RACE-II: Lenient <110 bpm versus Strict <80 bpm Rate Control in Patients with Atrial Fibrillation[1]

The RAte Control Efficacy in Permanent Atrial Fibrillation: a Comparison between Lenient versus Strict Rate Control II

BOTTOM LINE

- In a relatively low risk population, lenient rate control was as effective as strict rate control for preventing cardiovascular events in patients with permanent atrial fibrillation (AF). The targeted resting heart rate (HR) for the lenient control group was set for <110 beats per minute (bpm) & <80 bpm for the strict control group, and the mean resting HR by the end of the study was 85 ±14 bpm & 76 ±14 bpm, respectively.
- Less stringent rate control was not more harmful, and may be beneficial. The target heart rate in the lenient rate control strategy group was easier to achieve, with fewer medications, lower doses & less physician visits.
- The Canadian Cardiovascular Society Atrial Fibrillation Guidelines recommend a target resting HR of <100 bpm for patients with persistent or permanent AF and atrial flutter.[2] Prior to RACE II, the recommended target resting HR was <80 bpm.[3] However, the Guideline panel selected 100 bpm, instead of 110 bpm, since the majority of patients in the RACE II lenient rate control group had a HR of <100 bpm over 3 years.
- Patients may remain symptomatic regardless of which rate control approach is used. The degree of symptoms is also linked to the severity of underlying cardiac disease, age & gender. The target HR should be tailored to patient symptoms & preferences.

BACKGROUND

- AFFIRM, RACE, PIAF, STAF & HOT-CAFÉ demonstrated that rate versus rhythm control in AF patients resulted in similar mortality & morbidity outcomes.[4,5,6,7,8] Subsequently, rate control has become the preferred strategy for many AF patients.[3]
- The previous recommended target HR of <80 bpm was based on epidemiological studies involving patients with a similar degree of heart disease but in normal sinus rhythm. The optimal level of HR control in AF patients was unknown.
- Strict rate control (<80 bmp):
  - Proposed advantages: ↓ symptoms & HF; improved QOL, hemodynamics, exercise tolerance & survival.
  - Proposed disadvantages: high doses → ↑ adverse effects (e.g. bradycardia, syncope, falls), & preventable pacemaker implantation.
- AFFIRM used strict rate control, whereas RACE employed a lenient rate control (<100 bpm).[4,5] Retrospective analysis of matched participants from these two studies showed no difference in mortality, cardiovascular hospitalization and myocardial infarction.[9]

TRIAL BACKGROUND[10]

- **DESIGN**: Randomized, multi-centre 33 centres in the Netherlands, non-inferiority, open-label, blinded endpoint adjudication, intention-to-treat controlled trial with concealed allocation. Funded by Netherlands Heart Foundation & unrestricted educational grants from pharmaceutical & device companies.
- **INTERVENTION**: strict rate control strategy → target resting HR <80 bpm & moderate exercise HR <110 bpm, versus
  lenient rate control strategy → target resting HR <110 bpm
  Rate control medication: mono- or combination therapy with β-blocker, calcium channel blocker & digoxin. Doses were titrated & medications added every two weeks until the target HR was achieved.
- **INCLUSION**: permanent AF ≤ 1 year confirmed by ECG x 2, ≤ 80 years old, mean resting HR >80 bpm with or without rate control medications & current use of an oral anticoagulant or ASA if no thromboembolic risk factors.
- **EXCLUSION**: paroxysmal AF; CI to strict or lenient rate control e.g. previous AE on negative chronotropic drugs; unstable HF NYHA IV or hospitalization for HF <3 months prior; cardiac surgery <3 months prior; any stroke; current or foreseen pacemaker, internal cardioverter defibrillator &/or cardiac resynchronization therapy; signs of sick sinus syndrome or AV conduction disturbances i.e. symptomatic bradycardia or asystole >3 seconds or escape rate <40 bpm in awake symptom free patients; untreated hyperthyroidism or <3 months euthyroidism; inability to walk or bike.
- **POPULATION** at baseline (n=614 over a minimum of 2 years & a maximum of 3 years): Age 68 ±8 years; ~65% ♂; median duration any AF 18 months interquartile range 6-60 months, median duration of permanent AF 3 months interquartile range 1-6 months; previous electrical cardioverson ~72%, HTN ~61%, CAD ~18%, valvular heart disease ~20%, COPD 13%, DM 11%, lone AF ~2%, previous hospitalization for HF ~10%; CHADS2 score: ≤1 ~61%, =2 ~26%, =3-6 ~13%; palpitations ~24%, dyspnea ~35%, fatigue ~30%; BMI 29 kg/m^2 ±5; mean resting heart rate 96 bpm ±13; NYHA class I 65%, II 30%, III ~5%; rate control medication use ~90%: β-blocker 45%, verapamil or diltiazem 6%, digoxin ~7%, β-blocker + verapamil or diltiazem ~3%, β-blocker + digoxin ~17%, β-blocker 45% + digoxin + verapamil or diltiazem 1.1%, sotalol 5%, amiodarone ~1% (note: overall, 65.6% of patients were on a β-blocker as either mono- or combination therapy); other baseline medications: ACE-I or ARB ~50%, diuretic ~40%, statin ~29%, vitamin K antagonist ~98%, ASA ~2%; left ventricular ejection fraction ≤40% ~15%.
  - Differences in baseline characteristics: see comment section in Table 1
    - Lenient rate control group had a higher prevalence of CAD, statin & ACE-I/ARB use, $CHADS_2$ score of 2 & higher DBP.
    - Strict rate control group had a longer median duration of any AF & higher prevalence of palpitations.

RESULTS

follow-up: minimum 2 years, maximum 3 years (ITT)

TABLE 1: EFFICACY & SAFETY

CLINICAL ENDPOINTS	LENIENT RATE CONTROL (n=311)	STRICT RATE CONTROL (n=303)	HR (90% CI) non-inferiority margin 1.40	COMMENTS
PRIMARY ENDPOINT: composite of death from CV causes; hospitalization for HF; stroke; systemic embolism; major bleeding; arrhythmic events including syncope, sustained ventricular tachycardia, cardiac arrest; life-threatening adverse effects of rate-control drugs & implantation of a pacemaker or cardioverter-defibrillator.				
Composite see above	**12.9% (n=38)**	**14.9% (n=43)**	**0.84 (0.58-1.21)**	**Primary Composite Endpoint:** - HR 0.8 (90% CI, 0.55-1.17) after statistically adjusting for ↑ CAD, statin use & DBP in the lenient group. Other baseline differences were not adjusted for.
SECONDARY ENDPOINTS				
Death from CV causes	2.9% (n=9)	3.9% (n=11)	0.79 (0.38-1.65)	
Hospitalization for HF	3.8% (n=11)	4.1% (n=11)	0.97 (0.48-1.96)	
Stroke	**1.6% (n=4)**	**3.9% (n=11)**	**0.35 (0.13-0.92)**	**Stroke:** also see Sub-group Analysis - INR TTR:[11] Lenient 50.4% vs Strict 50.5%, NS
Systemic embolism	0.3% (n=1)	0	-	**Non-Inferiority vs Superiority**: Had the same results occurred in a higher powered trial & tested for superiority: - 1° Endpoint: NNT=50 (i.e. one less event per 50 patients in the lenient rate control group over 3 years). - Stroke: **NNT=44** (95% CI 21-942)
Bleeding	5.3% (n=15)	4.5% (n=13)	1.12 (0.6-2.08)	
Syncope	1% (n=3)	1% (n=3)	-	
Life-threatening adverse events	1.1% (n=3)	0.7% (n=2)		
Sustained ventricular tachycardia or fibrillation	0	0.3% (n=1)		**Sub-group Analysis for 1° Outcome:** - $CHADS_2$ <2: lenient 11.8% vs Strict 9.2%, p=0.02 - $CHADS_2$ ≥2: lenient 12.8% vs Strict 23%, p<0.001
Cardioverter-defibrillator implantation	0	0.3% (n=1)		
Pacemaker implantation	0.8% (n=2)	1.4% (n=1.4)		**Other Outcomes at End of Follow-up:** - NS for AF symptoms (dyspnea, fatigue, palpitations), hospitalizations & adverse events.
Death from any cause	5.6% (n=17)	6.6% (n=18)	0.91 (CI 0.52-1.59)	

TABLE 2: ADDITIONAL DATA ON RATE-CONTROL TARGETS & DRUG THERAPY

RATE-CONTROL TARGETS & DRUG THERAPY	LENIENT RATE CONTROL (n=311)	STRICT RATE CONTROL (n=303)	P-VALUE	COMMENTS
AT END OF DOSE-ADJUSTMENT PHASE (doses titrated & medications added every 2 weeks until the target HR was achieved)				
Resting HR – mean ± SD	93 ±9 bpm	76 ±12 bpm	p<0.001	**Sub-group Analysis for 1° Outcome:** - Outcome was similar across HR categories, **at the end of the dose-adjustment period**. **Difference in Resting HR**: - From 1 year till the end of the study, the difference in HR between the two groups was only 9-11 bpm. **Dose of Rate Control Agents:** Diltiazem: NS difference in dose Digoxin: - Lenient 0.19±0.8mg vs Strict 0.21±0.8mg, NS. - Serum concentration levels were not available.[11]
Visits to achieve target resting HR n (median, interquartile range)	75 (0, 0-0)	684 (2, 1-3)		
Failure to reach target HR due to drug-related adverse events	0	8.3% (n=25)		
Rate control with no therapy	10.3% (n=32)	1% (n=0.3)		
Rate control* with monotherapy	55% (n=171)	27% (n=82)	- Lenient: > BB or dig monotx - NS for CCB monotherapy	
Rate control* with dual therapy	29% (n=90)	59% (n=180)	- Strict: > BB+CCB or BB+dig - NS for CCB + digoxin	
Rate control* with triple therapy	1% (n=3)	8.9% (n=29)	p<0.001	
Dose of β-blocker† - mean ± SD	120 ± 78mg	162 ± 85mg		
Dose of verapamil - mean ± SD	166 ± 60mg	217 ± 97mg		
RESTING HEART RATE AT OTHER TIME POINTS (mean ± SD)				
After 1 year	86 ±15 bpm	75 ±12 bpm	p<0.001	
After 2 years	84 ±14 bpm			
End of follow-up	85 ±14 bpm	76 ±14 bpm		

*Rate control medications included β-blocker, calcium channel blocker (verapamil or diltiazem) & digoxin

† normalized to metoprolol equivalent doses

STRENGTHS, LIMITATIONS, & UNCERTAINTIES

STRENGTHS: ♦ first RCT to assess rate control strategies in AF

LIMITATIONS: ♦low risk population ♦non-inferiority study with intention-to-treat but without per-protocol analysis (PPA) see below ♦open-label design ♦small population size n=614 ♦short study duration 2-3 years for the type of outcomes assessed in a low risk group ♦some baseline characteristics differed between the two groups

UNCERTAINTIES: ♦the true difference between patients with lenient versus strict rate control intention-to-treat was used, but per-protocol analysis was not included ♦best rate control strategy for moderate to high risk patients ♦ impact of lenient versus strict rate control on severity of AF symptoms only assessed prevalence of symptoms ♦is lenient rate control better than strict rate control only tested for non-inferiority, not superiority ♦ the authors stated quality of life was assessed, but these results were not reported

Non-inferiority Studies: Intention-to-treat vs Per-Protocol Analysis[12,13,14]

For **superiority trials**, intention-to-treat (ITT) analysis is recommended. ITT analyzes patients in the study group they were assigned to, regardless of whether they actually received the treatment or not. ITT maintains randomization & has a conservative effect on outcome. However, it may underestimate adverse drug reactions as patients who did not receive the treatment are included in the safety analysis.

For **non-inferiority** trials, it is recommended that both ITT & per-protocol analysis (PPA) be done. PPA analysis excludes patients who violated study protocol (e.g. patients who crossed over to the other group, were lost to follow-up, were non-compliant, etc). The concern with ITT & non-inferiority trials is that the study groups may end up being similar in terms of the intervention – & non-inferiority trials are designed to show no difference in outcomes between the study groups. As such, a PPA analysis may be a better estimate of the true difference from exposure to the intervention. However, PPA may be biased in favour of the intervention.

As mentioned above, ideally both ITT & PPA analysis are included in a non-inferiority trial. If the results of both the ITT & PPA analysis are similar, the reader can have greater confidence in the study results.

For additional information on non-inferiority trials, refer to the Reporting of Noninferiority and Equivalence Randomized Trials: An Extension of the CONSORT Statement: http://www.ncbi.nlm.nih.gov.cyber.usask.ca/pubmed/16522836

♂=male **1°**=primary **ACE-I**=angiotensin converting enzyme inhibitor **AE**=adverse event **AF**=atrial fibrillation **ARB**=angiotensin receptor blocker **ASA**=acetylsalicylic acid **AV**=atrioventricular **BB** or **β-blocker**=beta blocker **BMI**=body mass index **bpm**=beats per minute **CAD**=coronary artery disease **CCB**=calcium channel blocker **$CHADS_2$**=congestive heart failure, HTN, age >75 years, DM, stroke or transient ischemic attack **CI**=contraindicated **CI**=confidence interval **COPD**=chronic obstructive pulmonary disease **DBP**=diastolic blood pressure **DM**=diabetes mellitus **ECG**=electrocardiogram **HF**=heart failure **HR**=hazard ratio & heart rate **HTN**=hypertension **INR**=international normalized ratio **ITT**=intention to treat **NNT**=number needed to treat **NS**=non-significant **NYHA**=New York Heart Association **RCT**=randomized controlled trial **SD**=standard deviation **TTR**=time in therapeutic range **tx**=therapy **QOL**=quality of life

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