

RATE VS. RHYTHM CONTROL FOR ATRIAL FIBRILLATION:

THE AFFIRM TRIAL⁵⁵

“[In older patients with atrial fibrillation and cardiovascular risk factors] the strategy of restoring and maintaining sinus rhythm [has] no clear advantage over the strategy of controlling the ventricular rate ...”

- The AFFIRM Investigators⁵⁵

Research Question: Should patients with atrial fibrillation be managed with a strategy of rate-control or rhythm-control?

Funding: The National Heart, Lung, and Blood Institute.

Year Study Began: 1997

Year Study Published: 2002

⁵⁵ The AFFIRM Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. N Engl J Med. 2002 Dec 5;347(23):1825-33.

Study Location: 200 sites in the U.S. and Canada

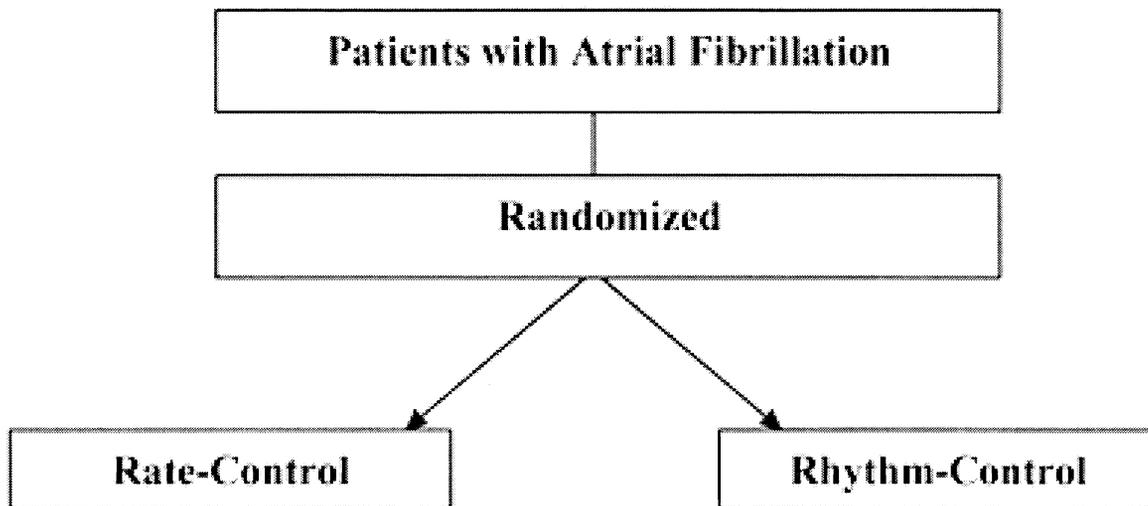
Who Was Studied: Adults with atrial fibrillation who were at least 65 or who had other risk factors for stroke. In addition, only patients likely to have recurrent atrial fibrillation requiring long-term treatment were eligible.

Who Was Excluded: Patients in whom anticoagulation was contraindicated.

How Many Patients: 4,060

Study Overview:

Figure 1: Summary of AFFIRM's Design



Study Intervention: Patients in the rhythm-control group received antiarrhythmic drugs (most commonly amiodarone and/or sotalol) at the discretion of the treating physician. If needed, physicians could attempt to cardiovert patients to sinus rhythm. Anticoagulation with warfarin was encouraged, but could be stopped at the physician's discretion if the patient remained in sinus rhythm for at least 4 (and preferably 12) consecutive weeks.

Patients in the rate-control group received beta-blockers, calcium-channel blockers, or digoxin at the discretion of the treating physician. The target heart rate was ≤ 80 beats per minute at rest and ≤ 110 beats per minute during a six-minute walk test. All patients in the rate-control group received anticoagulation with warfarin.

Follow-Up: Mean of 3.5 years

Endpoints: Primary outcome: All-cause mortality. Secondary outcomes: A composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest; and hospitalizations.

RESULTS:

- in the rate-control group, at the five-year visit, 34.6% of patients were in sinus rhythm and over 80% of those in atrial fibrillation had adequate heart rate control
- in the rhythm-control group, at the five-year visit, 62.6% of patients were in sinus rhythm
- after five years, 14.9% of patients in the rate-control group crossed over to the rhythm-control group, most commonly due to symptoms such as palpitations or episodes of heart failure
- after five years, 37.5% of patients in the rhythm-control group crossed over to the rate-control group, most commonly due to an inability to maintain sinus rhythm or due to drug intolerance
- throughout the study, more than 85% of patients in the rate-control group were taking warfarin compared to approximately 70% of patients in the rhythm-control group; most strokes in both groups occurred among patients not receiving a therapeutic dose of warfarin

Table 1: Summary of AFFIRM's Key Findings

Outcome	Rate-control Group	Rhythm-control Group	P Value
All-cause mortality	25.9%	26.7%	0.08
Composite of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, and cardiac arrest	32.7%	32.0%	0.33
Hospitalizations	73.0%	80.1%	<0.001

Criticisms and Limitations: The trial did not include young patients without cardiovascular risk factors, especially those with paroxysmal atrial fibrillation, and therefore the results may not apply to these patients.

In addition, approximately half of the patients in the study had symptomatic episodes of atrial fibrillation less than once a month. It is possible that patients with more frequent or persistent symptoms would derive a benefit from rhythm-control.

Other Relevant Studies and Information:

- A number of smaller randomized trials comparing rate-control and rhythm-control in patients with atrial fibrillation have come to similar conclusions as AFFIRM^{56,57,58,59}
- Trials comparing rate-control vs. rhythm-control in patients with atrial fibrillation and heart failure have also failed to show a benefit of rhythm-control^{60,61}

SUMMARY AND IMPLICATIONS:

In high risk patients with atrial fibrillation, a strategy of rate-control is at least as effective as a strategy of rhythm-control. Rhythm-control does not appear to obviate the need for anticoagulation. Because the medications used for rate control are usually safer than those used for rhythm control, rate-control is the preferred strategy for treating most high risk patients with atrial fibrillation. These findings do not necessarily apply to younger patients without cardiovascular risk factors who were not included in AFFIRM, however.

56 Van Gelder IC et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med.* 2002;347(23):1834-40.

57 Hohnloser SH et al. Rhythm or rate control in atrial fibrillation—Pharmacological Intervention in Atrial Fibrillation (PIAF): a randomised trial. *Lancet.* 2000;356(9244):1789-94.

58 Carlsson J et al. Randomized trial of rate-control vs. rhythm-control in persistent atrial fibrillation: the Strategies of Treatment of Atrial Fibrillation (STAF) study. *J Am Coll Cardiol.* 2003;41(10):1690-6.

59 Opolski G et al. Rate control vs rhythm control in patients with nonvalvular persistent atrial fibrillation: the results of the Polish How to Treat Chronic Atrial Fibrillation (HOT CAFE) Study. *Chest.* 2004;126(2):476-86.

60 Roy D et al. Rhythm control vs. rate control for atrial fibrillation and heart failure. *N Engl J Med.* 2008;358(25):2667-77.

61 Kober et al. Increased mortality after dronedarone therapy for severe heart failure. *N Engl J Med.* 2008;358(25):2678-87.

CLINICAL CASE: RATE VS. RHYTHM CONTROL IN ATRIAL FIBRILLATION

CASE HISTORY:

A 75 year old woman with diabetes and hypertension is noted on routine examination to have an irregular heart rate of approximately 120 beats per minute. She denies chest pain, shortness of breath, and other concerning symptoms. An EKG confirms a diagnosis of atrial fibrillation.

Based on the results of AFFIRM, how should this patient be treated?

SUGGESTED ANSWER:

AFFIRM showed that rate-control is at least as effective as rhythm-control for managing atrial fibrillation. Because the medications used for rate control are usually safer than those used for rhythm control, rate-control is generally the preferred strategy for managing the condition.

The patient in this vignette is typical of patients included in AFFIRM. Thus, she should be treated initially with a rate-control strategy (beta-blockers are frequently used as first-line agents). In the unlikely event that this patient's heart rate could not be controlled or if she were to develop bothersome symptoms that did not improve with a rate-control strategy, rhythm-control might be considered. In addition, this patient should receive anticoagulation to reduce her risk for stroke.

MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM²⁰⁶

“This study provides strong evidence against the hypothesis that MMR vaccination causes autism.”

- Madsen et al.²⁰⁶

Research Question: Does the Measles, Mumps, and Rubella vaccine (MMR) cause autism?

Funding: The Danish National Research Foundation, the Centers for Disease Control and Prevention, and the National Alliance for Autism Research.

Year Study Began: data from 1991 – 1999 were included (the data were collected retrospectively)

Year Study Published: 2002

Study Location: Denmark

²⁰⁶ Madsen et al. A population-based study of measles, mumps, and rubella vaccination and autism. NEJM. 2002 Nov 347;19: 1477-1482.

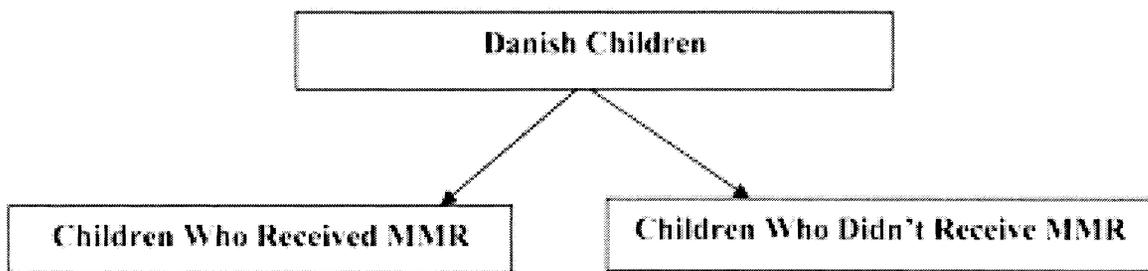
Who Was Studied: All children born in Denmark between January 1991 and December 1998 (all Danish children are entered into a national registry at birth).

Who Was Excluded: Children with tuberous sclerosis, Angelman's syndrome, fragile X syndrome, and congenital rubella – all of which are associated with autism.

How Many Patients: 537,303 children, 82% of whom received the MMR vaccine and 18% of whom did not.

Study Overview: The rates of autism among children who received the MMR vaccine were compared to the rates among those who did not.

Figure 1: Summary of the Study's Design



The authors used data from the Danish National Board of Health to determine which children received the MMR vaccine as well as the age of vaccine administration. The national vaccination program in Denmark recommends that children receive the MMR vaccine at 15 months of age followed by a booster at the age of 12 years.

Children were identified as having autism, as well as other autistic-spectrum disorders, using data from a national psychiatric registry (in Denmark, all patients with suspected autism are referred to child psychiatrists, and when a diagnosis of autism is made it is entered into the registry). The authors also recorded the date when the diagnosis was made, allowing them to determine the time interval between vaccine administration and autism diagnosis.

The authors controlled for differences between vaccinated and unvaccinated children. They did this by adjusting for factors such as age, sex, socioeconomic status, mother's education level, and the child's gestational age at birth.

Follow-Up: Children were monitored for autism from the time they reached one year of age until the end of the study period (December 31, 1999). The mean age of children at the end of the study period was approximately 5 years.

Endpoints: Rates of autism and rates of autistic-spectrum disorders.

RESULTS:

- 82% of children in the study received the MMR vaccine, and the mean age of vaccination was 17 months
- among children diagnosed with autism, the mean age of diagnosis was 4 years and 3 months
- the prevalence of autism among eight-year-olds in the study was 7.7 per 10,000 (0.08%), which was consistent with rates from other countries at the time

Table 1: Summary of the Study's Key Findings

Outcomes	Adjusted Relative Risk of Autism Among Vaccinated vs. Unvaccinated Children^a (95% Confidence Intervals)
Autism	0.92 (0.68-1.24)
Autistic-Spectrum Disorders	0.83 (0.65-1.07)

^aA relative risk <1.0 means a lower rate of autism among vaccinated children compared with unvaccinated children.

- there was no clustering of autism diagnoses at any time interval after vaccination, nor was there an association between the age at which the vaccine was given and the subsequent development of autism (arguing against a link between vaccination and the development of autism)

Criticisms and Limitations: The authors attempted to control for differences between vaccinated and unvaccinated children. However, since this was not a randomized trial, it is possible that the authors did not control for all potential confounders. For example, parents of children with a family history of autism may have been more likely to withhold vaccination because of media reports warning about a link between the MMR vaccine and autism. As a result, children with a family history of autism – and presumably an increased risk – may have disproportionately opted not to be vaccinated, potentially masking an increased rate of autism due to the vaccine.

In addition, although the authors did not identify a clustering of autism diagnoses at various time intervals following vaccination, the dataset did not contain the date when the first symptoms of autism were noted. Thus, it is

possible that there was a clustering of first autism symptoms – but not diagnoses – at certain time intervals following vaccination.

Other Relevant Studies and Information:

- Children typically begin to show signs and symptoms of autism in the second and third years of life – shortly after most guidelines recommend that children receive the MMR vaccine. This may explain why some parents (and experts) associate the vaccine with autism.
- Several other observational studies have also failed to show a link between the MMR vaccine and autism^{207,208,209}. Several studies have also failed to show a link between thimerosal – a mercury-containing ingredient that used to be included in many childhood vaccines – and autism^{210,211,212}.
- One widely cited article²¹³, which was subsequently retracted by the journal that published it²¹⁴, reported on a series of children who appeared to develop GI symptoms as well as signs of autism soon after receiving the MMR vaccine. The article generated considerable media attention as well as concern among parents, however the results have widely been called into question due to concerns about falsified data.

SUMMARY AND IMPLICATIONS:

This large cohort study did not identify a link between MMR vaccination and autism or autism-spectrum disorders. In addition, there was no clustering

207 Taylor et al. Autism and measles, mumps, and rubella vaccine: no epidemiological evidence for a causal association. *Lancet*. 1999;353(9169):2026-9.

208 Mrozek-Budzyn et al. Lack of association between measles-mumps-rubella vaccination and autism in children: a case-control study. *Pediatr Infect Dis J*. 2010;29(5):397-400.

209 Smeeth et al. MMR vaccination and pervasive developmental disorders: a case-control study. *Lancet*. 2004;364(9438):963-9.

210 Madsen et al. Thimerosal and the occurrence of autism: negative ecological evidence from Danish population-based data. *Pediatrics*. 2003;112(3 Pt 1):604-6.

211 Hviid et al. Association between thimerosal-containing vaccine and autism. *JAMA*. 2003;290(13):1763-6.

212 Thompson et al. Early thimerosal exposure and neuropsychological outcomes at 7 to 10 years. *N Engl J Med*. 2007;357(13):1281-92.

213 Wakefield et al. Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 1998;351(9103):637-41.

214 Retraction–Ileal-lymphoid-nodular hyperplasia, non-specific colitis, and pervasive developmental disorder in children. *Lancet*. 2010;375(9713):445.

of autism diagnoses at any time interval after vaccination. These findings argue against a link between vaccination and the development of autism.

CLINICAL CASE: MEASLES, MUMPS, AND RUBELLA VACCINATION AND AUTISM

CASE HISTORY:

Nervous parents bring their 15-month old baby girl to your office. Their previous pediatrician suggested that they find a new doctor after they declined MMR vaccination for their daughter. The girl's mother is concerned about the MMR vaccine because her nephew developed symptoms of autism shortly after he was vaccinated. The parents want your perspective on the vaccine. Do the data support a link between MMR vaccination and autism? Will you care for their child if they decline vaccination?

SUGGESTED ANSWER:

This study, as well as several others, have failed to show a link between MMR vaccination and autism. In addition, the most widely cited analysis suggesting a link between MMR vaccination and autism has been called into question due to concerns about falsified data. Although none of these studies has conclusively ruled out a very small link between MMR vaccination and autism, the preponderance of evidence suggests that there is not.

One way to respond to these parents would be to explain that numerous studies of high methodological quality have failed to demonstrate a link between the MMR vaccine and autism. While it is impossible to entirely exclude a very small association, it is likely that there is not. You should also emphasize to the parents that there are clear and proven benefits of the vaccine, and that major professional organizations such as the American Academy of Pediatrics strongly recommend vaccination for all children. If the parents remain concerned, they might consider delaying vaccination for several months until the child is older.

If the parents opt not to have their daughter vaccinated, you will need to decide whether to continue caring for their child. Most physicians will care for unvaccinated children while continuing to encourage vaccination, however a small percentage choose not to.