Ablation Should **Not** Be Used as Primary Therapy for Treatment of Patients with Atrial Fibrillation

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*Update in Electrocardiography and Arrhythmias*

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AF Epidemiology

- Prevalence of AF in Framingham cohort:
  - 0.5% from age 50-59y
  - 8.8% from age 80-89y

- Most common underlying etiologies:
  - HTN--up to 50%
  - Ischemic heart disease--29%
  - Valvular disease

- Associated RR for excess mortality for AF in Framingham cohort:
  - 1.5 for men
  - 1.9 for women
Cumulative Risk for Development of AF

CVA Risk by Type of AF

- European Heart Survey corroborates current guideline that *type of AF should not be taken into account when deciding oral anticoagulation*
- Paroxysmal AF pts have higher risk of stroke than persistent AF pts
- No difference in CVA risk with asx or sx AF
- Warfarin Rx as determined by CHADS2 score

Nieuwlaat, R et al *Eur Heart J* 2006
Nieuwlaat, R et al *Eur Heart J* 2008
Savalieva I et al *JICE* 2000
Rhythm control vs. Rate control

• In patients with paroxysmal or persistent AF, is restoration of sinus rhythm superior to rate control and allowing persistence of AF?
Rate Control and Anticoagulation: Trial Evidence

• AFFIRM, *NEJM* 2002; 347: 1825-33
  - 4060 paroxysmal or persistent AF pts randomized to rhythm vs. rate control
  - Mean 70y, 40% female, 25% CHF, 50% HTN, 50% CAD
  - 3.5 ± 2 y F/U, trend toward lower mortality in rate control arm, lower hospitalizations

• RACE, *NEJM* 2002; 347: 1834-40
  - 522 persistent AF pts randomized to rhythm control or rate control
  - After 2.3 ± 0.6 y F/U, trend toward lower composite end point of CV death, CHF, CVA in rate control arm

• These trends likely due to inadequate anticoagulation in rhythm control arm, thus both approaches require chronic warfarin if indicated
All-Cause Mortality in AFFIRM

- Cumulative Mortality (%)
- Years

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P=0.08

NO. OF DEATHS

- Rhythm control: 0, 80 (4), 175 (9), 257 (13), 314 (18), 352 (24)
- Rate control: 0, 78 (4), 148 (7), 210 (11), 275 (16), 306 (21)

NEJM 2002; 347: 1825-33
High Incidence of Asymptomatic AF in Rhythm Control

Up to 50% of episodes of AF are asymptomatic and missed by F/U ECG surveillance

Israel CW et al. JACC 43: 47-52, 2004
Which Patients for Rhythm Control?

• Thus, the major reason to pursue rhythm control is to **improve symptoms and quality of life**

• Although NSR was associated with better survival in AFFIRM, *no studies* have shown a reduction in stroke or CHF with rhythm control approach

• For older pts, persistent/chronic AF, or with structural heart disease:
  – Careful assessment of sx in rate control
  – Warfarin per CHADS2 score
  – DCCV + AAD if sx

• For younger pts, paroxysmal AF, and structurally normal hearts
  – Often sx even with rate control
  – Goal is restoration of NSR
  – AAD, radiofrequency catheter ablation (RFCA)
Current ACC/AHA/ESC 2006 Guidelines for the Treatment of Atrial Fibrillation

Current guidelines recommend RFCA as **2nd line** Tx option after AAD failure
AAD Options

• Increment in efficacy compared with placebo:
  – Class IA: 22%
  – Class IC: 33%
  – Class III: 17%
• Often poorly tolerated with side effects
• Amiodarone associated with cumulative end-organ effects
• Class III agents concern for torsade de pointes
• Class I agents can increase mortality in CAD and structural heart disease

Nichol G et al *Heart* 2002
Amiodarone vs. Propafenone and Sotalol

- Canadian Trial of Atrial Fibrillation
- 403 symptomatic paroxysmal AF pts randomized

Time to AF Recurrence in AFFIRM

Current Status of RFCA for AF

- AF RFCA can achieve relief of symptoms and QOL for paroxysmal and permanent AF
- Apparent success rates for AF recurrence highly dependent on mode and intensity of monitoring
- Trial hard endpoints such as mortality, CHF, hospitalization, CVA, costs are entirely lacking
- Best data for symptomatic AF with no or minimal structural heart disease
Current AF RFCA Approaches

• Numerous approaches:
  – Circumferential PV isolation (PVI)
  – LA ablation
  – CFAE ablation
  – Ganglionic plexi ablation
  – Hybrid therapy: RFCA + AADs

• PVI:
  – 251 pts (179 paroxysmal, 72 permanent)
  – Major complication (tamponade, CVA) rate 0.8%
  – Mean 10 F/U, 85% paroxysmal AF in NSR
  – 68% permanent AF in NSR

• Chronic AF:
  – 27 pts with drug-refractory chronic AF
  – Mean F/U 21 mo, overall 63% NSR
  – structural heart disease: 25% NSR
  – structurally normal hearts: 74% NSR

• Up to 40% require at least 1 repeat RFCA

Pappone C Circ 2001
Sanders P Eur Heart J 2007
AF Recurrence after RFCA

- **Early AF**, typically up to 3 mo
  - Often treated with AAD + cardioversion
- **Late AF**
  - 20% at 6 mo
  - 15% (paroxysmal), 32% (permanent) at 10 mo
  - 22% at 16 mo
  - 22% at 3y
  - More likely in pts w/ underlying HTN or structural disease
- **Left AT/AFL** (iatrogenic)
  - ~20% incidence

Saad EB *Ann Int Med* 2003
Verma A *JACC* 2005
Long-term Efficacy of RFCA

- AF is a diverse disease with multiple mechanisms operative
- Epidemiology suggests increased incidence with age, HTN, CAD
- Aging can cause EP and anatomic changes in atria
- Eliminating triggers (PV) or substrate modification (LA) may forestall recurrence, rather than “cure” AF
Anticoagulation after RFCA

- Role of chronic anticoagulation after successful RFCA is uncertain
- Embolic risk has not been well defined
- Late recurrent AF in 20-30%, but may be an underestimate
- Unknown if asx AF increases risk for RFCA pts
- 755 pts w/ chronic or persistent AF undergoing RFCA
  - Anticoagulation D/C 3 mo after RFCA in the majority of 522 successful pts
  - Median F/U 25 mo, 0 CVA
  - Study cohort had a very low baseline CVA risk, mean age 55y, mean EF 56%, 3% CHF
- Thus, even after successful RFCA, pts should be risk stratified by CHADS2 score

Oral H et al Circ 2006
Issues with RFCA for AF

- Recurrence increases as the intensity of monitoring increases
- Recurrence increases with longer F/U
  - F/U data only reported up to 3 y
- Iatrogenic arrhythmias
  - Burden of iatrogenic AT/AFL not considered in success rates
Deficiencies in Current RFCA Technique

• Delayed clinical response, ~3 mo
• EP outcomes may not correspond to clinical outcomes
• Partial responses are very frequent
  – Multiple procedures necessary in ~1/3 of pts
  – Hybrid therapy with drugs necessary in ~1/3 to 1/2 of pts
• Asymptomatic AF recurrence
  – 60 pts asx after RFCA --> 12% had recurrence of AF 2y after RFCA
• No data on long-term efficacy
  – Several highly experienced centers report 70-95% initial success (< 1y f/u)

Oral H JCE 2004
Open Questions for RFCA for AF

- Which pts are the best candidates?
- At what stage in AF to offer the procedure?
- What are the likely long-term outcomes?
- What are long-term efficacy, morbidity, and mortality outcomes?
- ACC/AHA/ESC stresses need for sufficiently powered multicenter, randomized trials
- RFCA commonly decreases burden of AF, but the “cut-off point” for defining low risk AF burden has not been defined
- Publication bias
RFCA vs. AADs

- Direct comparisons difficult
- Pt groups heterogeneous, outcome measures vary
- Most data neither controlled nor randomized
- Observational study of 1171 consecutive pts
  - complete PVI (589 pts) or AAD (582 pts) based upon pt preference and M.D. judgment
  - Median F/U 2.5 y
  - AF recurrence 120 versus 340, HR 0.30
  - Fewer deaths, CHF, CVA, better QOL in RFCA group
- Randomized trial of 70 pts newly dx sx AF assigned to RFCA or AAD
  - At 1y F/U, RFCA lower symptomatic AF recurrence (13 vs. 63%) and hospitalization rates (9 vs 54%)
  - Higher 6 mo QOL score in RFCA

Pappone C JACC 2003
Pappone C JACC 2006
RFCA vs. AADs: Trials

- Randomized trial of 137 pts with AAD refractory persistent or paroxysmal AF
  - Further AAD alone or AAD + RFCA
  - After 1 mo blanking period, daily transtelephonic monitor for 3 mo, repeat Holters at 1, 4, 7, 10, and 13 mo
  - Median F/U of 12 mo, RFCA 56% NSR, AAD 9% NSR

- Randomized trial of 198 pts with longstanding (mean 6y) AAD refractory PAF randomized to another AAD or RFCA
  - After 1 y F/U, RFCA 86% NSR, AAD 22% NSR
  - Very low rates of structural heart disease (4 to 7%), mean LVEF 60%

- Randomized trial in chronic AF: 146 pts assigned to RFCA or amiodarone
  - < 10% structural heart disease, daily transtelephonic monitoring
  - At 1 y, 74% RFCA arm NSR off amio, but 32% required repeat RFCA
  - 77% crossover
  - AAD arm only 3 mo of low-dose amiodarone + 2 DCCV

Stabile G _Eur Heart J_ 2006
Oral H _NEJM_ 2006
RFCA vs. AADs

- Pt selection in observational study -- high likelihood of bias
- AAD refractory pts
- Intensity of F/U monitoring highly variable
- Inadequate AAD dosing
- High crossover rates from AAD to RFCA arm
- RFCA can produce long-term restoration of NSR in pts with paroxysmal or chronic, AAD refractory AF and minimal structural heart disease
- Efficacy of RFCA in those with structural or pulmonary disease unknown
- Relative efficacy of RFCA vs. appropriately dosed and prolonged AAD is unknown
- Relative efficacy of RFCA vs. AAD as first line therapy has never been studied
Complications with RFCA for AF

- CVA 0-5%
- Perforation
- Iatrogenic left AT/AFL, sx up to 20%
- Pericardial effusions (asx or sx)
- Symptomatic pericarditis
- Atrioesophageal fistula
  - Rare but lethal
  - Risk factors undefined
- Pyloric spasm and gastric hypomotility 1.1%
  - Indigestion after RFCA ~15% (usually transient)
- PV stenosis, previously up to 3%
  - Subclinical PV stenosis rate unknown
  - Long-term effects unknown
- Air embolism
- MV chordae tear with acute MR
Complications with RFCA for AF

Major Complications With Pulmonary Vein Ablation in 1,049 Patients (7 Series)

- Air emboli: n=5
- Bradycardia: n=3
- Tamponade: n=13
- TIA: n=8
- CVA: n=3
- PV stenosis: n=4
- Phrenic nerve: n=1
- PV dissect: n=1

Packer D JCE 2003
Other Deleterious Effects After RFCA

- Beyond overt complications, unknown potential deleterious effects
- Silent embolic CNS events
- Subclinical PV stenosis
- Left atrial mechanical dysfunction
- Effects of autonomic modulation
- Recurrent asx AF episodes
- Exposure to fluoroscopy, 60-120 min per procedure
Comparative Costs of RFCA and AADs for AF

- **France**
  - Cost comparison favored RFCA after 5 y
  - Assumes continuous 5y success of 72%, but only validated to 32 w

- **Canada**
  - Costs for AAD and RFCA meet between 3-8 y
  - Assumes success of 50-75% for 1st RFCA, 60-85% after 2nd, 70-90% after 3rd

- **US: Markov decision model**
  - RFCA: 11.1 QALY, $52K
  - Rate control: 10.8 QALY, $39K
  - Rhythm control: 10.8 QALY, $43K
  - Incremental cost effectiveness
    - $51K per QALY for pts w/ moderate CVA risk
    - $99K per QALY for pts w/ low CVA risk

Weerasooriya R PACE 2003
Khaykin Y JCE 2007
Chan PS JACC 2006
Real-World AF RFCA Experience

- Operator and center experience highly important
- Clinical practice surveys indicate lower success rates than reported in clinical trials
  - 181 centers, 11,762 AF RFCA procedures in 9370 pts
  - Mean success rates off AAD:
    - 53% for paroxysmal AF (65 centers)
    - 49% for paroxysmal/persistent AF (17 centers)
    - 57% for all forms of AF (8 centers)
  - Overall complication rate 6%, but death (0.05%) and TIA/CVA (0.66%) rare
- 4x increase in AF RFCA procedures between 2000-03
- Academic centers accounted for 64% of all RFCA procedures and had significantly better short- and long-term success rates
Determinants of Primary Therapy

• Issue is not whether ablation cure is useful or achievable in many pts, but whether it is appropriate as “first-line” therapy
• Evidence-based short- and long-term efficacy and safety
• Complications and risk for AADs known in certain risk groups
• Complications of RFCA can occur in any pt, including those with normal hearts
• Later effects of RFCA not known
Patient Subgroups for RFCA as Primary Therapy

- Mild or no structural heart disease
- Highly sx pts with clearly focally triggered AF
- Highly sx pts with contraindications to AADs
- Centers with high volume, experience
- Treatable causes should be addressed:
  - Alcohol
  - Obesity
  - Sleep apnea
Conclusions

- RFCA not ready for prime time as primary therapy
- Only AF pts who are sx should be considered for rhythm control
- Only those failing at least 1 AAD
- Only those understanding risks of procedures, unknowns of long-term effects
- Up to 50% of RFCA pts will take AADs anyway
- No data for D/C warfarin after successful RFCA, so many pts will take warfarin anyway
- Taking evidence-based approach may delay some pts for RFCA until techniques improve, long-term outcomes are known