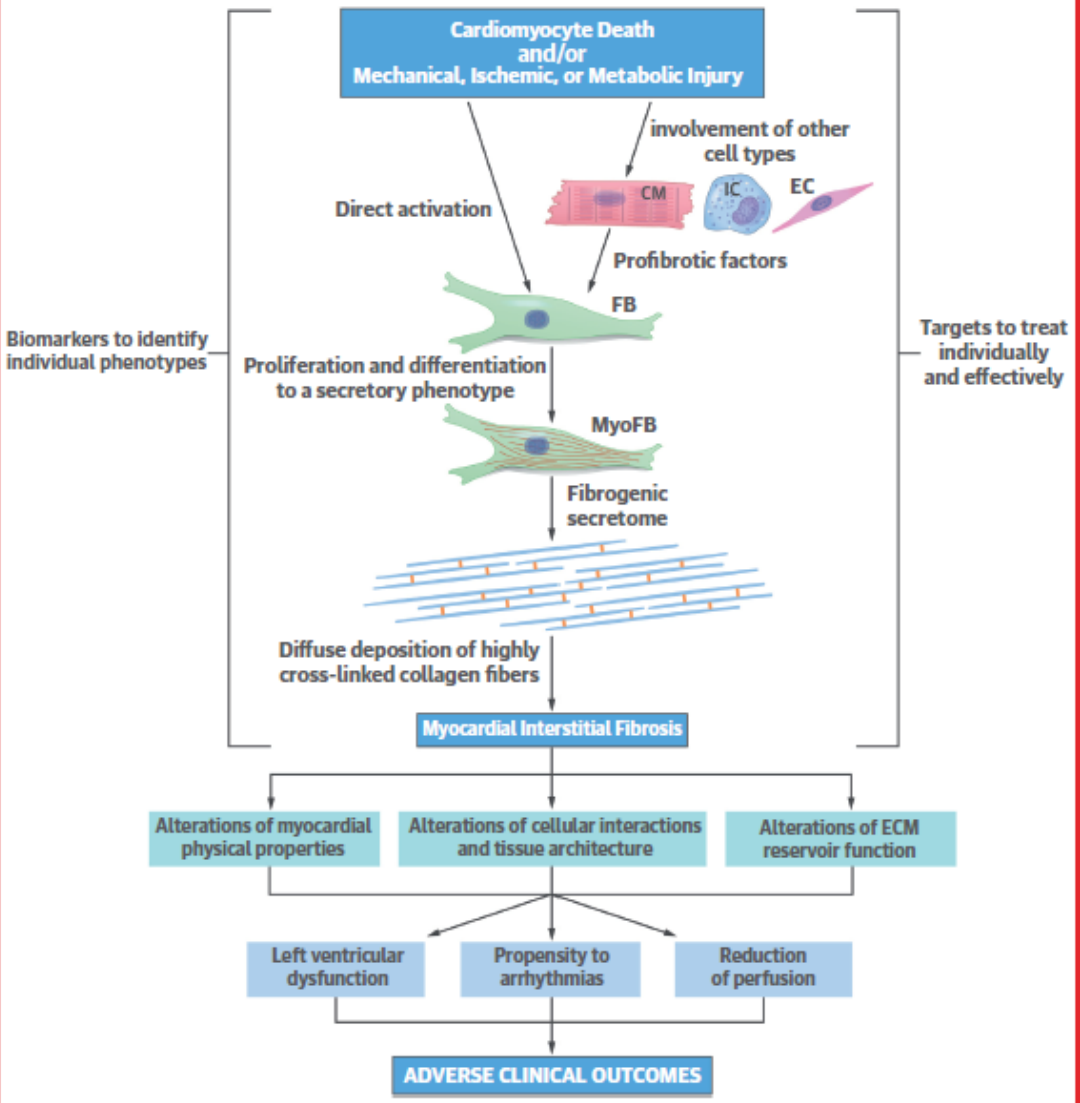
Tradeoff between increasing AF yield and reduced stroke risk as screening intensity increases. BP indicates blood pressure; ECG, electrocardiogram; ICM, implanted cardiac monitor.

FIGURE 2 A Schematic Representation of the Natural History of AF



Atrial fibrillation (AF) often begins as short-lasting episodes, but becomes more long lasting over time as the AF-maintaining substrate progresses because of cumulative remodeling. Each AF episode that lasts for more than 24 h causes atrial remodeling, which reverses (but not necessarily completely) when AF terminates. In addition to AF-induced remodeling, remodeling due to intercurrent cardiac disease, as well as the normal aging process, contributes to the AF substrate. The remodeling processes cause atrial cardiomyopathic changes.
CV = cardiovascular; PV = pulmonary vein.

CENTRAL ILLUSTRATION Developmental Phases in Myocardial Interstitial Fibrosis and Their Impact on the Heart and Related Clinical Consequences



González, A. et al. J Am Coll Cardiol. 2018;71(15):1696-706.

CM = cardiomyocyte; EC = endothelial cell; ECM = extracellular matrix; FB = fibroblast; IC = inflammatory cell; MyoFB = myofibroblast.

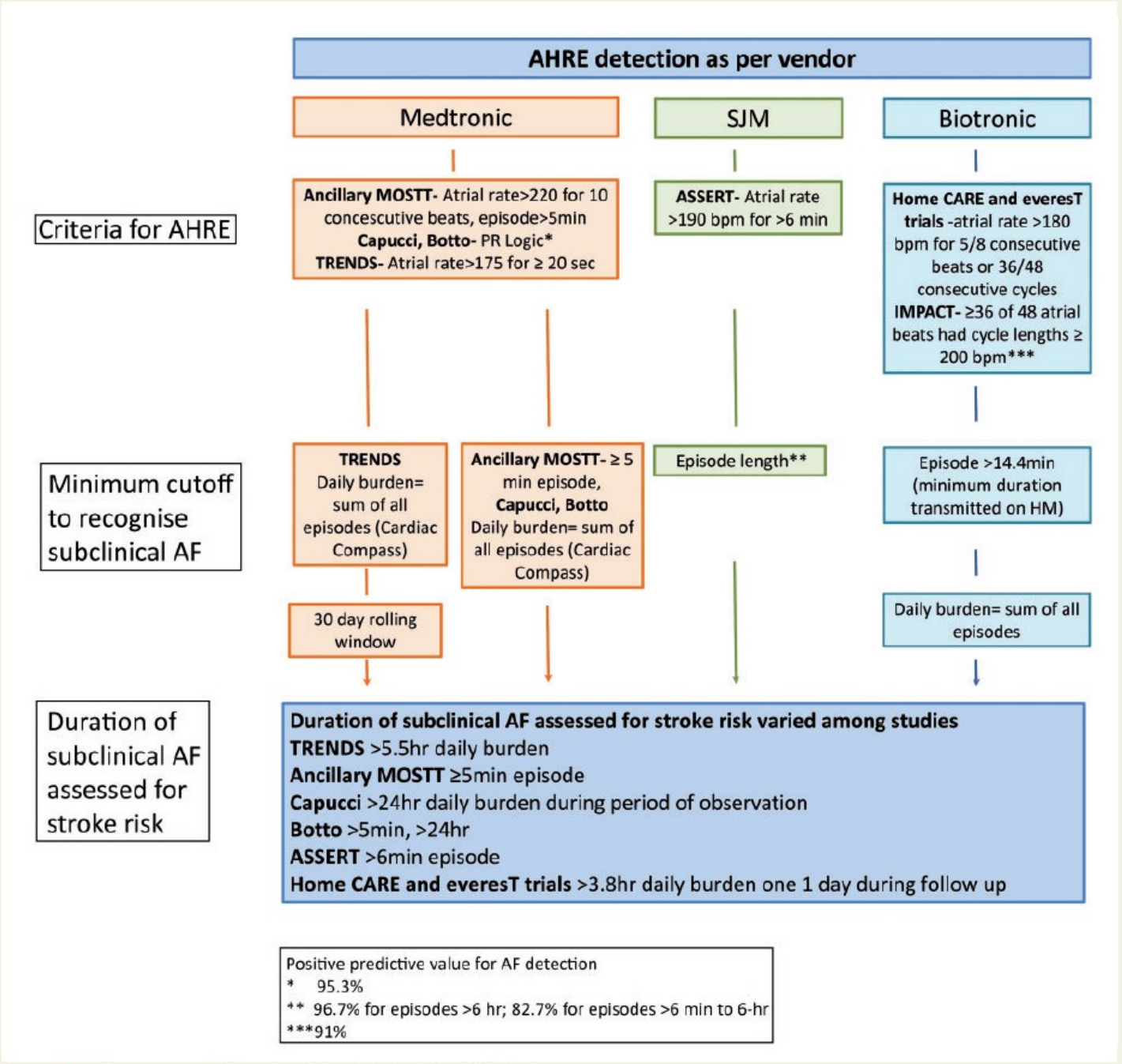


Figure 2 Criteria and cut-off for detection of subclinical atrial fibrillation.

Table 1 Study design and definition of subclinical atrial fibrillation in the included studies

Study[a]	Study design	Sample size	Follow-up (years)	Adjudication 1 = Y, 0 = N	AF at time of enrolment	Cut-off for AF/AHRE detection and duration associated with stroke risk
Ancillary MOSTT	Retrospective observational	312	2.3	0	Sinus node dysfunction. Sinus rhythm at randomization	Atrial rate >220 b.p.m. for 10 consecutive beats AHRE ≥***5 min episode.*** Medtronic pacemakers
Capucci	Prospective multi-centre observational	725	1.8	1	Bradycardia with dual chamber pacing indication. Previous AF. Permanent AF excluded	PR logic[b] ***24 h AF*** (cardiac compass) ***episode during period of observation.*** Medtronic pacemakers
Botto	Retrospective observational	568	1	0	Brady-tachy syndrome. Permanent AF excluded	PR logic[b] AHRE ***>5 min on 1 day of year, 24 h*** (cardiac compass). Medtronic pacemakers
TRENDS	Prospective observational	2486	1.4	0	Patients with or without prior PAF. $CHADS_2 \geq 1$. Permanent AF excluded	Atrial rate >175 b.p.m. for ≥20 s AHRE ≥ 5 min. ***Rolling window, day burden >5.5 h AF on 1 day.*** Medtronic pacemakers
ASSERT	Randomized	2580	2.5	1	Excluded prior AF. Hypertension.	Atrial rate >190 b.p.m. for >6 min ***>6 min AF episodes.*** St Jude Medical pacemakers
Home CARE and everesT trials	Prospective observational	560	1	0	Prior history of AF in 178 of 382 patients. Heart failure cohort. Permanent AF excluded	Atrial rate >180 b.p.m. for 5/8 consecutive beats or 36/48 consecutive cycles, 14.4 min/day (1% home monitor burden) for detection. ***3.8 h AF burden on 1 day during follow-up.*** BiotroniK ICD/CRT CIEDs
SOS AF	Three registries	10016[c]	2	0	Prior history of paroxysmal or persistent AF included. Permanent AF excluded	Atrial rate >175 b.p.m. for ≥20 s ***≥1 h AF burden on 1 day during follow-up***
IMPACT[d]	Randomized	2718	2	1	$CHADS_2 \geq 1$. Only permanent AF excluded	≥36 of 48 atrial beats had cycle lengths ≤200 b.p.m. ***>5.5 h AF burden.*** BiotroniK ICD/CRT CIEDs

Table 6 Types of ambulatory cardiac monitoring devices

Type of recorder	Typical monitoring duration	Continuous recording	Event recording	Auto trigger	Unique features
Holter monitor	24–48 hours, approximately 7–30 days	Yes	Yes	N/A	Short term, provides quantitative data on arrhythmia burden
Patch monitor	1–3 weeks	Yes	Yes	N/A	Intermediate term, can provide continuous data for up to several weeks; improved patient compliance without lead wires
External loop recorder	1 month	Yes	Yes	Variable	Good correlation between symptoms and even brief arrhythmias
External nonloop recorder	Months	No	Yes	No	May be used long term and intermittently; will not capture very brief episodes
Smartphone monitor	Indefinite	No	Yes	No	Provides inexpensive long-term intermittent monitoring; dependent on patient compliance; requires a smartphone
Mobile cardiac telemetry	30 days	Yes	Yes	Yes	Real time central monitoring and alarms; relatively expensive
Implantable loop recorder	Up to 3 years	Yes	Yes	Yes	Improved patient compliance for long-term use; not able to detect 30-second episodes of AF due to detection algorithm; presence of AF needs to be confirmed by EGM review because specificity of detection algorithm is imperfect; expensive
Pacemakers or ICDs with atrial leads	Indefinite	Yes	Yes	Yes	Excellent AF documentation of burden and trends; presence of AF needs to be confirmed by electrogram tracing review because specificity of detection algorithms is imperfect; expensive
Wearable multisensor ECG monitors	Indefinite	Yes	Yes	Yes	ECG 3 leads, temp, heart rate, HRV, activity tracking, respiratory rate, galvanic skin response

AF, atrial fibrillation; ICD, implantable cardioverter defibrillator; ECG, electrocardiogram; HRV, heart rate variability.

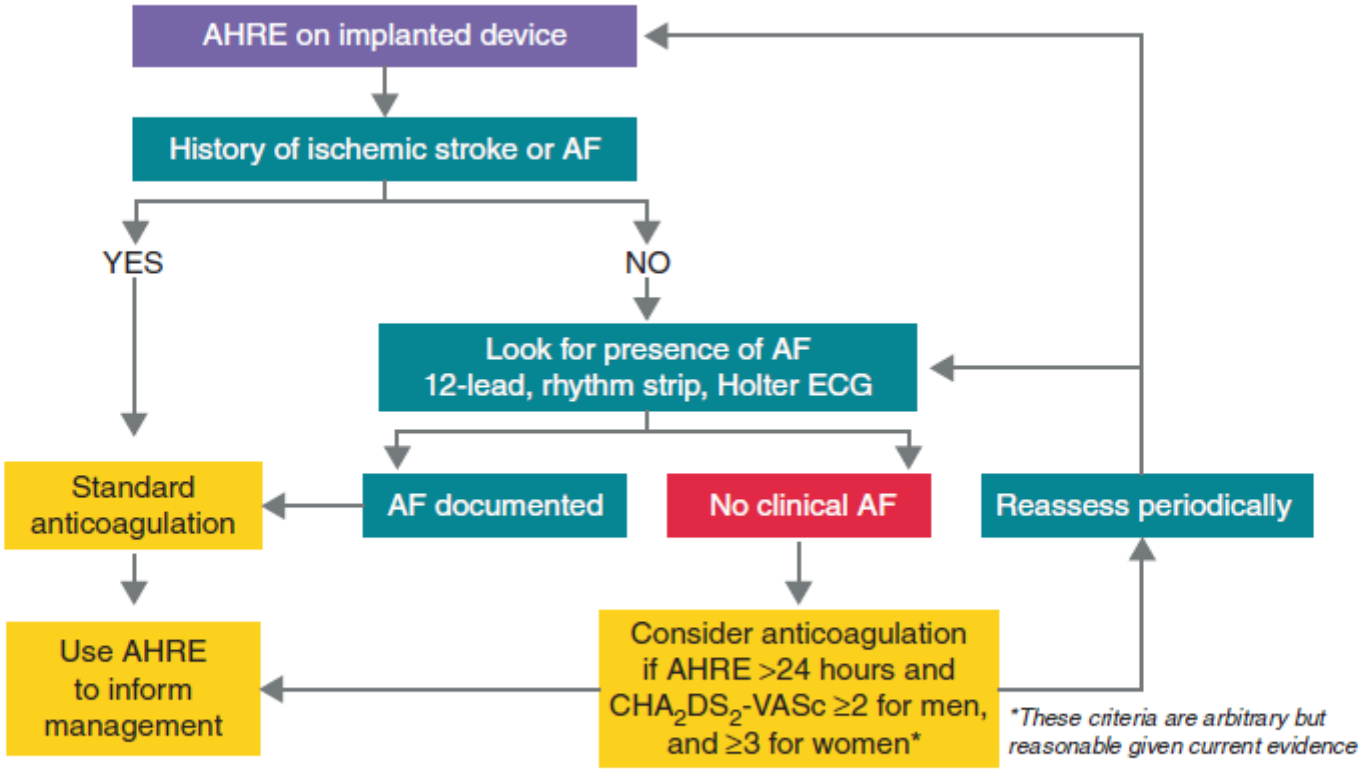


Figure 5 Suggested treatment algorithm for management of patients with AHREs. Adapted from Kirchhof *et al.*[70]

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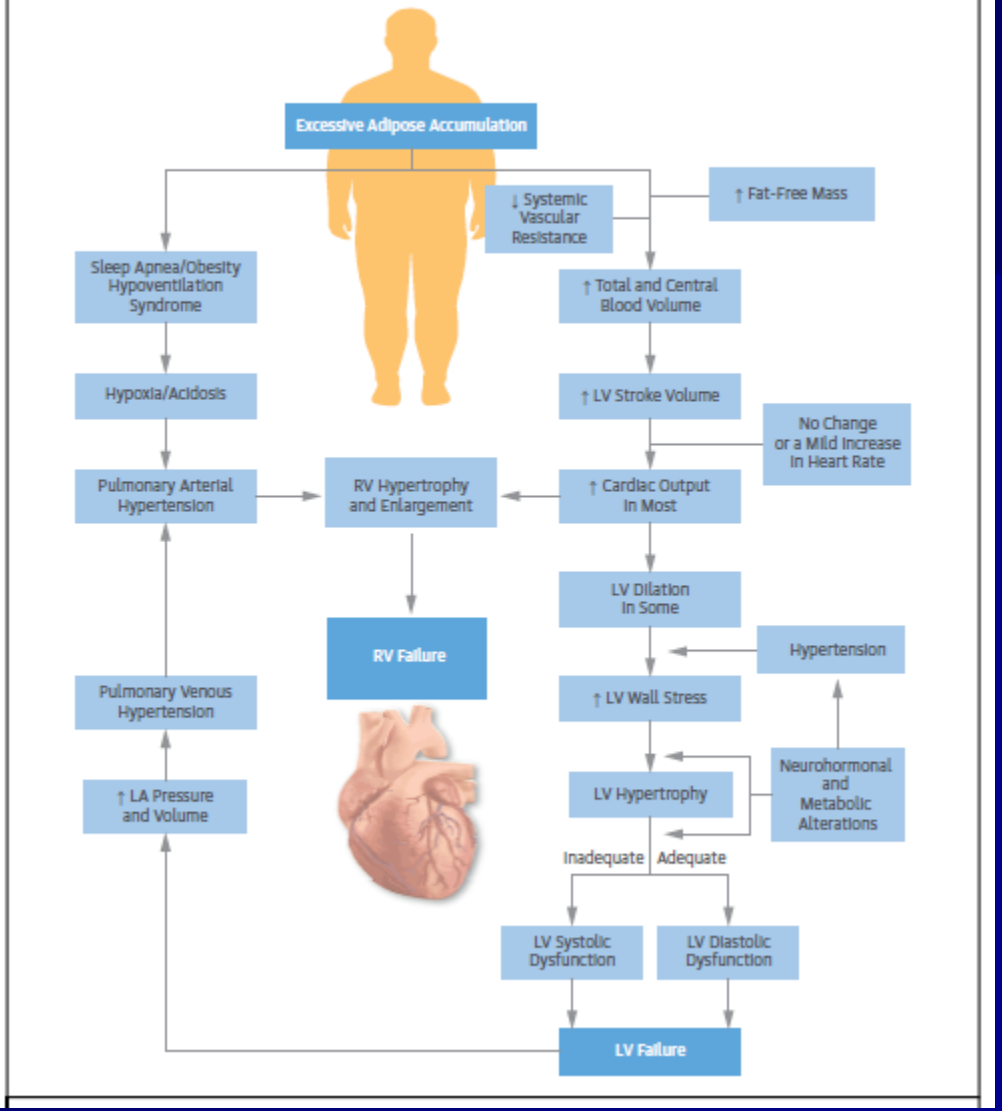
Valutazione dello score di rischio di ES nel 2017

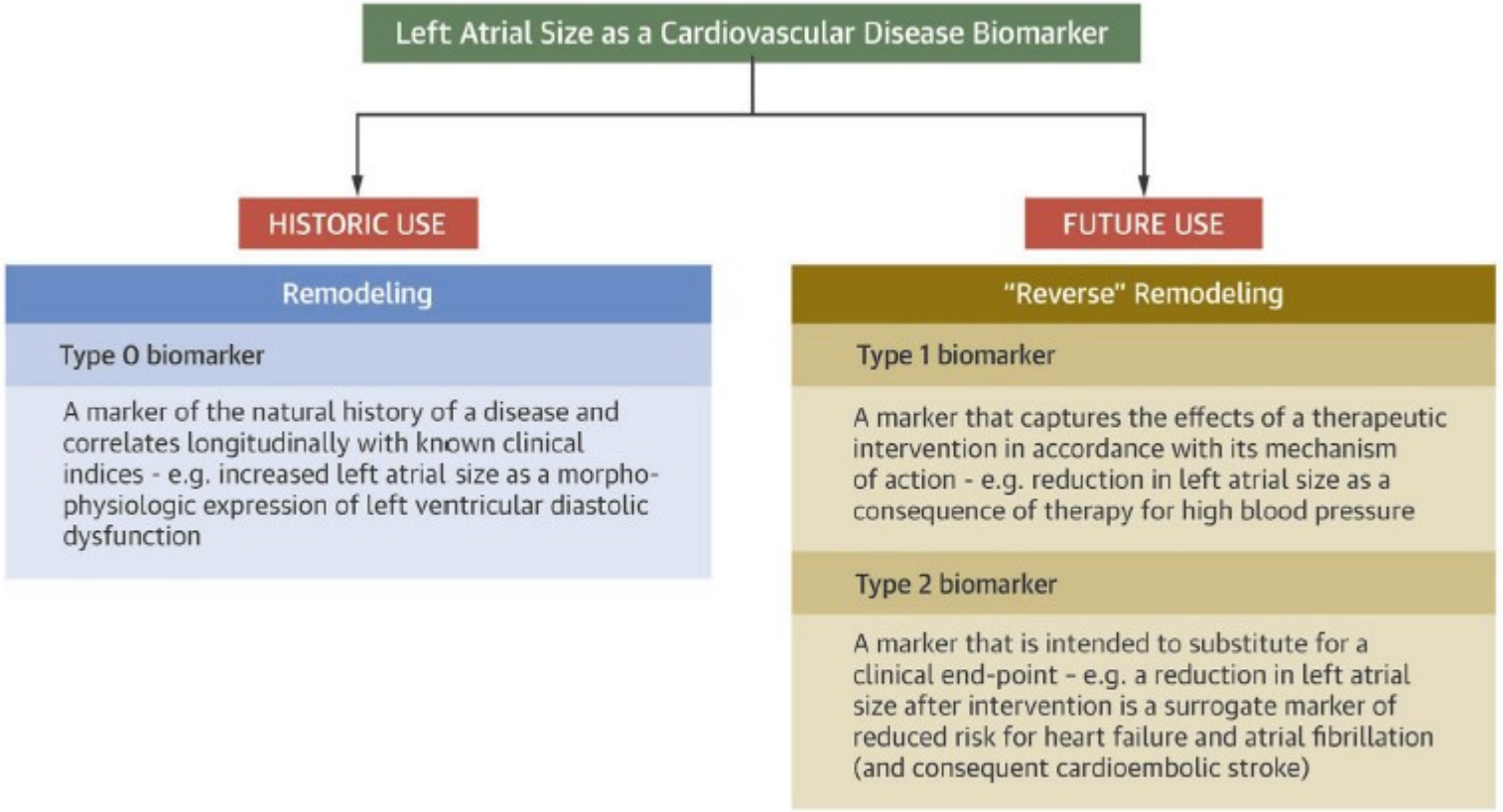
- CHADS2-Vasc
- GFR/BNP/Troponina
- Obesità (sedentarietà)-SAS
- Valutazione anatomo-funzionale LA con ecocardiogramma LAVIi-LALS-LAAVel

- E' da chiarire definitivamente se una combinazione di parametri clinici, elettrici, strutturali, laboratoristici identifichino pz ad alto rischio di ES anche prima che compaia (pz. prefibrillatori!?) AF o anche in assenza di AF, da sottoporre a TAO.
- "Precision Medicine"

FIGURE 1 Obesity and CVD



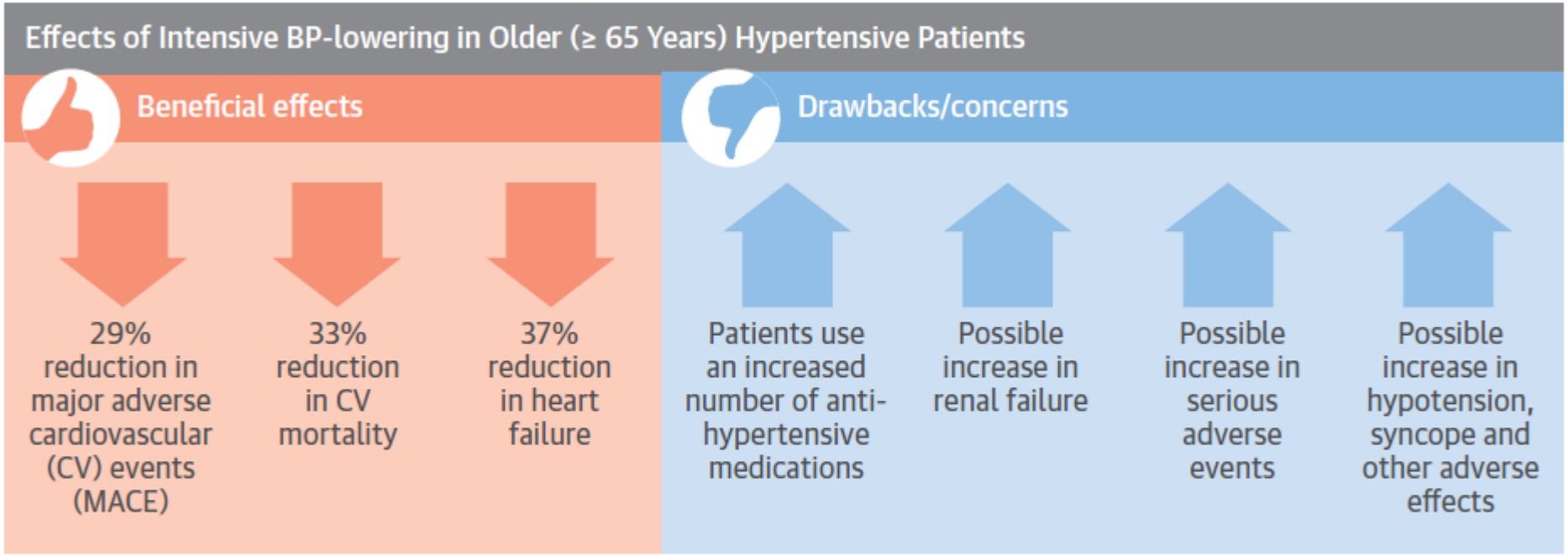
CENTRAL ILLUSTRATION **Left Atrial Remodeling and "Reverse" Remodeling as a Biomarker of Cardiovascular Disease**



Thomas, L. et al. J Am Coll Cardiol Img. 2017;10(1):65–77.

Historically, left atrial remodeling has been assessed as an integrative marker of pathophysiologic processes. More research is required to establish the use of "reverse" remodeling to confirm the benefits of medical therapy at the individual patient level, and as a surrogate marker of reduced risk for adverse cardiovascular events.

CENTRAL ILLUSTRATION Intensive BP Lowering and Cardiovascular and Safety Outcomes in Older Hypertensive Patients



Bavishi, C. et al. J Am Coll Cardiol. 2017;69(5):486-93.

BP = blood pressure; CV = cardiovascular; MACE = major adverse cardiovascular event(s).

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Consensus statements

Consensus statements		Class
1.	Incidence of subclinical AT/AF varies depending on the clinical characteristics of the population studied.	
2.	• The vast majority of AF episodes are asymptomatic. • Symptoms do not affect long-term prognosis, but they do increase the probability of making a correct diagnosis and offering proper treatment.	
3.	• The likelihood of detecting subclinical AT/AF increases as the duration of monitoring lengthens. • A variety of technologies, both non-invasive and invasive now exist for prolonged cardiac monitoring to detect subclinical AT/AF.	
4.	• The appearance of subclinical AT/AF predisposes to thromboembolic events. • The minimum duration of AT/AF episode or AT/AF burden which confers increased thromboembolic risk is not precisely defined, but may be	

Continued

Continued

Consensus statements		Class
	as brief as several minutes to several hours. • There is no established cut-point for increase in risk, and NO minimum duration that is without risk.	
5.	• There does not seem to be a close temporal relationship of device-detected atrial arrhythmias to the occurrence of strokes. • This implies that, in the majority of device patients with AHREs and thromboembolic events, the mechanism of stroke may not be related to the AF episodes.	
6.	If available, review of stored intracardiac electrograms to confirm diagnosis and exclude artifact or reduce the effect of oversensing/undersensing by automated algorithms is recommended	
7.	The presence or absence of symptoms has no bearing on determining the need for anticoagulation	

8.	Consider no antithrombotic therapy for any patient with CHA_2DS_2-VASc score of 0 in males or 1 in females, irrespective of AHRE	
9.	Consider oral anticoagulation for AF burden (longest total duration of AF on any given day) of > 5.5 h in patients with one additional CHA_2DS_2-VASc risk factor (i.e. score=1 in males or = 2 in females)	
10.	For patients with two additional CHA_2DS_2-VASc risk factors (ie. ≥2 in males, ≥3 in females) oral anticoagulation is recommended for AF burden >5.5 h/day (if there are no contraindications). Lower duration may merit OAC if multiple risk factors are present.	
11.	• Novel user-friendly external devices for AF detection have the potential to increase the	

Continued

Continued

Consensus statements		Class
	yield of identifying silent AF as an aetiology for ischemic stroke. • However, comparative effectiveness studies on these various external devices and cost-effectiveness analyses on the use of these devices still need to be done.	
12.	Remote monitoring may be used for detection of AF: • Even when an inductive remote monitoring system (without automatic alerts) is studied, RM performs better than standard follow-up in pacemaker patients for detection of AF. • Compared to standard scheduled follow-up, detection of AF occurs 1–5 months earlier with remote monitoring.	
13.	• There is a positive net clinical benefit for oral anticoagulants in overt AF with the presence of ≥1 stroke risk factors. • This benefit is less clear for AHRE, especially where arrhythmia burden is low.	
14.	Whether oral anticoagulation will have a net benefit in reducing TE events for SCAF remains to be determined. Until larger trials or registries are conducted, it is important to consider following established guidelines regarding anticoagulation (See above).	
15.	ESVEA documented by Holter monitoring can be considered as a surrogate marker for paroxysmal AF.	

TABLE 1 Impact of Obesity on Hemodynamics and Cardiac Structure and Function

A. Hemodynamics
   1. Increased blood volume
   2. Increased stroke volume
   3. Increased arterial pressure
   4. Increased LV wall stress
   5. Pulmonary artery hypertension

B. Cardiac structure
   1. LV concentric remodeling
   2. LV hypertrophy (eccentric and concentric)
   3. Left atrial enlargement
   4. RV hypertrophy

C. Cardiac function
   1. LV diastolic dysfunction
   2. LV systolic dysfunction
   3. RV failure

D. Inflammation
   1. Increased C-reactive protein
   2. Overexpression of tumor necrosis factor

E. Neurohumoral
   1. Insulin resistance and hyperinsulinemia
   2. Leptin insensitivity and hyperleptinemia
   3. Reduced adiponectin
   4. Sympathetic nervous system activation
   5. Activation of renin-angiotensin-aldosterone system
   6. Overexpression of peroxisome proliferator-activator receptor

F. Cellular
   1. Hypertrophy
   2. Apoptosis
   3. Fibrosis

LV = left ventricular; RV = right ventricular.

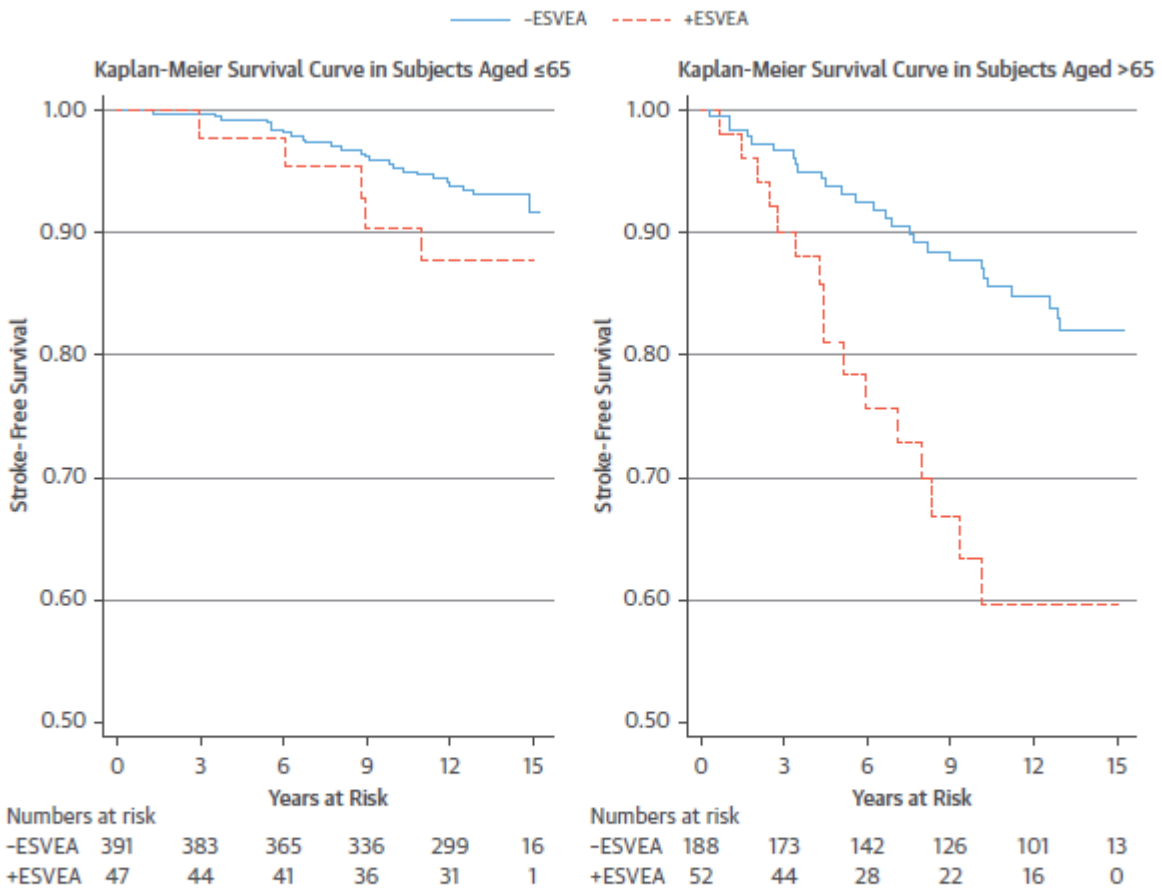
LARSEN et al "Excessive atrial ectopy and short atrial runs increase the risk of stroke beyond incident AF"

JACC 2015, 66:232

Ipotesi: ESVEA (excessive SV ectopic acvtivity) aumenta, in maniera indipendente, il rischio di stroke ischemico (IS), comparabile ad AF

- In p. di età medio-avanzata senza evidente cardiopatia, ma con più di un fattore di rischio CV, ESVEA, valutata con Holter di 48h, si associa ad un aumentato rischio di IS, al di là della insorgenza di AF
- P. con ESVEA hanno maggior rischio di MG e AF anche prima di IS , anche se 82% non sviluppa AF ad un f.up di 15aa
- Solo 14% di p. con ESVEA e IS ha evidenziato una AF
- Rischio assoluto di IS in p. con ESVEA e CHA2DS2-VASc $\geq$ 2 era 2,4/anno, equivalente a quello di p. con AF e score di 2 (alto rischio → TAO)
- Considerare ESVEA come nuovo fattore di rischio indipendente di AF e più riproducibile e precoce , in grado di chiarire genesi di molti stroke criptogenici (CS)

FIGURE 2 Kaplan-Meier Survival Estimate of Stroke-Free Survival Stratified on Age-Groups and ESVEA



The risk of stroke associated with excessive supraventricular ectopic activity (ESVEA) was greater in patients >65 years of age ($p = 0.0007$), but not in patients ≤65 years of age ($p = 0.2086$).

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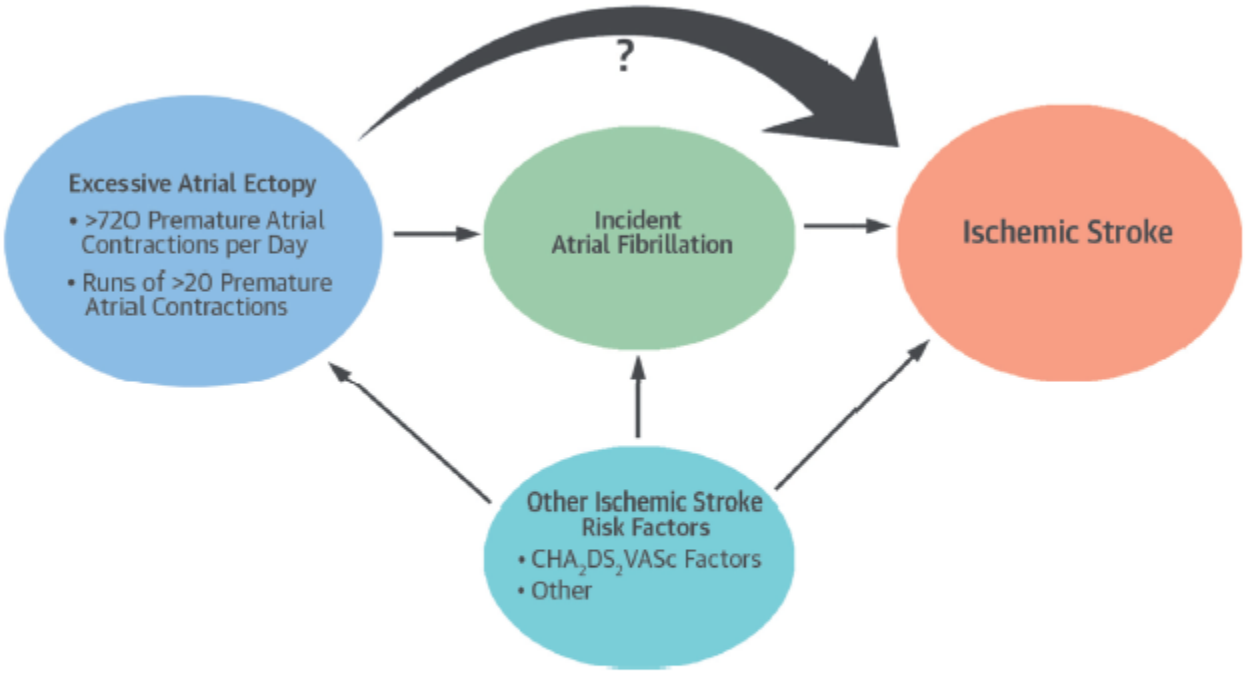
EDITORIAL COMMENT

Premature Atrial Contractions

A Wolf in Sheep's Clothing?*

Gregory M. Marcus, MD, MAS,† Thomas A. Dewland, MD‡

CENTRAL ILLUSTRATION Excessive Atrial Ectopy and Other Risk Factors in Relation to Ischemic Stroke



Larsen, B.S. et al. J Am Coll Cardiol. 2015; 66(3):232–41.

Excessive atrial ectopy and short atrial runs are associated with an increased risk of ischemic stroke beyond atrial fibrillation. However, the exact mechanism is not known and may be caused by undiscovered incident atrial fibrillation or an increased vascular risk profile.
CHA_2DS_2-VASc = congestive heart failure, hypertension, age 75 years or older, diabetes mellitus, previous stroke or transient ischemic attack, vascular disease, age 65 to 74 years, female.

AF e Stroke criptogenico (1)

- AF manifesta è causa comune (almeno 25%) di tutti IS e di almeno 50% di IS di origine tromboembolica (TE)
- Una elevata % di IS rimane, dopo valutazione standard, senza causa apparente: CS!
- Progredire di metodiche diagnostiche (ci sono oltre 200 cause note di IS!) riduce la % di CS dal 40% al 15-20%, ma nella comune pratica clinica, CS sono circa 25-30% dei casi (in USA 120-180 mila/anno)

AF e Stroke criptogenico (2)

- Attuali device impiantabili (PM e Def) sono in grado di registrare in continuo, immagazzinare e trasmettere (Home monitoring) in continuo episodi AHRE (atrial high rate episodes)
- Veri studi (MOST, ASSERT, TRENDS…) hanno evidenziato elevata, ed imprevista, % di AHRE asintomatici in p. senza una storia clinica di AF e di TIA/IS
- Non definito il "burden" aritmico atriale oltre cui aumenta il rischio di IS, ma molti studi indicano che già 1 episodio di FAP>5 min aumenta significativamente rischio di IS

Table. Examples of Recent Studies Investigating the Relationship Between Device-Detected Atrial Tachyarrhythmias and Stroke/Thromboembolism

Study	n	Main Findings	Conclusion
TRENDS[10]	2486 Patients with ≥1 stroke risk factors with pacemakers or defibrillators that monitor AT/AF burden	Mean follow-up, 1.4 y Annualized thromboembolism risk (including transient ischemic attacks) was 1.1% for no-burden, 1.1% for low-burden, and 2.4% for high-burden subsets of 30-d windows. Compared with the zero-burden subset, adjusted HRs in the low- and high-burden subsets were 0.98 (95% CI, 0.34–2.82; *P*=0.97) and 2.20 (95% CI, 0.96–5.05; *P*=0.06), respectively.	Thromboembolism risk is a quantitative function of AT/AF burden. AT/AF burden ≥5.5 h on any of 30 prior days doubled thromboembolism risk.
ASSERT[7]	2580 Patients ≥65 y of age with hypertension and no history of AF, with pacemaker or defibrillator	Mean follow-up, 2.5 y Subclinical atrial tachyarrhythmias were associated with an increased risk of ischemic stroke or systemic thromboembolism (HR, 2.49; 95% CI, 1.28–4.85; *P*=0.007). Subclinical atrial tachyarrhythmias remained predictive of the primary outcome after adjustment for predictors of stroke (HR, 2.50; 95% CI, 1.28–4.89; *P*=0.008).	Subclinical atrial tachyarrhythmias, without clinical AF, occurred frequently in patients with pacemakers and were associated with a significantly increased risk of ischemic stroke or systemic embolism.
IMPACT[9]	2718 Patients with dual-chamber and biventricular defibrillators 2-Arm RCT: (1) start and stop anticoagulation on the basis of remote rhythm monitoring vs (2) usual office-based follow-up	Median follow-up, 2 y 945 Patients (34.8%) developed AT, and AF was confirmed in 91%. Primary events (2.4 vs 2.3 per 100 patient-y) did not differ between trial arms (HR, 1.06; 95% CI, 0.75–1.51; *P*=0.732). In patients with AT, thromboembolism rate was 1.0 vs 1.6 per 100 patient-y (*P*=0.251). No temporal relationship between AT and stroke was seen.	Anticoagulation based on remotely detected AT did not prevent thromboembolism.

AF indicates atrial fibrillation; ASSERT, Asymptomatic Atrial Fibrillation and Stroke Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial; AT, atrial tachycardia; CI, confidence interval; HR, hazard ratio; IMPACT, Multicenter, Randomized Study of Anticoagulation Guided By Remote Rhythm Monitoring in Patients With Implantable Cardioverter-Defibrillator and Resynchronization Devices; RCT, randomized, controlled trial; and TRENDS, The Relationship Between Daily Atrial Tachyarrhythmia Burden From Implantable Device Diagnostics and Stroke.

AF e Stroke criptogenico (3)

- Numerosi studi prospettici e 2recenti RCT (EMBRACE e CRYSTAL-AF) hanno dimostrato, utilizzando sistemi di monitoraggio non invasivi ed invasivi, in p. con CS in assenza di AF clinica come, prolungando il tempo di monitoraggio, aumentava nettamente la possibilità di rilevare episodi, più o meno prolungati, di PAF.

AF e Stroke criptogenico (4)

- EMBRACE: registratore esterno di eventi utilizzato per 30gg consecutivi entro 6 mesi da CS

  PAF nel 16% rispetto a 3.2% dei controlli
- CRYSTAL-HF: utilizzato un ILR con durata fino a 3 aa
- PAF: 8,9% a 6 mesi, vs 1.4%;

  12.4% a 12 mesi vs 2%

  30% a 3 aa vs 3%

AF e Stroke criptogenico (5)

- Tutti gli studi hanno evidenziato una relazione tra burden aritmico atriale (non solo AF) e CS, anche se non è definita l'entità del burden atriale significativa per il rischio di IS
- Vari studio suggeriscono che già un AF di durata >5min aumenta significativamente il rischio di AF
- Le attuali LG suggeriscono un monitoraggio prolungato di almeno 30gg da effettuare entro sei mesi dall'insorgenza di CS (ma non danno indicazioni sulla entità del burden aritimico utile!!)

PACs basali e CS

- EMBRACE: N° di PACs basali forte fattore indipendente di AF (16%) a 3 mesi) con identificazione di p. a basso, medio e alto rischio (da 7 a 40%), con indicazione a monitoraggio variabile. 50% di p. con CS avrebbe frequenza PACs >720/24 h

- CRYSTAL: PACs non predittivi di sviluppo di AF

KEY CLINICAL POINTS

CRYPTOGENIC STROKE

- One quarter of patients with ischemic stroke have no probable cause found after standard workup, including echocardiography, inpatient cardiac telemetry or 24-hour Holter monitoring, magnetic resonance imaging or computed tomographic (CT) imaging of topographic features of the infarct in the brain, and magnetic resonance or CT angiographic assessment of neck and brain arteries. Additional investigation identifies a likely mechanism in more than half these patients.
- Most cryptogenic ischemic strokes are embolic in origin, arising from proximal arterial sources, the heart, or venous sources (with right-to-left shunts).
- Investigation in patients with cryptogenic stroke typically includes evaluation for atherosclerotic and nonatherosclerotic arteriopathies, cardiac sources of embolism (structural and rhythm abnormalities), and disturbances of coagulation.
- Patent foramen ovale is found in up to half of young adults with cryptogenic stroke but is also found in one quarter of healthy persons.
- Occult, low-burden, paroxysmal atrial fibrillation is increasingly recognized as a source of cryptogenic stroke, especially in older patients.

CS e PFO

- Nel CRYSTAL c'è correlazione fra AF e PFO, specie nei p. più giovani
- AF si rileva, durante monitoraggio, in % simile sia in p. con che senza PFO
- Pertanto non è corretto attribuire CS al PFO in assenza di monitoraggio prolungato che escluda AF, specie nei p. più anziani

CV in AF di durata inferiore a 48h

- Tutti gli studi citati hanno evidenziato che una AF di durata fino a 48h aumenta nettamente il rischio di AF

- Le attuali LG ritengono concordemente che una PAF di durata <48h possa essere cardiovertita con sicurezza anche in assenza di una precedente TAO!!!

The NEW ENGLAND JOURNAL of MEDICINE

CLINICAL PRACTICE

Caren G. Solomon, M.D., M.P.H., *Editor*

Cryptogenic Stroke

Jeffrey L. Saver, M.D.

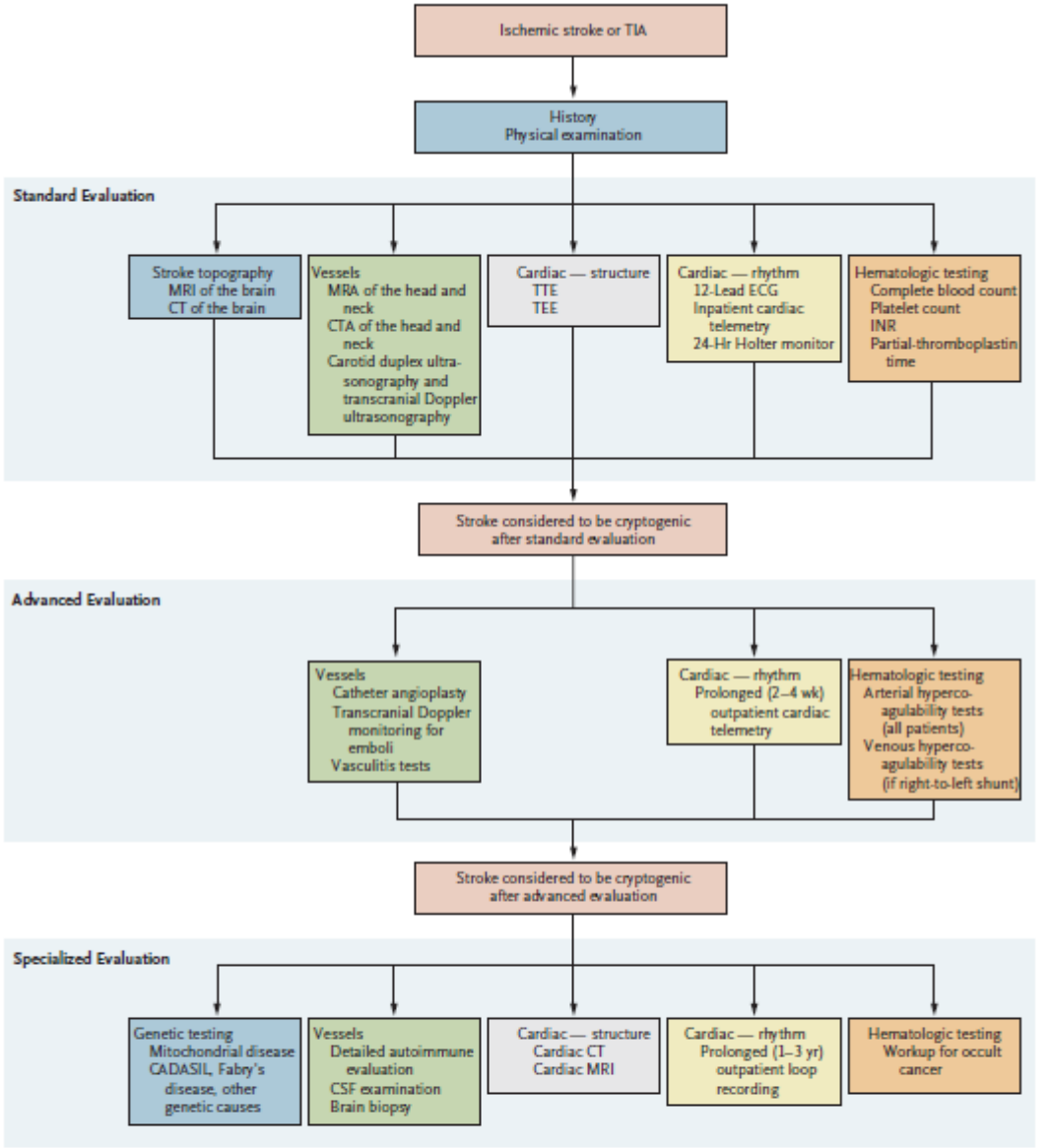


Figure 1. Algorithm for the Identification and Diagnostic Evaluation of Patients with Cryptogenic Ischemic Stroke or Transient Ischemic Attack (TIA).

Table S2 in the Supplementary Appendix lists additional considerations regarding advanced and specialized tests. CADASIL denotes cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy, CSF cerebrospinal fluid, CTA computed tomographic angiography, ECG electrocardiogram, INR international normalized ratio, MRA magnetic resonance angiography, TEE transesophageal echocardiography, and TTE transthoracic echocardiography.

Correlazione AF-IS: evidenze contrastanti (1)

- Vedute correnti basate su vecchie ipotesi (triade di Vir.) per cui AF→ stasi → trombosi atriale→IS

  Quindi AF, valutata in maniera dicotomica, considerata causa primaria di AF
- In tutti gli studi (retrospettivi, prospettici, RCT) non c'è stretta correlazione temporale tra IS e AF (o burden aritmico atriale in genere)
- In una minoranza di casi il rischio di IS aumenta nei30gg post AF, rispetto ai successivi 90 e 120gg

Correlazione AF-IS: evidenze contrastanti (2)

- Anche un singolo, breve episodio di AF può raddoppiare rischio di IS, ma solo negli anziani con i classici fattori di rischio cv. Nei giovani, senza fattori di rischio cv, anche in presenza di AF prolungata e sintomatica, non aumenta il rischio di IS!
- Se AF fosse la causa primaria di IS, AF dovrebbe essere associata ad IS in maniera specifica, ma > 10% di p. con AF presenta uno IS di tipo lacunare (cioè non TE)

Correlazione AF-IS: evidenze contrastanti (3)

- Se AF fosse causa primaria di IS, il mantenimento di RS dovrebbe prevenire IS. Ma un'ampia, recente meta-analisi dimostra che il mantenimento di RS non ha effetto significativo su IS.

  Non è verosimile che questo sia dovuto ad episodi occulti, recidivanti di AF, data la dimostrazione di un effettivo successo nel mantenimento cronico di RS in questi p.

- Nel modello sperimentale di AF, il rimodellamento atriale avviene solo dopo 1 settimana di pacing ad alta frequenza e pertanto è inverosimile che brevi episodi di PAF si associno ad aumentato rischio di IS. Quindi manca anche un'evidenza sperimentale che convalidi di AF come elemento imprescindibile e fondamentale della trombogenesi
-

Modello alternativo del meccanismo di IS nella AF (1)

- AF si associa in genere ad altri fattori di rischio che, di per se, possono causare anche IS (età, sesso M, ipertensione, obesità e sedentariaretà, diabete e s. metabolica, alcool, fumo, cardiopatie organiche varie, HF, CKD, malattie infiammatorie, SAS….)

- La associazione AF-IS si riduce di molto quando sono presenti numerosi fattori di rischio, pur rimanendo AF un fattore indipendente (ma solo per IS di tipo TE, non lacunare)

Modello alternativo del meccanismo di IS nella AF (2)

- AF coesiste in genere con varie anomalie atriali, elettriche e meccaniche (disfunzione endoteliale, fibrosi, dilatazione e disfunzione meccanica, disfunzione LAA), evidenziate da ECG (morfologia e durata di P, anomalie di P-Q, burden aritmico), Ecocardio (specie con spekle tracking..). RMC!..

- Questa cardiopatia atriale può svilupparsi autonomamente da AF e gioca un ruolo essenziale nella genesi del TE atriale anche indipendentemente da AF, certamente con meccanismi diversi

n

- Il burden aritmico atrìale (AF, ma anche PACs, run atriali, PSVT..) può essere semplicemente un marker della atriopatia, anche se ovviamente le aritmie atriali possono aumentare il rischio TE, con un potenziamento reciproco

- Pur trattando con successo AF, la cardiopatia atriale rimane!

Modello alternativo del meccanismo di IS nella AF (3)

- Questo modello alternativo spiega ampiamente la incongruenza della associazione AF-IS.
- Continuando a ritenere AF condizione obbligata per i fenomeni TE, non sarebbe possibile riconoscere come TE anche IS in assenza di AF
- Si comprende anche come, fra i vari score di rischio atti ad identificare i p. maggiormente predisposti ad IS, sempre più spesso venga proposto il CHA2DS2Vasc che ingloba molti dei dei maggiori fattori di rischio sistemici sia per AF che per TE. Nei p. con score più elevato, è anche elevato il rischio di IS, indipendentemente dalla presenza o meno di AF (in presenza di cardiopatia atriale trombogenica, AF potrebbe essere un semplice "bystander")

Modello alternativo del meccanismo di IS nella AF (4)

- Attualmente non risolto il problema di una ottimale predizione di AF sia nella popolazione generale che nei p. con CS, dato che associando fattori di rischio sistemici (inclusi i biomarker) con quelli legati alla cardiopatia atriale, il VPP rimane non soddisfacente

Ricadute terapeutiche nella nuova interpretazione di relazione AF-IS (1)

- La vecchia convinzione che AF sia la causa di TE rende riluttanti medici e p. a continuare TAO dopo scomparsa, comunque ottenuta, di AF
- Prestare un' attenzione prioritaria alla cardiopatia atriale trombogena, che può di per sé causare AF e che comunque persiste dopo scomparsa di FA. Questo rinforza l'idea di continuare comunque TAO!!
- La terapia "rhythm control" (farmacologica od ablativa) non deve essere vista come un mezzo di profilassi TE!!

Ricadute terapeutiche nella nuova interpretazione di relazione AF-IS (2)

- Il nuovo modello implica che, più che il ripristino di RS, è efficace, per ridurre il rischio TE, la regressione della cardiopatia atriale, tramite un trattamento globale, intensivo dei fattori di rischio CV (che, tra l'altro, favoriscono anche IS di origine non atriale)

- Quindi non focalizzarsi solo su TAO, anche se le attuali LG non trattano la terapia globale dei fattori di rischio

- Importante che il nuovo modello abbia l'ambizione di incidere anche sulla prevenzione di IS in p. senza AF, ma con substrato atriale aritmogeno e fattori di rischio sistemico.

Martin et al "IMPAFCT investigators. RCT of atrial arhytmias minitoring to guide anticoagulation in pts withICDand CAT devices" *Eur Heart J 2015, 36-1660*

La TAO, guidata dal monitoraggio H del device, iniziata precocemente, ma sospesa in assenza di di AF per almeno 3 mesi, non ha migliorato la prognosi rispetto alla terapia convenzionale

Significativo il fatto (a parte la conferma di dissociazione temporale AF-IS) che oltre 50% di p. che hanno avuto IS, non hanno presentato, al monitoraggio prolungato, AF. IS invece correla con CHA2DS2Vasc elevato, a conferma che indicazione TAO va basata su valutazione individuale globale, indipendentemente da presenza di AF.

Conclusioni

- Sono in corso numerosi CRT riguardanti una più valida identificazione dei p. a rischio di AF e IS e le ottimali strategie terapeutiche
- Solo in base ai risultati di questi RCT potremo trattare il p. giusto al tempo giusto con la giusta terapia.

Conclusioni (3)

- Le meccaniche atriali sinistre sono influenzate dalle condizioni di carico e dalle funzioni sisto-diastoliche del Vs, per cui rimane ancora da chiarire il ruolo clinico delle meccaniche di As al di là delle meccaniche di Vs
- Solo ulteriori studi potranno fornire una comprensione più approfondita della storia atriale del rimodellamento atriale, la eventualità e la entità della regressione delle alterazioni della meccanica dell' As con differenti terapie e l'impatto di eventuali cambiamenti sulla prognosi
- Alla luce della importanza e complessità delle informazioni fornite dall'eco, che richiedono elevate competenze professionali e risorse strumentali ad alta tecnologia, occore certamente ripensare la riorganizzazione degli ambulatori di ecocardiografia nelle attuali realtà sia ospedaliere che extra-ospedaliere

Conclusioni (2)

- Vari motivi giustificano al momento questa cautela
- Occorrono ulteriori studi di conferma su più ampie ed omogenee casistiche per testare la validità della tecnica
- Occorre valutare meglio il tipo di tecnica da utilizzare (eco strain 2D o 3D o VVI)
- Valutare meglio i parametri da misurare (strain strainR o entrambi)
- Mancanza di standardizzazione di acquisizioni di immagini
- Definire in maniera uniforme i cut-off relativi alle diverse applicazioni, la sede di valutazione della parete atriale, la fase del ciclo atriale da considerare
- Valutazione definitiva del reale vantaggio delle funzioni Asx in aggiunta alle dimensioni atriali e alle variabili doppler convenzionali nei riguardi della stratificazione prognostica.

Conclusioni (1)

- L'ecocardiografia ha un ruolo fondamentale in tutte le fasi di valutazione e gestione di fa.
- Nell'era di imaging cv non invasivo l'analisi funzionale atriale mediante strain (insieme alla caratterizzazione tissutale mediante MRI) sta assumendo una importanza sempre maggiore nella valutazione globale e nella stratificazione prognostica dei p. con FA, con possibilità concreta di adattare il trattamento al singolo paziente. La FA non è una malattia unica ma una realtà eterogenea che rappresenta una difficile sfida per il medico
- Tuttavia nonostante sia sempre più emergendo la rilevanza clinica di studi sulla funzione atriale fornita dallo strain e questa tecnica sia considerata un mezzo promettente nella pratica clinica, tale metodica non viene ancora considerata un esame clinico routinario nella valutazione dei pazienti con fa e infatti non viene preso in considerazione nelle più recenti LG

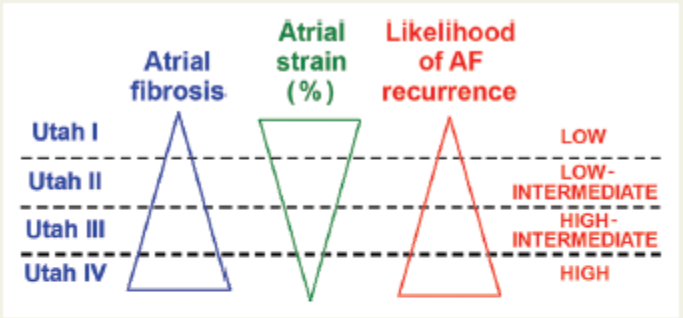


Figure 2 Schematic showing the use of atrial fibrosis and strain to determine the likelihood of atrial fibrillation (AF) recurrence. The blue triangle represents the degree of atrial fibrosis according to Utah classification, the green triangle represents atrial longitudinal strain and the red triangle represents the likelihood of AF recurrence. The chance of AF recurrence correlates directly to atrial performance during reservoir phase and inversely correlates to degree of atrial fibrosis.

Classificazione UTAH in base all'entità di fibrosi valutata mediante DE della parete atriale alla CMR

UTAH I: ≤5% DE : successo 100% recidive 0%

UTAH II: >5 to 20% DE: successo 81.8% recidive 28%

UTAHIII: >20 to 35% DE: successo 62.5% recidive 35%

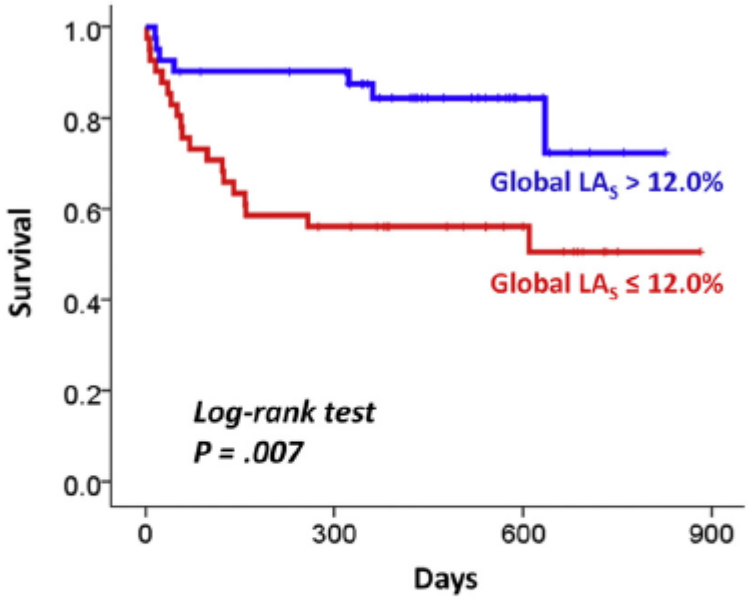
UTAH IV: >35% DE successo 0% recidive 56%

La classificazione UTAH integrata con la valutazione dio strain atriale dovrebbe aiutare nella pratica clinica a personalizzare l'approccio alla terapia di FA

Table 5 LA ε and SR in AF

Study	Population	Methodology	Year	Main findings
Inaba *et al.*[29]	27 AF patients (8 permanent, 19 paroxysmal) 50 controls	DTI QRS timed	2005	SR_R, SR_{CD}, and SR_{CT} were lower in AF patients than in age-matched controls.
Novo *et al.*[52]	50 AF patients 50 controls	2D ST QRS timed	2012	LA ε_R was lower in AF patients than in controls and was lower in subjects with recurrent AF than in those with a first episode of AF.
Mochizuki *et al.*[34,53]	40 AF patients[53] (29 paroxysmal, 11 permanent) 77 controls 47 AF patients[34] (31 paroxysmal, 16 permanent) 55 controls	3D ST	2012	3D longitudinal, circumferential and area ε of the reservoir and contractile LA phases were lower for paroxysmal AF patients than for controls, and further reductions were identified for the permanent AF patients. 3D ST was more accurate than 2D ST to identify the paroxysmal AF patients from a control group.
Cho *et al.*[83]	158 CHF patients	DTI QRS timed	2009	Atrial dyssynchrony (standard deviation of the time to peak $\varepsilon_R > 39$ msec) and LA dimensions were independent predictors for new onset AF in patients with CHF.
Thromboembolic risk				
Shih *et al.*[55]	66 permanent AF patients: 20 with stroke 46 without stroke	2D ST QRS timed	2011	Decreased LA ε_R and SR_{CT} were independently associated with stroke in patients with permanent AF.
Saha *et al.*[56]	36 AF patients 41 controls	2D ST QRS timed	2011	LA ε_R was a predictor of a high risk of stroke ($CHADS_2$ score ≥ 2). LA ε_R and LAVI increased the accuracy of the $CHADS_2$ score to predict a combined end point (hospitalization for cardiac causes and/or death).
Shih *et al.*[55]	66 permanent AF patients: 20 with stroke 46 without stroke	VVI QRS timed	2012	Compared with controls, AF patients with a history of stroke/TIA and a low $CHADS_2$ score (≤ 1) had lower LA ε_R and ε_{CT}. LA ε_{CT} was the stronger predictor of stroke/TIA when adjusted to LAVI, LVEF, and LV mass.
Response CV				
Di Salvo *et al.*[ ]	65 AF patients 40 controls	DTI QRS timed	2005	Baseline (pre-CV) LA ε_R and SR_R were independent predictors of SR maintenance, up to 9 mo after CV. Baseline $\varepsilon_R > 22\%$ had sensitivity of 77% and specificity of 86% and baseline $SR_R > 1.8\ sec^{-1}$ had sensitivity of 92% and specificity of 79% to predict the maintenance of SR, 9 mo after CV.
Boyd *et al.*[62]	39 AF patients 34 controls	DTI QRS timed	2008	In chronic AF patients, LA myocardial velocity during the LA contraction phase improved up to 6 mo after successful CV but remained lower compared with age-matched controls.
Wang *et al.*[59]	42 AF patients 27 controls	DTI QRS timed	2007	Baseline LA $SR_{CD} > 2.18\ sec^{-1}$ had sensitivity of 83% and specificity of 64.3% to predict the maintenance of SR 4 wk after CV. LA SR_{CD} and LA dimension were independent predictors of CV failure.
Kaya *et al.*[61]	22 AF patients	DTI QRS timed	2008	One day after successful CV, LA ε_R, ε_{CD}, SR_R, and SR_{CD} were lower compared with the baseline values. Ten days after, all values improved significantly. This was similarly to the LAA emptying velocities.
Response to ablation				
Donal *et al.*[60]	31 AF patients 15 controls	DTI QRS timed	2010	LA mechanics (ε_R, SR_R, SR_{CD}, and SR_{CT}) improved significantly up to 1 y after AF catheter ablation although the values remained lower compared with a control group.

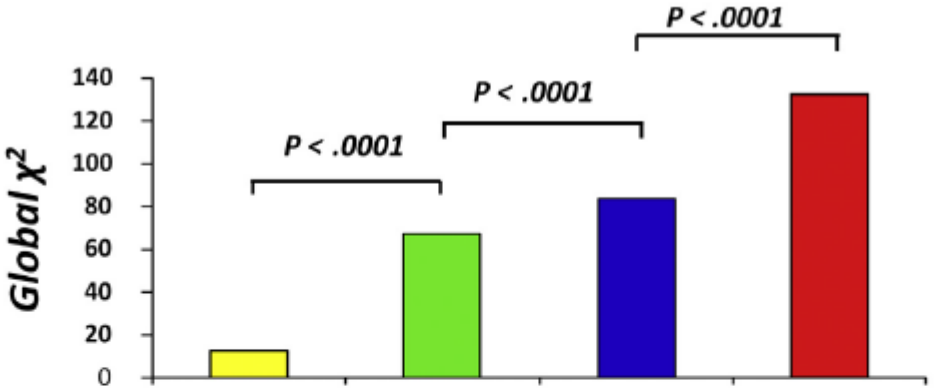
(*Continued*)



Number at risk

Global LA$_S$>12.0%	41	34	10
Global LA$_S$≤12.0%	41	22	10

Figure 4 Kaplan-Meier survival curves generated from patients with acute embolism, stratified by median global LA$_S$. Survival was lower in patients with acute embolism and global LA$_S$ ≤ 12.0% (*red line*) compared with >12.0% (*blue line*).



Models	Model 1 (χ2 12.8)	Model 2 (χ2 67.4)	Model 3 (χ2 83.9)	Model 4 (χ2 132.4)
Variable	CHA_2DS_2-VASc score	+ OAC use	+ LA emptying fraction	+ Global LA_S
CHA_2DS_2-VASc score	1.35 (1.14-1.61) *P* < .001	1.47 (1.21-1.79) *P* < .001	1.45 (1.19-1.76) *P* < .001	1.11 (0.88-1.40) *P* = .362
OAC use	-	0.12 (0.06-0.22) *P* < .001	0.12 (0.06-0.23) *P* < .001	0.10 (0.05-0.21) *P* < .001
LA emptying fraction	-	-	0.95 (0.92-0.98) *P* < .001	0.98 (0.95-1.01) *P* = .151
Global LA_S	-	-	-	0.75 (0.68-0.83) *P* < .001

Figure 2 Incremental value of LA strain over CHA_2DS_2-VASc scores for embolism risk stratification. Adding LA emptying fraction improved the model on the basis of the conventional RSS (CHA_2DS_2-VASc score) and use of OAC drugs. Diagnostic value was further increased by adding global LA_S.

Differentiation of Patients with Acute Embolism from AF Controls

CHA_2DS_2-VASc scores and global LA_S distinguished patients with acute embolism from controls, with areas under the curve of 0.64 ($P < .0001$) and 0.83 ($P < .0001$) ($P < .0001$ vs CHA_2DS_2-VASc score; Figure 1 and Supplemental Figure S1 [available at www.onlinejase.com]). Global $LA_S < 15.4\%$ (95% confidence interval, 14.7–15.8) identified patients with acute embolism with 83% sensitivity and 75% specificity (positive and negative likelihood, 3.30 and 0.23, respectively).

Left Atrial Strain Provides Incremental Value for Embolism Risk Stratification over CHA_2DS_2-VASc Score and Indicates Prognostic Impact in Patients with Atrial Fibrillation

Masaru Obokata, MD, Kazuaki Negishi, MD, PhD, Koji Kurosawa, MD, PhD, Rieko Tateno, MD, Shoichi Tange, MD, Masashi Arai, MD, PhD, Masao Amano, MD, and Masahiko Kurabayashi, MD, PhD, *Gunma, Japan; Hobart, Australia*

Background: The aim of this study was to investigate whether left atrial (LA) strain has incremental value over the CHA_2DS_2-VASc score for stratifying the risk for embolism in patients with atrial fibrillation (AF) and whether LA strain predicts poststroke mortality.

Methods: Consecutive patients with paroxysmal or persistent AF with acute embolism (82 patients) or without (204 controls) were prospectively enrolled. Global peak LA longitudinal strain during ventricular systole (LA_S) was assessed during AF rhythm. Global LA_S was compared between the groups in the first cross-sectional study. Then, the 82 patients with acute embolism were prospectively followed during the second prospective cohort study.

Results: Global LA_S was lower in patients with acute embolism than in controls ($P < .001$). Global $LA_S < 15.4\%$ differentiated patients with acute embolism from controls, with an area under the curve of 0.83 ($P < .0001$). In multivariate analysis, global LA_S was independently associated with acute embolism (odds ratio, 0.74; 95% confidence interval, 0.67–0.82; $P < .001$) and had an incremental value over the CHA_2DS_2-VASc score ($P < .0001$). Furthermore, 26 patients with acute embolisms died during a median follow-up period of 425 days. Global LA_S independently predicted mortality after embolism.

Conclusions: In this observational study, LA strain provided incremental diagnostic information over that provided by the CHA_2DS_2-VASc score, suggesting that LA strain analysis could improve the current risk stratification of embolism in patients with AF. LA strain can also predict poststroke mortality. (J Am Soc Echocardiogr 2014;27:709-16.)

Keywords: Atrial fibrillation, Left atrial function, Left atrial strain, Stroke, Speckle-tracking

Importanza emergente dello strain atriale nella stratificazione del rischio TE

- Strain e strain rate atriale diminuiscono proporzionalmente con l'aumentare di CHA_2DS_2VASc. Ambedue i parametri sono predittori indipendenti di rischio TE anche aggiustati per età e volumi atriali

(JACC 2012, 59:1266)

- Lo strain atriale, associato in questo caso a volume atriale aumenta l'accuratezza di CHA_2DS_2VASc nel predire la mortalità CV e reH

(J Am Soc Echoc 2011, 24:516)

- In pz con $CHA_2DS_2VASc \leq 1$ lo strain atriale è un fattore indipendente di rischio TE quando aggiustato per volumi atriali, FE, massa Vs

(J Am Soc echoc 2012, 25:327)

- Lo strain atriale ridotto è un fattore di rischio indipendente di TE e, associato al CHA_2DS_2VASc, fornisce un valore addittivo per la stratificazione di rischio TE

(J Am Soc Echoc 2014, 237:709)

- Circa 1/3 dei pz con FA non ha AS dilatato! Sicchè anche molti pz ad alto rischio TE possono avere AS nei limiti
- Viceversa una disfunzione AS (frazione di svuotamento atriale) è presente nei ¾ pazienti con FA e nel 50% dei pz con AS di dimensioni normali
- Per una ottimale stratificazione del rischio TE appare quindi obbligatorio valutare, oltre alle dimensioni, anche e soprattutto le funzioni di AS i cui valori andrebbero inseriti nello score di rischio CHA_2DS_2VASc

Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48

Aims The complex relationship between left atrial (LA) structure and function, electrical burden of atrial fibrillation (AF) and stroke risk is not well understood. We aimed to describe LA structure and function in AF.

Methods and results Left atrial structure and function was assessed in 971 subjects enrolled in the echocardiographic substudy of ENGAGE AF-TIMI 48. Left atrial size, emptying fraction (LAEF), and contractile function were compared across AF types (paroxysmal, persistent, or permanent) and $CHADS_2$ scores as an estimate of stroke risk. The majority of AF patients (55%) had both LA enlargement and reduced LAEF, with an inverse relationship between LA size and LAEF ($R = -0.57, P < 0.001$). With an increasing electrical burden of AF and higher $CHADS_2$ scores, LA size increased and LAEF declined. Moreover, 19% of AF subjects had impaired LAEF despite normal LA size, and LA contractile dysfunction was present even among the subset of AF subjects in sinus rhythm at the time of echocardiography.

Conclusions In a contemporary AF population, LA structure and function were increasingly abnormal with a greater electrical burden of AF and higher stroke risk estimated by the $CHADS_2$ score. Moreover, LA dysfunction was present despite normal LA size and sinus rhythm, suggesting that the assessment of LA function may add important incremental information in the evaluation of AF patients. Clinical Trial Registration: http://www.clinicaltrials.gov; ID = NCT00781391.

Keywords Atrial fibrillation • ENGAGE AF-TIMI 48 • Left atrium • Echocardiography • Stroke

European Heart Journal 2013

Funzione dell'atrio sinistro

ENGAGE TIMI AF 48

Left atrial structure and function in atrial fibrillation: ENGAGE AF-TIMI 48

Deepak K. Gupta[1], Amil M. Shah[1], Robert P. Giugliano[2], Christian T. Ruff[2], Elliott M. Antman[2], Laura T. Grip[2], Naveen Deenadayalu[2], Elaine Hoffman[2], Indravadan Patel[3], Minggao Shi[3], Michele Mercuri[3], Veselin Mitrovic[4], Eugene Braunwald[2], and Scott D. Solomon[1]*, for the Effective aNticoaGulation with factor xA next GEneration in AF-Thrombolysis In Myocardial Infarction 48 (ENGAGE AF-TIMI 48) Echocardiographic Study Investigators

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European Heart Journal 2013

Original Article

Left Atrial Volume: Important Risk Marker of Incident Atrial Fibrillation in 1655 Older Men and Women

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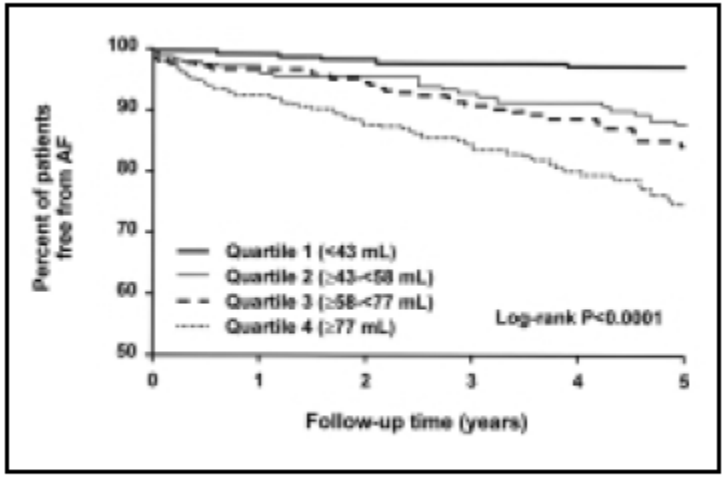

Figure 1. Percentage of patients free of atrial fibrillation (AF) during a 5-year period after baseline echocardiography, stratified by left atrial volume quartiles.

• *Conclusion*: This study showed that a larger LA volume was associated with a higher risk of AF in older patients. The predictive value of LA volume was incremental to that of clinical risk profile and conventional M-mode LA dimension.

Mayo Clin Proc. 2001;76:467-475

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Echocardiography

Prediction of Cardiovascular Outcomes With Left Atrial Size

Is Volume Superior to Area or Diameter?

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Rochester, Minnesota

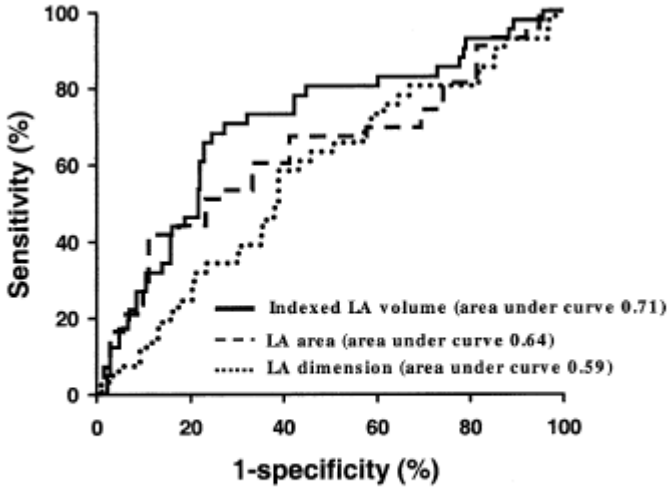

Figure 1. Receiver-operator characteristic curves for the overall performance of left atrial (LA) diameter, LA area, and indexed LA volume for the prediction of cardiovascular events in patients with sinus rhythm.

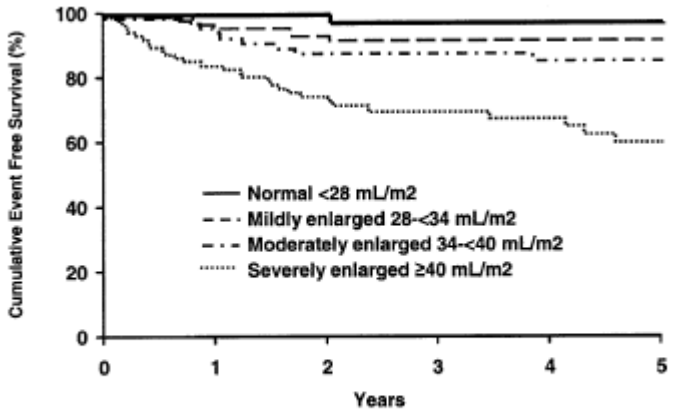

Figure 2. Graded relationship between Kaplan-Meier cumulative event-free survival and categorical increment of indexed left atrial (LA) volume.

CONCLUSIONS Left atrial volume is a more robust marker of cardiovascular events than LA area or diameter in subjects with sinus rhythm. The predictive utility of LA size for cardiovascular events in AF was poor, irrespective of the method of LA size quantitation. (J Am Coll Cardiol 2006; 47:1018–23) © 2006 by the American College of Cardiology Foundation

Grandezza atrio sinistro (1)

- Indicatore di disfunzione diastolica cronica, di elvata pressione sinistra e di rimodellamento atriale
- E' marker indipendente di rischio CV e di TE in pz con e senza FA
- Diametro AP M-mode predittore indipendente di TE e valore predittivo aggiunto ai fattori di rischio clinici (*SPAF Ann Intern Med 1992*) Nello studio di Framingham, ad un aumento di 5 mm delle dimensioni atriali, corrisponde un aumentato rischio del 39% di sviluppo di FA.
- Comunque il diametro AP atriale non rappresenta una accurata valutazione della grandezza dell'atrio sx (l'atrio sinistro non si dilata necessariamente in maniera simmetrica….)
- Il volume 2D biplanare valuta più accuramente le dimensioni e il rimodellamento dell'atrio sinistro ed ha un valore prognostico superiore rispetto al diametro AP
- 3D non ancora disponibile in tutti i centri

Rischio tromboembolico ed ETT (2)

- "C": scompenso cardiaco congestizio (LG ESC 2012):
  -Scompenso cronico sistolico : FE $\leq$ 40%
  -Scompenso acuto sia sistolico che diastolico (FE preservata)
- "VASc" : malattia vascolare
  -Infarto miocardico pregresso (ECG bassa sensibilità nell'IMA sia subendocardico che transmurale spt se IMA inferiore, posteriore o laterale . ECO: alterazioni strutturali e/o funzionali)
  - Placche aortiche (studio radice aortica, arco e anche aorta toracica discendente e addominale: placche aortiche complesse
  -Arteriopatia periferica

$CHAD_2DS_2$-VASc score per la valutazione del rischio tromboembolico nei pazienti con fibrillazione atriale.

	Punteggio
Fattori di rischio "maggiori"	
Pregresso ictus, TIA o embolia sistemica	2
Età ≥75 anni	2
Fattori di rischio clinicamente rilevanti "non maggiori"	
Età 65-74 anni	1
Sesso femminile	1
Scompenso cardiaco o disfunzione sistolica ventricolare sinistra da moderata a severa (FE ≤40%)	1
Ipertensione	1
Diabete mellito	1
Malattia vascolare (pregresso infarto miocardico, arteriopatia periferica, placca aortica)	1
Score massimo	**9**

FE, frazione di eiezione; TIA, attacco ischemico transitorio.

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Strain echocardiographic assessment of left atrial function predicts recurrence of atrial fibrillation

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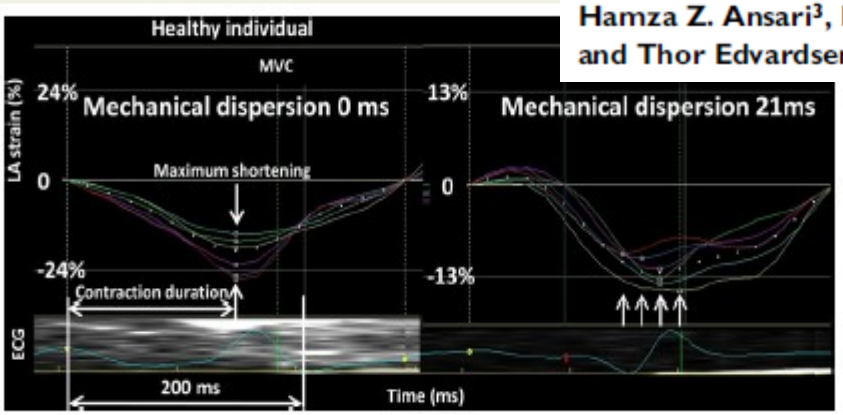

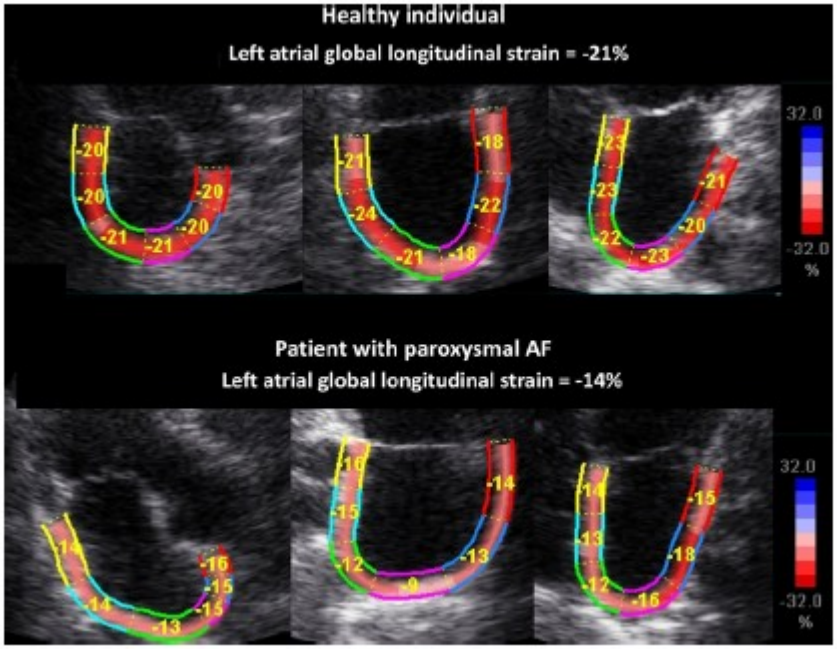

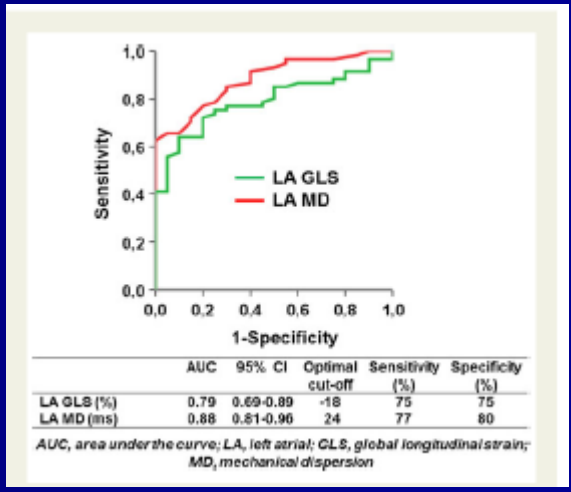

	AUC	95% CI	Optimal cut-off	Sensitivity (%)	Specificity (%)
LA GLS (%)	0.79	0.69-0.89	-18	75	75
LA MD (ms)	0.88	0.81-0.96	24	77	80

AUC, area under the curve; LA, left atrial; GLS, global longitudinal strain; MD, mechanical dispersion

Conclusions

We found a dispersed LA contraction pattern and reduced LA deformation in patients with PAF and normal or only mildly enlarged LA, and apparently normal LV structure and function when comparing with healthy individuals. LA MD before RFA treatment was most pronounced in AF patients who experienced recurrence of AF after RFA. We propose that LA MD by strain echocardiography may be useful as a marker of PAF and as a predictor of AF recurrence after RFA.

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REVIEW

Imaging

Myocardial strain imaging: how useful is it in clinical decision making?

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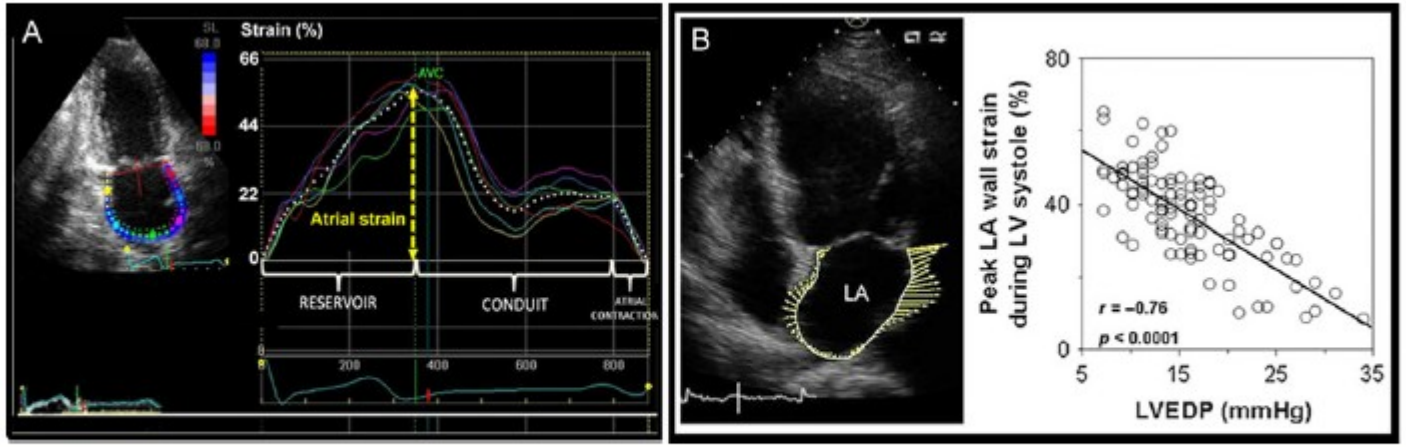


Figure 14 (*A* and *B*) Left atrial (LA) strain by two different speckle-tracking software. (*A*) Segmental traces of LA strain and average strain (white-dashed trace). Yellow arrow indicates peak strain. Modified from Cameli *et al.*[74] (*B*) Relationship between LA strain and left ventricular end-diastolic pressure.[73]

Advances in Cardiovascular Imaging

Atrial Fibrillation Pathophysiology and Prognosis

Insights From Cardiovascular Imaging

Konstantinos C. Siontis, MD; Jeffrey B. Geske, MD; Bernard J. Gersh, MB, ChB, DPhil

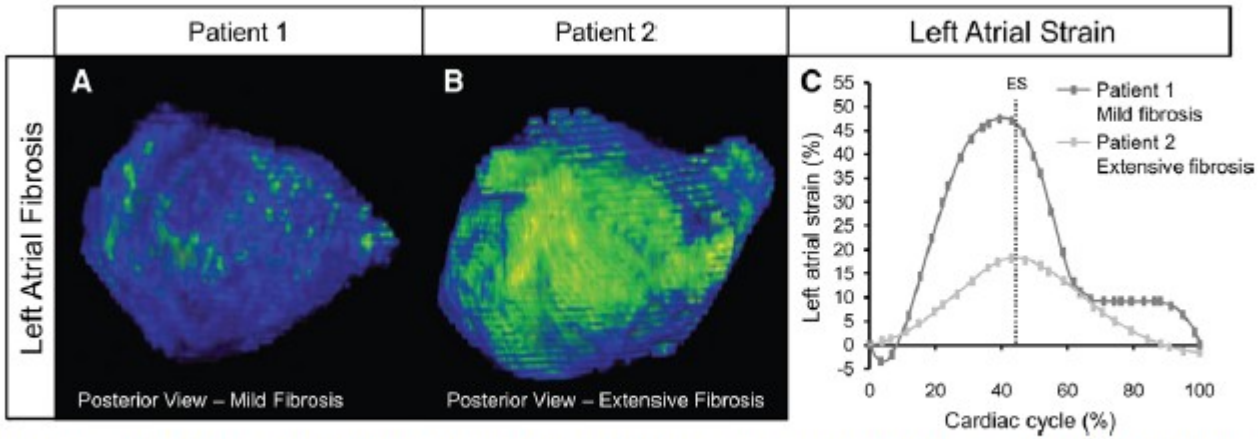
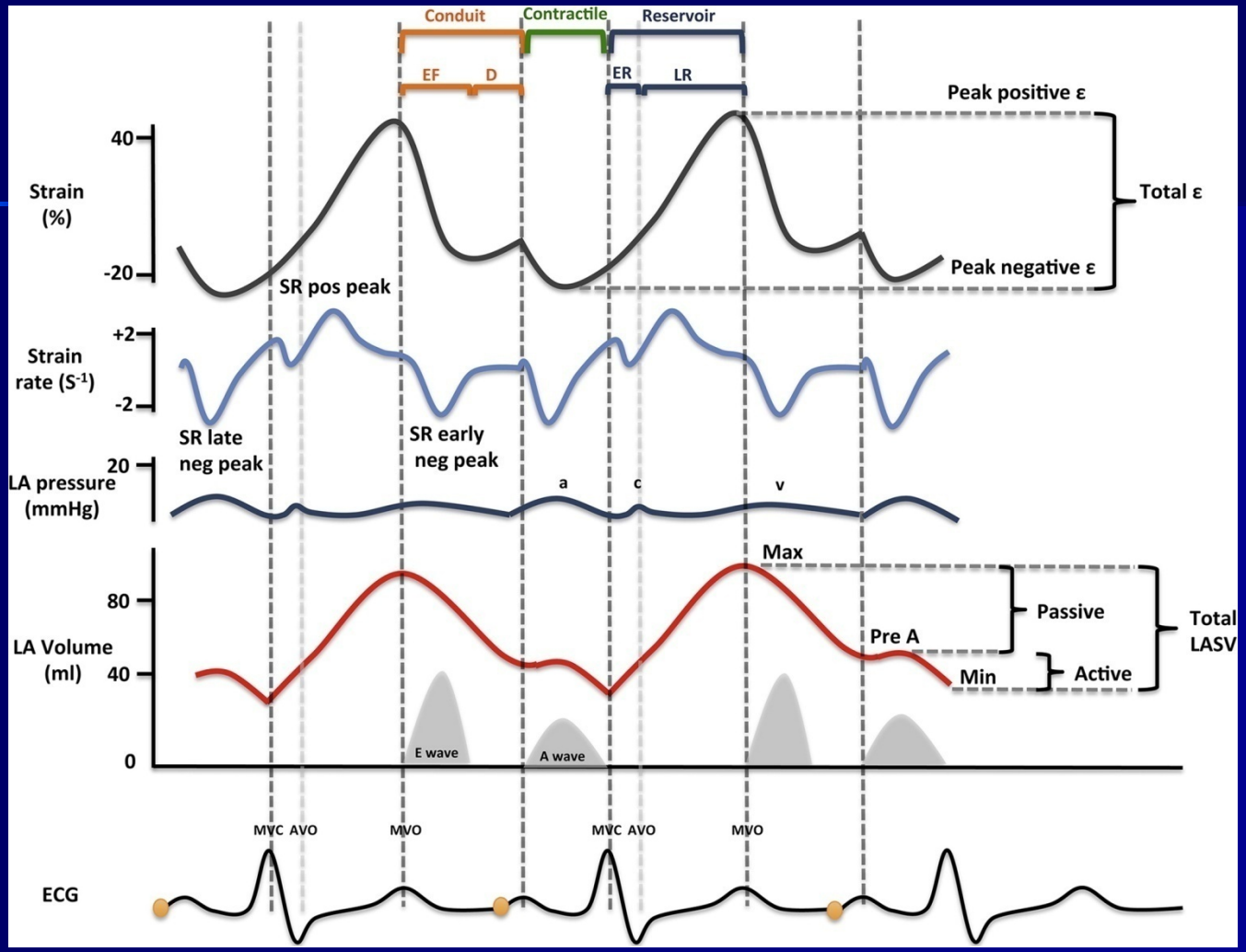


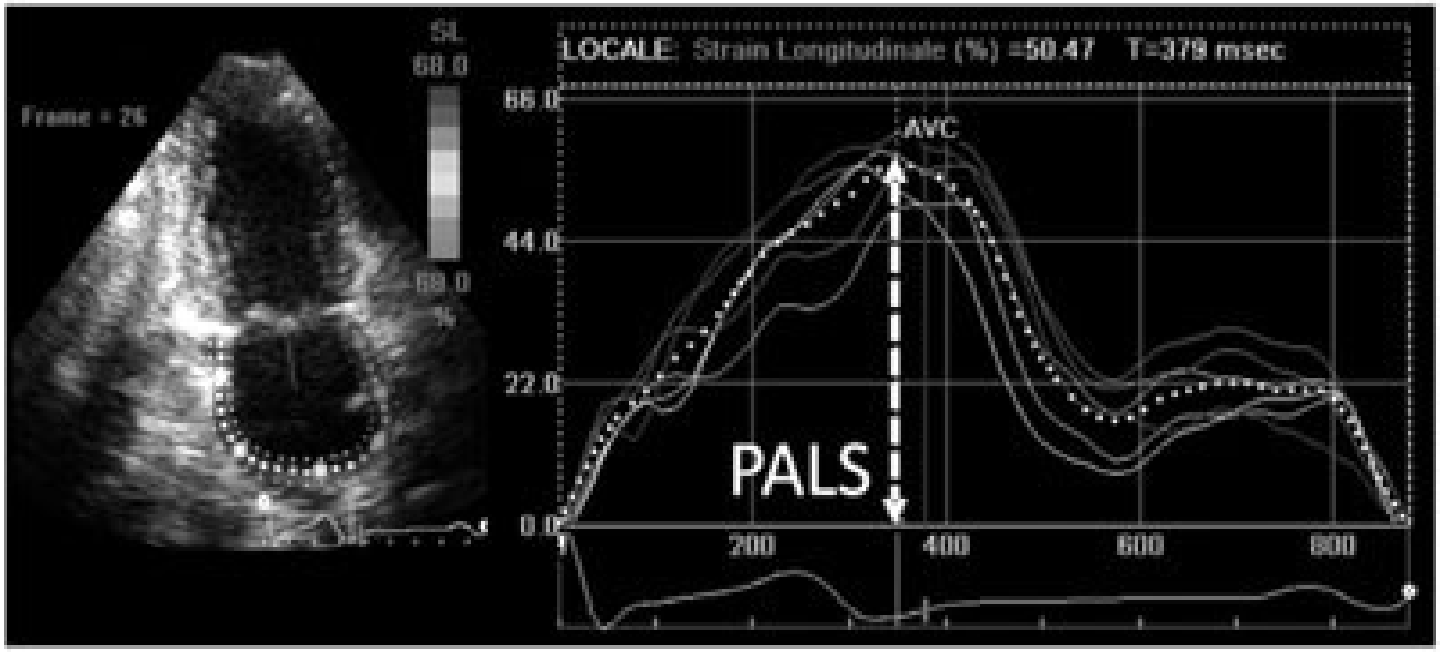
Figure 4. Comparison of left atrial midlateral strain by velocity vector imaging and extent of left atrial posterior wall fibrosis by delayed enhancement MRI in 2 patients. Reprinted from Kuppahally et al[48] with permission of the publisher. Copyright @ 2010, Wolters Kluwer Health.

Circ Cardiovasc Imaging 2015, 8:30-20

Figure 1



Journal of the American Society of Echocardiography 2014 27, 463-478DOI: (10.1016/j.echo.2014.01.021)

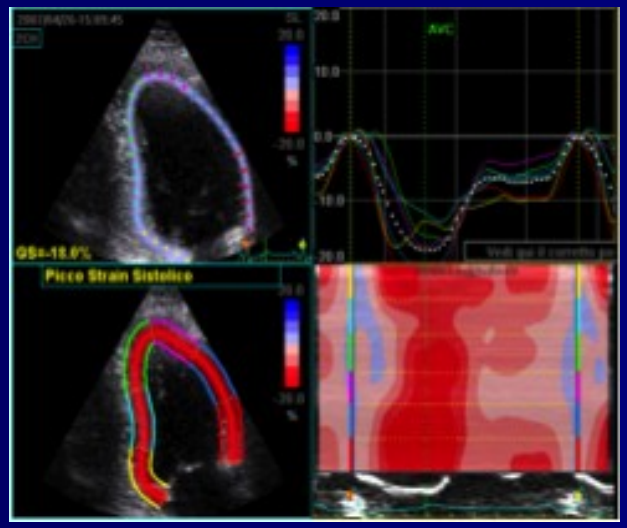


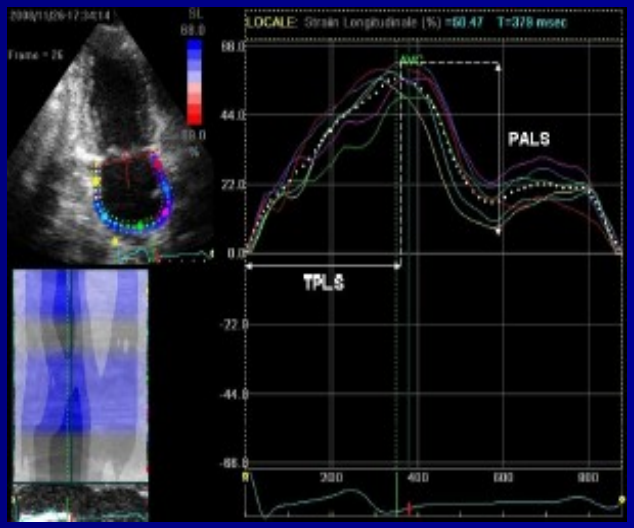
Esempio di valutazione dello strain atriale. Nell'immagine a sinistra si riconosce la regione di interesse posizionata sulla parete atriale di una sezione apicale 2 camere. Le curve continue a destra rappresentano la deformazione longitudinale regionale dell'atrio mentre la curva tratteggiata rappresenta la deformazione globale.
AVC, chiusura della valvola aortica; PALS, picco dello strain atriale longitudinale.

STRAIN

Strain is defined as the change in length of a segment of myocardium relative to its resting length and is expressed as a percentage;

Strain rate (SR) is the rate by which the deformation occurs (deformation or strain per time unit).





Rimodellamento atriale (3)

Attualmente, nonostante la indiscutibile importanza del rimodellamento atriale (e correlata fibrosi) nella genesi e mantenimento di FA, le Linee Guida più recenti sulla FA non prevedono, per vari motivi, l'utilizzo mirato di parametri eco nella valutazione diagnostica, prognostica e terapeutica della FA, che si basa ancora essenzialmente su parametri clinici piuttosto che su caratteristiche pato-fisiologiche individuali degli atri del singolo paziente.

Rimodellamento atriale (2)

- Sta emergendo sempre più chiaramente come i parametri eco più validi nell'analizzare il rimodellamento atriale sono rappresentati dalla analisi funzionale mediante strain e strain rate che evidenzia una stretta correlazione inversa con l'entità della fibrosi atriale indipendentemente da altri parametri eco.

- Quindi recentemente sono sempre più insistentemente proposti lo strain e lo strain rate atriali come le nuove e più attendibili metodiche non invasive per valutare il grado di fibrosi atriale e come marker surrogati di rigidità atriale.

- Tuttavia non è ancora chiaro in quale momento il processo di rimodellamento atriale diventa irreversibile.

Rimodellamento atriale (1)

- Cambiamento nelle dimensioni, funzioni e proprietà strutturali ed elettriche dell'atrio, tempo –dipendente, in relazione a "stressors" di varia natura: substrato ottimale per la insorgenza, le recidive, la progressione e la cronicizzazione di FA
- L'elemento caratterizzante il rimodellamento atriale è la fibrosi atriale, associata ad una progressiva dilatazione e rigidità della parete, con conseguente compromissione ingravescente delle funzioni meccaniche (pompa, reservoir e conduit) ed elettriche dell'atrio
- La entità della fibrosi atriale (valutata con maggior precisione in base a DE-MRI) appare strettamente correlata al grado di compromissione funzionale

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INVITED EDITORIAL

The left atrium: an old 'barometer' which can reveal great secrets

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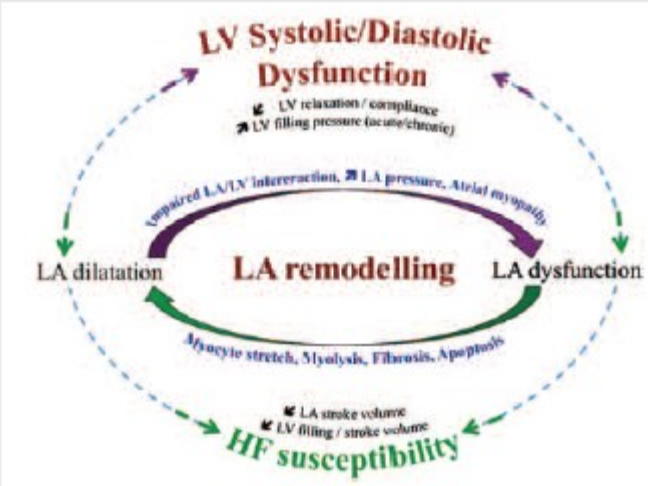
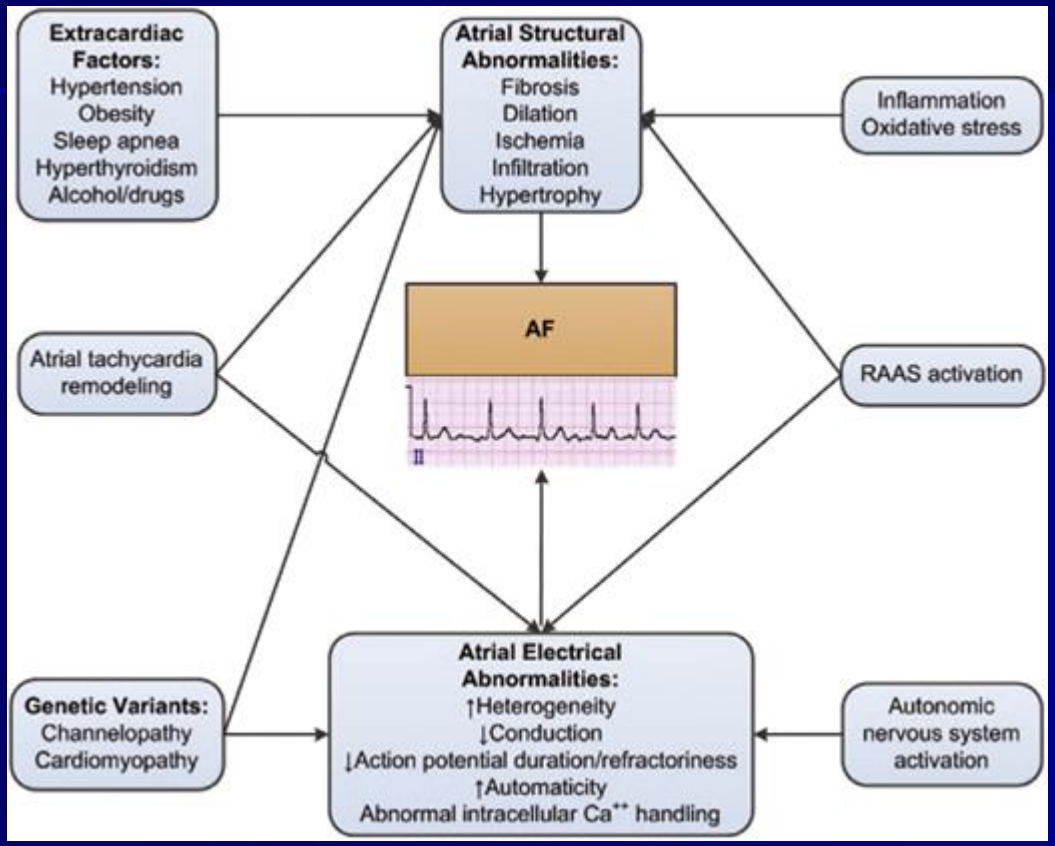


Figure 1 Relationship between left atrial (LA) remodelling, left ventricular (LV) function and heart failure (HF).

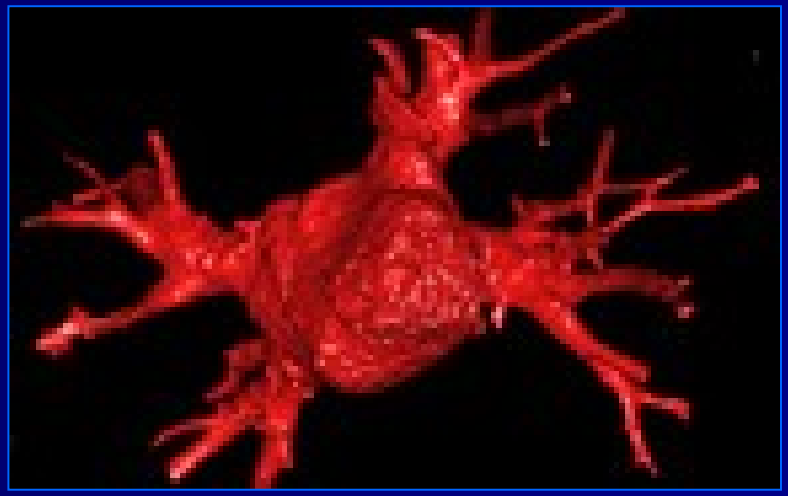

Extracardiac Factors:
Hypertension
Obesity
Sleep apnea
Hyperthyroidism
Alcohol/drugs
Atrial Structural Abnormalities:
Fibrosis
Dilation
Ischemia
Infiltration
Hypertrophy
Inflammation
Oxidative stress
AF
Atrial tachycardia remodeling
RAAS activation
Genetic Variants:
Channelopathy
Cardiomyopathy
Atrial Electrical Abnormalities:
↑Heterogeneity
↓Conduction
↓Action potential duration/refractoriness
↑Automaticity
Abnormal intracellular Ca++ handling
Autonomic nervous system activation

Left atrial Remodeling

Recent interest on

the impact of its function

in outcome of various diseases



- Ipertensione arteriosa (IA), Stroke ischemico (IS) e Fibrillazione atriale (FA) rappresentano 3 emergenze e problematiche strettamente correlate che interessano soprattutto gli anziani.
- IA, presente nel 50-70% della popolazione anziana, è considerata il più importante fattore di rischio per IS ed è presente nel 70-90% dei p. con FA.
- FA: oltre il 25% dei soggetti di 40 aa svilupperà FA nel corso della vita. FA considerata la causa "certa" di IS in almeno 25-30% dei casi e "probabile" in un altro 30% di IS considerato cripto-genico (o ESVS)
- IS: è la II causa di morte (circa 10%) specie negli anziani

Mappaggio elettro-anatomico e CMPAF

- Aree di basso voltaggio al mappaggio elettro-anatomico invasivo (indicative di tessuto fibroso) possono quantificare l'estensione di fibrosi e guidare ATC.

- Ma considerare che l'effetto di ogni ATC crea ulteriori aree di DE-MRI!!

Table 2. Crude Incidence Rates at 1 Year of Follow-up in the Heart Failure Study Population, Stratified According to Prior Diagnosis of Atrial Fibrillation[a]

End Points	Overall	No. of Additional Risk Factors on CHA_2DS_2-VASc Score					
		1 (HF Only)	2	3	4	5	≥6
Patients Without Atrial Fibrillation							
Patients, No. (%)	33 592	2366 (7.0)	4503 (13.4)	7462 (22.2)	9183 (27.3)	5958 (17.7)	4120 (12.3)
Ischemic stroke							
Events, No.	977	29	62	141	258	212	275
Person-years, No.	9 448 812	711 473	1 393 807	2 180 746	2 529 593	1 599 137	707 004
Incidence rate, % (95% CI)	1.0 (1.0-1.1)	0.4 (0.3-0.6)	0.4 (0.3-0.6)	0.6 (0.5-0.8)	1.0 (0.9-1.2)	1.3 (1.2-1.5)	2.6 (2.4-3.0)
Thromboembolism[b]							
Events, No.	3187	110	276	548	853	683	717
Person-years, No.	9 040 950	696 366	1 348 456	2 104 494	2 421 856	1 518 482	652 067
Incidence rate, % (95% CI)	3.5 (3.4-3.6)	1.6 (1.3-1.9)	2.0 (1.8-2.3)	2.6 (2.4-2.8)	3.5 (3.3-3.8)	4.5 (4.2-4.8)	7.5 (7.0-8.1)
Death							
Events, No.	6956	149	332	1256	2239	1596	1384
Person-years, No.	9 596 399	715 795	1 404 213	2 201 781	2 566 123	1 632 315	731 311
Incidence rate, % (95% CI)	7.2 (7.1-7.4)	2.1 (1.8-2.4)	2.4 (2.1-2.6)	5.7 (5.4-6.0)	8.7 (8.4-9.1)	9.8 (9.3-10.3)	12.9 (12.2-13.6)
Patients With Atrial Fibrillation							
Patients, No. (%)	9395	606 (6.5)	931 (9.9)	1752 (18.7)	2571 (27.4)	137 (20.6)	1598 (17.0)
Ischemic stroke							
Events, No.	318	8	11	32	82	80	105
Person-years, No.	1 592 497	55 019	110 265	294 757	477 528	365 633	180 083
Incidence rate, % (95% CI)	2.0 (1.8-2.2)	1.5 (0.7-2.9)	1.0 (0.6-1.8)	1.1 (0.8-1.5)	1.7 (1.4-2.1)	2.2 (1.8-2.7)	3.6 (3.0-4.4)
Thromboembolism[b]							
Events, No.	651	18	31	85	158	169	190
Person-years, No.	1 551 095	54 425	107 277	287 648	468 813	357 479	172 156
Incidence rate, % (95% CI)	4.2 (3.9-4.5)	3.3 (2.1-5.2)	2.9 (2.0-4.1)	3.0 (2.4-3.7)	3.4 (2.9-3.9)	4.7 (4.1-5.5)	6.9 (6.0-8.0)
Death							
Events, No.	2153	11	47	282	677	561	575
Person-years, No.	1 630 977	55 347	111 192	297 304	489 042	373 574	186 490
Incidence rate, % (95% CI)	13.2 (12.7-13.8)	2.0 (1.1-3.6)	4.2 (3.2-5.6)	9.5 (8.4-10.7)	13.8 (12.8-14.9)	15.0 (13.8-16.3)	18.9 (17.4-20.5)

[a] CHA_2DS_2-VASc score is calculated as congestive heart failure (1 point), hypertension (1 point), age 75 years or older (2 points), diabetes (1 point), stroke/transient ischemic attack/thromboembolism (2 points), vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque; 1 point), age 65 to 75 years (1 point), female sex (1 point). All study patients had heart failure at baseline.

[b] Composite end point of ischemic stroke, transient ischemic attack, systemic embolism, pulmonary embolism, or acute myocardial infarction.

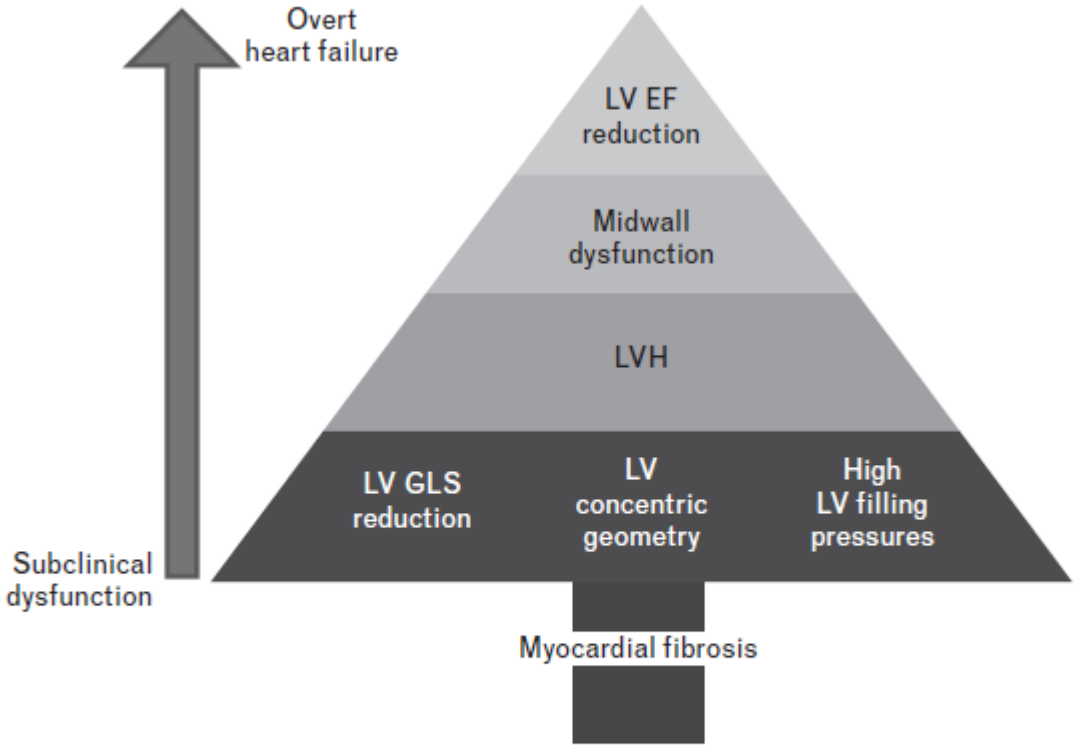
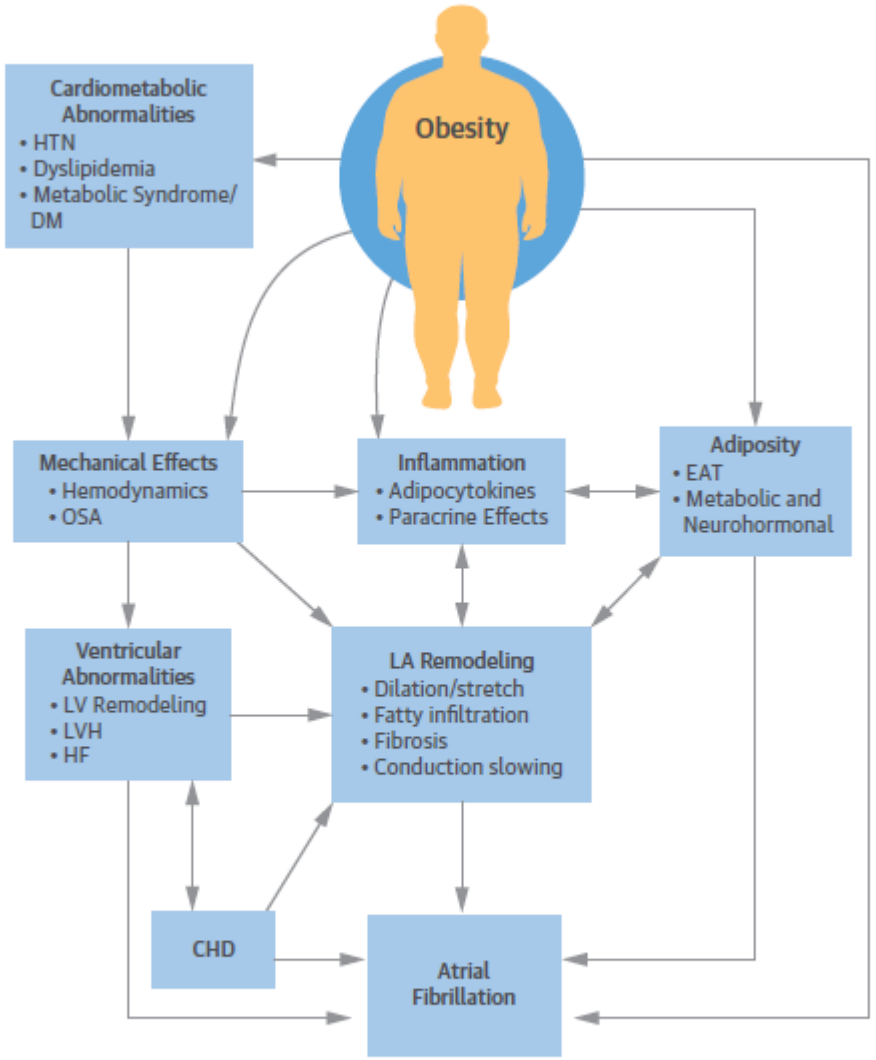


FIGURE 1 The novel 'tree' progression of LV dysfunction in arterial hypertension: myocardial fibrosis is the '*primum movens*' of all the structural and function abnormalities of the left ventricle leading to the final development of overt heart failure. EF, ejection fraction; GLS, global longitudinal strain; LV, left ventricular; LVH, left ventricular hypertrophy.

FIGURE 2 Obesity and AF



Proposed mechanisms explaining the increased risk of atrial fibrillation in obesity. CHD = coronary heart disease; DM = diabetes mellitus; EAT = epicardial adipose tissue; HF = heart failure; HTN = hypertension; LVH = left ventricular hypertrophy; OSA = obstructive sleep apnea; other abbreviations as in Figure 1.

ANCE – Regione Lazio

Corso di formazione: " Ipertensione e danni d'organo"

Ipertensione Arteriosa, Stroke ischemico e Fibrillazione atriale: nuovi modelli riguardo le reciproche relazioni

Roma 18 Febbraio 2017

Prof. F. Bellocci

Centro per la prevenzione della Morte Improvvisa

Policlinico Universitario A. Gemelli – Roma-

Rationale and design of a large-scale, app-based study to identify cardiac arrhythmias using a smartwatch: The Apple Heart Study

Mintu P. Turakhia, MD, MAS,[a,b] Manisha Desai, PhD,[c] Haley Hedlin, PhD,[c] Amol Rajmane, MD, MBA,[d] Nisha Talati, MBA,[d] Todd Ferris, MD, MS,[e] Sumbul Desai, MD,[f] Divya Nag[f] Mithun Patel, MD,[f] Peter Kowey, MD,[g] John S. Rumsfeld, MD, PhD,[h] Andrea M. Russo, MD,[i] Mellanie True Hills, BS,[j] Christopher B. Granger, MD,[k] Kenneth W. Mahaffey, MD,[d] and Marco V. Perez, MD[l] *Stanford, Palo Alto, Cupertino, CA; Philadelphia PA; Denver Colorado; Camden NJ; Decatur TX; Durham NC*

Background Smartwatch and fitness band wearable consumer electronics can passively measure pulse rate from the wrist using photoplethysmography (PPG). Identification of pulse irregularity or variability from these data has the potential to identify atrial fibrillation or atrial flutter (AF, collectively). The rapidly expanding consumer base of these devices allows for detection of undiagnosed AF at scale.

Methods The Apple Heart Study is a prospective, single arm pragmatic study that has enrolled 419,093 participants (NCT03335800). The primary objective is to measure the proportion of participants with an irregular pulse detected by the Apple Watch (Apple Inc, Cupertino, CA) with AF on subsequent ambulatory ECG patch monitoring. The secondary objectives are to: 1) characterize the concordance of pulse irregularity notification episodes from the Apple Watch with simultaneously recorded ambulatory ECGs; 2) estimate the rate of initial contact with a health care provider within 3 months after notification of pulse irregularity. The study is conducted virtually, with screening, consent and data collection performed electronically from within an accompanying smartphone app. Study visits are performed by telehealth study physicians via video chat through the app, and ambulatory ECG patches are mailed to the participants.

Conclusions The results of this trial will provide initial evidence for the ability of a smartwatch algorithm to identify pulse irregularity and variability which may reflect previously unknown AF. The Apple Heart Study will help provide a foundation for how wearable technology can inform the clinical approach to AF identification and screening. (Am Heart J 2019;207:66-75.)

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