ΤΡΟΠΟΠΟΙΗΣΗ ΠΑΡΑΓΟΝΤΩΝ ΚΙΝΔΥΝΟΥ ΚΑΙ ΜΕΤΑΒΟΛΗ ΤΟΥ ΤΡΟΠΟΥ ΖΩΗΣ ΣΤΗΝ ΚΟΛΠΙΚΗ ΜΑΡΜΑΡΥΓΗ

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ΓΝΑ «Ο Ευαγγελισμός»
Epidemiology of AF

- AF has become an epidemic world wide:
  - “An outbreak or product of sudden rapid spread, growth or development.”
- Over 5 million people have AF at this time and this is expected to increase to over 12 million in the next 20 years.

Incidence Per Age Group
Epidemiology

- Lifetime risk of developing AF in individuals over 40 is 1 in 4.
- AF is seen in 1% of the population and the prevalence in adults under 55 is 0.1% and 9% in octogenarians.
- Prevalence increases with the severity of heart failure or valvular heart disease.
- Occurs more often in men than women.
- Accounts for 34.5% of all patients hospitalized for arrhythmia.
- Transient AF can occur in 15-40% of CV surgery patients.

Economic Burden of AF

$6.65 billion in total treatment costs:

Hospital: $4.88 billion
Outpatient: $1.53 billion
Medications: $235 million

Coyne, et al. (2006).
Not only is AF an economic burden to the citizens of the world, but the secondary effects of AF are also costly:

- Stroke
- Disability
- Tachycardia induced heart failure
- Heart failure
- Decreased quality of life
Significance of Problem

- Overall risk of developing AF is rising.
- Increasing prevalence and incidence of AF
- Disabling co-morbid conditions such as heart failure, CHF, stroke, depression, anxiety and other arrhythmias.
- Medical and interventional treatments are available but are not without risk, adverse effects and do not cure AF or decrease mortality or morbidity.
- 80% of subjects which present with AF have at least one risk factor.

Priorities in the Management of AF

The Patient Care Pathway

- Rhythm Control
- Prevention of Thromboembolism
- Rate Control
Despite the aging population, history of CHF, MI and hypertension, these factors alone are not sufficient to explain the growing incidence of AF.
Known Risk Factors of AF

- Hypertension
- Advancing Age
- Valvular Disease (RHD)
- Hyperthyroidism
- Cardiomyopathy
- Heart Failure
- Coronary Artery Disease
- Diabetes Mellitus
- Sepsis

- Obesity
- Obstructive Sleep Apnea
- Metabolic Syndrome
- Genetic predisposition
- Cardiothoracic surgery: CABG and valvular surgery
- Previous episodes of AF
- Esophageal resection

Wu et al., 2005; Chen & Shen, 2007; Gami et al., 2007; Lip et al., 2007; Watanabe et al., 2008; Fuster et al., 2006; Otway, Vandenburg & Fatkin, 2007.
Can we prevent AF?

- Primary prevention of AF
- Focus on **modifiable risk factors**:
  - Obesity
  - OSA
  - Hypertension
  - Hyperthyroidism
  - Heart failure
  - Metabolic Syndrome
  - Cardiothoracic surgery
- Develop prevention/risk reduction strategies to reduce risk of primary and secondary AF.
Risk factors(1)

- Age
- Heart Disease:
  - Hypertension
  - DM, metabolic syndrome and insuline resistance.
  - CAD
  - CHF
  - Valvular Heart Disease and heart surgery
- Alcohol
- Family History
- Men

Risk factors(2)

- Echo:
  - ↑LA
  - LV hypertrophy
  - Relaxation abnormality
- Thyroid abnormalities: in hyperthyroidism 3 times risk for AF
- Inflammation (e.g. myocarditis, pericarditis, systematic inflammation, pneumonia)
- Sleep apnoea

New risk factors to AF or «not so-lone AF»

1. Obesity
2. OSA
3. \( \uparrow \text{CRP} \)
4. RAAS
# Pathophysiology of AF

- Atrial fibrosis and loss of muscle mass
- Expression of angiotension-converting enzyme increased 3-fold during persistent AF
- Increase in left ventricular hypertrophy led to increase in left atrial dimension which increases the risk of AF
- Atrial stretch can cause AF and AF can cause atrial dilation
- Inflammation
- Autonomic Nervous System activity
- Atrial ischemia
- LV diastolic dysfunction affects stretch receptors in the pulmonary veins or directly affects atrial myocardium.

AF Risk Factor Causal Model

Genetics

- Increased relative risk of 1.85% in offspring of one or both parents with AF
- Cannot change genetics
- Offspring should be evaluated for increased risk of AF

# Genetics-genes and Pathophysiology

| TABLE 1. THE GENETIC CULPRITS OF ATRIAL FIBRILLATION AND THEIR ASSOCIATED PATHOPHYSIOLOGY. |
|---|---|---|---|---|
| **Gene** | **Mode of Inheritance** | **Protein and Function** | **Functional Effect of Mutation** | **Mechanism for AF** |
| **Potassium Channels** | | | | |
| KCNQ1 | Autosomal Dominant | α-subunit of IKs | Gain-of-Function | Reduced atrial ERP |
| KCNE2 | Autosomal Dominant | β-subunit of background potassium current | Gain-of-Function | Reduced atrial ERP |
| KCNJ2 | Autosomal Dominant | Kir2.1 responsible for IK1 | Gain-of-Function | Reduced atrial ERP |
| KCNE5 | Sporadic | β-subunit of IKs | Gain-of-Function | Reduced atrial ERP |
| KCNA5 | Autosomal Dominant | Kv1.5 responsible for IKur | Loss-of-Function | Prolonged atrial APD |
| **Connexins** | | | | |
| GJA5 | Autosomal Dominant/ Sporadic | Connexin 40 responsible for cell coupling | Loss-of-Function | Conduction velocity dispersion |
| **Sodium Channels** | | | | |
| SCN5A | Autosomal Dominant | Nav1.5 responsible for iNa (Phase 0) | Loss-of-Function | Prolonged atrial APD |
| Autosomal Dominant | Gain-of-Function | Cellular hyperexcitability |
| **Circulating Hormones** | | | | |
| NPPA | Autosomal Dominant | Atrial Natriuretic Peptide | Unknown | Unknown |
Increasing Age

- Increased prevalence with increasing age.
- Risk higher in men, but women are now living longer, which places a larger population at risk for AF.
- Cannot change risk of age, only risk reduction of other risk factors.
AF Prevalence: Age and Gender

Prevalence of atrial fibrillation with age

- Women
- Men

JAMA 2001; 285: 2370
The CDC defines adults as **overweight** if the Body Mass Index (BMI) is **25-29.9** and **obese** as BMI **≥ 30**.

In 2006, prevalence of obesity in males was **33.3%** and **35.3%** in women.

72 million Americans are obese and adults aged 40-59 have the highest prevalence of all age groups.
Worldwide obesity has nearly tripled since 1975.

In 2016, >1.9 billion adults, 18 years and older, were overweight. Of these over 650 million were obese.

39% of adults aged 18 years and over were overweight in 2016, and 13% were obese.

Most of the world's population live in countries where overweight and obesity kills more people than underweight.

41 million children under the age of 5 were overweight or obese in 2016.

Over 340 million children and adolescents aged 5-19 were overweight or obese in 2016.

Obesity is preventable.
Obesity and AF

- Risk of AF increased 5% for each one unit increase in BMI.
- Significant difference noted in LAD in obese men compared to overweight men (p<.001).
- Increased risk of AF with increased LAD and LVH.

Obstructive Sleep Apnea (OSA)

- OSA affects 17-24% of adults and is present in 40-90% of overweight and obese subjects.
- A retrospective cohort study by Gami et al. (2007) followed 3542 subjects for 4.7 years and revealed that BMI and OSA are both strong predictors of AF together and independently.
From: New risk factors for atrial fibrillation: causes of ‘not-so-lone atrial fibrillation’
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OSA-pathophysiology

- Periodic reduction/cessation of breathing during sleep due to narrowing of the upper airways.
- Induces intermittent hypoxaemia/hypercapnia, sympathetic activation and changes in BP.
- The ↑intrathoracic pressure caused by inspiration against an obstructed airway → ↑transmural pressure gradient → atrial stretch.
- Hypoxaemia → pulmonary vasoconstriction → ↑pulmonary artery pressures.
- OSA → autonomic imbalance + diastolic dysfunction..

Hypertension

- Double-blind randomized study of 8831 pts with HTN.
- Received losartan and atenolol.
- Assessed LV size
- 12.4% lower risk of AF with decrease in LV size (Cornwell product)

SOLVD Trial

- Retrospective analysis revealed after 2.9 years of follow-up, 5.4% of patients receiving enalapril vs. 24% in placebo group developed AF.

Heart Failure

- The prevalence of AF in patients with HF ranges from 10 to 30%.
- This has been observed to increase in proportion to the severity of HF from <10% in those with New York Heart Association (NYHA) functional class I HF to approximately 50% in those with NYHA functional class IV.

Hyperthyroidism

- Increases risk of developing AF
- Thyroid hormone influences arrhythmogenic activity of atrial myocytes.
- AF occurs in 10-15% of patients with hyperthyroidism.
- Treat with thyroxine and beta blockers
- Treatment results in conversion to sinus rhythm is 2/3 of patients.

Metabolic Syndrome

- National Cholesterol Education Program defined MS if at least 3 of the following factors are met:
  - Elevated BMI
  - Elevated triglycerides
  - Low HDL
  - Increased BP
  - Impaired glucose tolerance
Metabolic Syndrome and AF

- 28,449 Japanese subjects followed for a mean of 4.5 years in a prospective study.
- AF developed in 265 participants
- All components except for high triglycerides contributed to the development of AF
- 3 or more components of MS revealed a HR of 3.27 and obesity and elevated BP contributed substantially to increased risk of AF.

Predictors of Post-op AF

- Advanced age
- Male gender
- Digoxin
- Peripheral arterial disease
- Chronic lung disease
- Valvular heart disease
- Left atrial enlargement
- Previous cardiac surgery
- Discontinuation of beta-blocker medication
- Preoperative atrial tachy-arrhythmias
- Pericarditis
- Elevated postoperative adrenergic tone

Creswell, et al. (1993)
Prevention of Peri-operative AF

- BMI >30.1 predicts increased risk of AF
- Post-operative amiodarone decreased risk of AF from 47% to 35%
- Beta blockers protected against AF
- Statin therapy pre-op not associated with decreased incidence of AF
- Sotalol was found to be more effective in reducing AF than beta blockers or placebo.
- PUFA’s lower risk of AF post CABG
- AF is self-limiting
- IV Magnesium Sulfate

Fuster, et. al. (2006); Calo, et al. (2005); Saravannan et al. (2009).
## Polyunsaturated Fatty Acids and AF (PUFA)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study Design</th>
<th>Subjects</th>
<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physician Health Study</td>
<td>Prospective</td>
<td>17679 pts</td>
<td>AF risk higher in PUFA group</td>
</tr>
<tr>
<td>Danish Study</td>
<td>Prospective</td>
<td>47949 pts</td>
<td>Stat. insignificant</td>
</tr>
<tr>
<td>Rotterdam Study</td>
<td>Prospective</td>
<td>5184 pts</td>
<td>Stat. insignificant</td>
</tr>
<tr>
<td>Mozaffarian et al.</td>
<td>Prospective</td>
<td>4815 pts</td>
<td>28% lower AF risk in broiled/baked fish group</td>
</tr>
<tr>
<td>Calo et al.</td>
<td>Prospective</td>
<td>160 CABG</td>
<td>AF risk lower in PUFA group</td>
</tr>
<tr>
<td>Saravanan et al</td>
<td>Prospective</td>
<td>CABG pts</td>
<td>AF risk lower in PUFA group</td>
</tr>
</tbody>
</table>

Vitamin C

Anti-oxidant and Anti-inflammatory

<table>
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<tr>
<th>Reference</th>
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<th>Conclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carnes et al. Vit C before and 5 days after CABG</td>
<td>43 pts</td>
<td>16.3% vs. 39% developed AF</td>
</tr>
<tr>
<td>Korantzopoulos et al. 2g Vit C 12 hr prior to CV and 500 mg BID for one week after CV</td>
<td>44 pts</td>
<td>4.5% vs. 36.3% developed AF after 1 week</td>
</tr>
</tbody>
</table>

Statin Therapy

- Pellegrini, et al. (HERS study) studied 2763 postmenopausal women with heart disease randomized to HRT or placebo.

- Data revealed 55% decrease in AF incidence compared to women not taking statins.

- 65% decrease in prevalence of AF in statin therapy subjects.
Statins: Meta-analysis

- 6 studies with total 3,557 subjects in sinus rhythm.
  - 3-studies with use of statins in PAF or persistent AF prior to CV;
  - 3 studies with primary prevention of AF in patients undergoing CABG or post MI.
- Use of statins was significantly associated with decreased risk of AF compared to controls (odds ratio 0.39).
- Benefit of statin therapy increased in secondary prevention of AF than new-onset or post-op AF (OR 0.60).
- * Use of statins was significantly associated with decreased risk of incidence or recurrence of AF in pts in sinus rhythm with history of AF, undergoing cardiac surgery or AMI.

Previous Episode of AF and Secondary Prevention

“Atrial fibrillation begets atrial fibrillation”
“Upstream Therapies”

- “Refers to the use of non-anti-arrhythmic drugs which modify the atrial substrate, or target-specific mechanisms of AF to prevent the occurrence or recurrence of arrhythmia”.
  - ACEI
  - Beta Blockers
  - ARB
  - PUFA
  - Vitamin C
  - Statins
- Although some retrospective and small study results in selected categories have been positive, larger prospective studies have generated controversial and mostly negative results.
- Results remain inconclusive.

Prevention of cardiovascular events and progression of heart disease (e.g. by modifying lipid metabolism)
Modulating thrombogenesis (e.g. via reduction in ICAM-1 and E-selectin)

Anti-inflammatory
Antioxidant
Antifibrotic
Regulation of MMP activity
Improvement of endothelial function
Metabolic protection via PPAR activation
Protection during ischemia via increased e-NOS activity

Underlying heart disease

Sympathetic activation
Modulating the autonomic nervous system
Reduction in sympathetic stimulation

Direct effects on ion channels (PUFAs)
Counteracting SAC channel activation (PUFAs)
Modulating Ca^{2+} handling
Prevention of gap junction remodeling
Indirect effects via angiotensin II-dependent pathway

Remodeling
Electrical
Structural
Autonomic
Metabolomic

Triggers
Reentry

Atrial fibrillation
Recommendations?

- Maintain lower BMI
- Control BP
- Treat OSA
- Treat abnormal thyroid function
- ACEI, ARB and BB for hypertension and heart failure (jury is still out…)
- Consider PUFA, Vitamin C
- Preoperative prophylaxis
Exercise Training in AF

**Benefits of Exercise Training in AF**

- **Frequency:** 3-5 days/wk
- **Intensity:** $\leq 95\%$ peak HR
- **Time:** 120 to 200 Min/Wk
- **Type:** Aerobic Exercise +/- Resistance Training

**Short-Term (<6 months)**
- Reduced AF Burden
- Reduced Symptom Severity
  (Malmo et al., 2015)

**Long-Term (>4 years)**
- Increased AF freedom
- Reduced Symptom Severity
  (Pathak et al., 2015)

**Potential Mechanisms**
- Reversed atrial remodeling
- Weight loss
- Improved BP control
- Improved glycemic control
- Reduced Inflammation
- Improved autonomic tone
Case Study #1

- Mr. P is a 75 year old male with a BMI of 29, hypertension, normal TSH, no family history of AF and snores with apneic episodes.
- Echo reveals LVH, left atrial dimension of 49 mm, EF of 51% and mild MVR.
- How can his health care provider lower his risk of AF?
Case Study #2

- Mrs. R is a 52 year old female with chronic diastolic heart failure, TSH of 0.01, mother with persistent AF and being prepared to undergo CV surgery for MV replacement.

- How can you decrease this patient’s risk for AF?
Lack of studies which focus on prevention of new-onset AF strategies with modifiable risk factors

New directed approaches for prevention of AF are necessary to halt this every-increasing public health crisis.

Implementing AF risk reduction strategies aimed at modifiable risk factors such as obesity, OSA, hypertension, heart failure and pre-operative interventions may impact the escalating incidence of AF in the population and will ultimately decrease the healthcare burden of associated co-morbidities of AF.
Συμπεράσματα/ Προτάσεις

- Χρειάζονται νέες κατευθυνόμενες προσεγγίσεις για την πρόληψη της ΚΜ ώστε να περιορίσουν την αυξανόμενη αυτή κρίση της δημόσιας υγείας.

- Υλοποίηση στρατηγικών ελάττωσης του κινδύνου της ΚΜ που στοχεύουν σε τροποποιήσιμους παράγοντες κινδύνου όπως η παχυσαρκία, η OSA, η υπέρταση, η KA και περιεπεμβατικές παρεμβάσεις μπορούν να επιδράσουν στην κλιμακούμενη επίπτωση της ΚΜ στον πληθυσμό και να ελαττώσουν το φορτίο των συνοσηροτήτων.

- Έλλειψη πολυκεντρικών μελετών που εστιάζονται στις στρατηγικές πρόληψης τις πρωτοεμφανιζόμενης ΚΜ με τροποποιήσιμους παράγοντες κινδύνου.
ΕΥΧΑΡΙΣΤΩ ΠΟΛΥ
ΓΙΑ ΤΗΝ ΠΡΟΣΟΧΗ ΣΑΣ.