EDITORIAL COMMENT

Lenient Versus Strict Rate Control in Atrial Fibrillation

Some Devils in the Details*

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At the turn of the century, a spate of randomized, controlled trials (RCTs) compared the 2 main pharmacological options for rhythm management for atrial fibrillation (AF): repeated attempts to restore and maintain sinus rhythm (rhythm control) and controlling the heart rate without any specific attempts to restore and maintain sinus rhythm (rate control) (1). Largely driven by results of the 2 largest studies (2,3), these RCTs showed little or no advantage with rhythm control. If anything, there was a trend for an advantage with rate control with respect to death, stroke, and cost (1,4). Similar “no difference” results were noted later for AF patients with congestive heart failure and reduced systolic function (5). A plethora of studies of various aspects of rate control should have followed such results. With the exception of RACE II (RAte Control Efficacy in permanent atrial fibrillation II), that has not happened.

See page 942

The paucity of new research on rate control for AF reflects one of the current problems with cardiovascular research. Whether we like it or not, the importance of publicly funded cardiovascular research has declined dramatically over the past 40 years. The current cardiovascular research agenda is driven largely by corporate-sponsored research. As there are few or no new products for rate control in AF, research on rate control for AF is an orphan. This research void exists despite the current AF epidemic (6).

Heart rate control for self-terminating and brief episodes of AF is empirical. There is no evidence that brief episodes of AF lead to anything more than transient deterioration of ventricular function, unless there has been a preceding episode of tachycardia-induced cardiomyopathy (7). It is likely that a wide and lenient range of rates is acceptable in paroxysmal AF, provided that symptoms of AF are tolerable.

The concept of heart rate targets only applies to more continuous persistent/permanent AF. There is truly a scant evidence base for the goals of ideal or even acceptable heart rate control for AF. Unanswered questions about heart rate control for AF are numerous. What was known before RACE II is based largely on relating R-R intervals or heart rate to hemodynamic measurements, usually derived from echocardiograms, in a trifling number of studies in a perilously small number of patients (8). The AFFIRM (Atrial Fibrillation Follow-up Investigation of Rhythm Management) investigators and the RACE II investigators compared outcomes with heart rates resulting from their own rather arbitrary rate control criteria (RACE II = resting heart rate <100 beats/min; AFFIRM = resting heart rate <80 beats/min plus criteria for activity heart rate; average resting heart rate = 83 vs. 76 beats/min, RACE II vs. AFFIRM) and showed no difference between the 2 for the composite outcome of death, cardiovascular hospitalization, or myocardial infarction (9). Such a post hoc analysis has a number of weaknesses.

To my knowledge, RACE II (10,11) is the first and only moderate-sized RCT that prospectively compared different criteria for heart rate control using clinical events as outcome measures. In this respect, it is a unique and important study. It provides the first objective information concerning clinical criteria for satisfactory rate control for AF. That is not to concede that it is the definitive word on this subject. Indeed there are some “devils in the details.”

The first “devil” is found in the heart rates achieved in the 2 arms of the study. In the main report, heart rates achieved are listed as those at the end of “titration” (median time after randomization: lenient = 0 weeks, strict = 4 weeks) (11). However, in the electronic supplement, the average heart rates over the 3-year duration of the study were approximately 85 (lenient) beats/min and 75 (strict) beats/min. Thus, the difference in heart rates between the 2 groups is rather modest and similar to that seen comparing AFFIRM and RACE II, despite the implication from the criteria themselves or from the rates at the end of “titration.” Importantly, the mean heart rates achieved in both groups are considerably <100 beats/min.

The second “devil” is the composite primary outcome chosen to overcome the modest size of the study. There are at least 8 components in the composite (10,11). Individual components are almost certainly not all of equal or near-equal value or importance. In some cases, it is difficult to imagine how heart rate would have an important impact (e.g., the risk of bleeding).

For these reasons, the results of RACE II require some interpretation before they are applied. The recently updated AF treatment guidelines (12) have not been circumspect

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enough on this point. As the criterion now listed in the
guidelines is a resting heart rate <110 beats/min (12), there
is an implication that a resting heart rate >100 beats/min is
acceptable. Examining the mean resting heart rate and its
variance from 1 year onward in RACE II (11), it is
extremely unlikely that any more than a handful of patients
in the lenient heart rate group had heart rates >100
beats/min. Furthermore, in the previously cited and larger
AFFIRM/RACE substudy, heart rates >100 beats/min in
permanent AF patients significantly increased risk com-
pared with successfully achieving either the AFFIRM or the
RACE rate control criteria (9). Accordingly, it seems
imprudent to imply that resting heart rates >100 beats/min
are acceptable.

In this issue of the Journal, the RACE II investigators
present the results of a pre-specified substudy concerning
the impact of lenient or strict rate control on structural
cardiac remodeling (13). Structural cardiac remodeling dur-
ding AF is an important pathophysiological process, insofar
as atrial enlargement, ventricular enlargement, reduced sys-
tolic function, and ventricular diastolic dysfunction can all
contribute to important clinical outcomes such as stroke and
congestive heart failure. In this substudy, differences in left
atrial and left ventricular end-diastolic dimensions measured
echocardiographically at baseline and at the end of the study
were related to baseline clinical variables and treatment
assignment (lenient vs. strict rate control). Although as-
signed treatment had no significant impact on changes in
cardiac chamber size, female sex did. These findings are of
interest, but, once again, there are “devils” in the details.

There was actually a “trend” for small (approximately 1-
to 2-mm and 3-ml differences between groups) favorable
changes in left atrial and ventricular size in the strict group
over the duration of the study. The study is too small to
exclude the possibility of a statistically significant differential
effect of this magnitude. It seems unlikely, but not impos-
sible, that a difference of this magnitude is important
clinically for some of the events in the primary outcome
measure. Once again, it is difficult to relate changes in these
echocardiographic measures to all the components of the
primary outcome in RACE II.

The main “devil” in the substudy is that there is little or
no background information about the time course of struc-
tural remodeling from the onset of AF in humans. The time
course of structural cardiac remodeling from the onset of AF
has been studied in animal models (14). Something is also
known about the time course of reverse remodeling after
initiation of rhythm management in humans (15). There
may be little structural change in the first couple of months
after the onset of AF (16). Some structural remodeling may
certainly begin before the onset of AF and be a “cause” rather
than an “effect.” We know from clinical observation that
tachycardia-induced cardiomyopathy takes some time to
develop (7). Like most things in biology, the time course of
structural remodeling during AF is probably curvilinear.
The patients in RACE II were enrolled with permanent
AF, and their median duration of any AF and permanent
AF was around 18 and 3 months, respectively. Where is the
steep part of the curve for structural remodeling in relation
to the onset of AF, and when exactly does it begin? The
time of intervention in RACE II may have affected the
opportunity to demonstrate a difference between the 2
treatments. Furthermore, there is no information on the
adequacy of rhythm management before enrollment in
RACE II. “Good” or “bad” rhythm management before
enrollment could affect the ability to observe a difference
between treatments in the substudy.

One can also quibble with the methodology used in
RACE II. Would atrial volume have been a better outcome
measurement if available for all patients? Would there have
been differences if there were a measurement of diastolic function? Finally, it is important to note that the number of
baseline variables is rather modest. Particularly with respect
to the finding concerning female sex, it remains possible
that other factors make important contributions to struc-
tural cardiac remodeling during AF that are not accounted
for in the model and could potentially negate the finding
with respect to sex. Thus, although the findings of this
substudy are novel and important, they raise as many
questions as they answer. More research on these important
issues is needed. Perhaps RACE II will provide a stimulus
for further research in this area.

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