

Abstract

Alzheimer's disease (AD) is an incurable neurodegenerative disease associated with numerous cardiac conditions such as hypertension, myocardial infarction, and heart failure despite some uncertainty regarding the pathophysiological connections. This study targeted AD clinical trials to determine the historical inclusion of cardiac conditions in AD clinical trials. The results identified a pronounced exclusion rate of 95.32% for the majority of cardiac conditions. Since there is an apparent correspondence between AD and some cardiac abnormalities, clinical trials should explore the potential benefits of co-treatment.

Background

Alzheimer's disease (AD) is an incurable neurodegenerative disease caused by an accumulation of amyloid proteins in the brain. AD is also associated with numerous comorbidities, including cardiovascular disease (CVD) and CVD risk factors (Santiago & Potashkin, 2021, 631770). For example, researchers propose that hypertension increases the risk of vascular cognitive impairment and AD (Ungvari et al., 2021, 639). Similarly, Yang et al. (2020) noted a clear relationship between AD and cardiac dysfunction, citing atrial fibrillation and heart failure as additional contributors to expedited cognitive decline. Moreover, researchers have identified a potential relationship between AD and myocardial infarction (MI) given the increased risk in those with short telomeres which protect DNA (Scheller Madrid et al., 2020, 147). To date, some pathophysiological ambiguity exists between AD and cardiac abnormalities/conditions, however, it's clear that the two are codependent.

Methods

ClinicalTrials.gov, the nation's largest clinical trials repository, was used in this study to assess the proportional inclusion of cardiac conditions in AD clinical trials (MeSHID D000544). The eligibility criteria of all AD clinical trial study reports from 1990 to 2022 were reviewed. Cardiac terms were collected and organized into inclusion and exclusion sections with the frequency of each term being the primary focus. Data were organized using the tidyverse (1.3.2) suite of R (4.2.2) packages. Search term matches were restricted to those related to specific, chronic cardiologic comorbidities. Synonymous search term matches (e.g., "CAD" and "coronary artery disease") were merged to represent one comorbid condition. Counts of term mentions per study eligibility section were converted to presence-absence data so that each search term was counted once per study in either the inclusion or exclusion criteria. Any clinical trials that lacked explicit inclusion and exclusion sections, as well as those that mentioned the same search term in both sections, were flagged and manually inspected to determine the correct term assignment. Data were analyzed using the R Stats package ('aov' function) to establish any significant trends. Figures were created using ggplot2 (3.4.0) in R. Search terms found most frequently are identified in Table 1 and illustrated in Figure 1.

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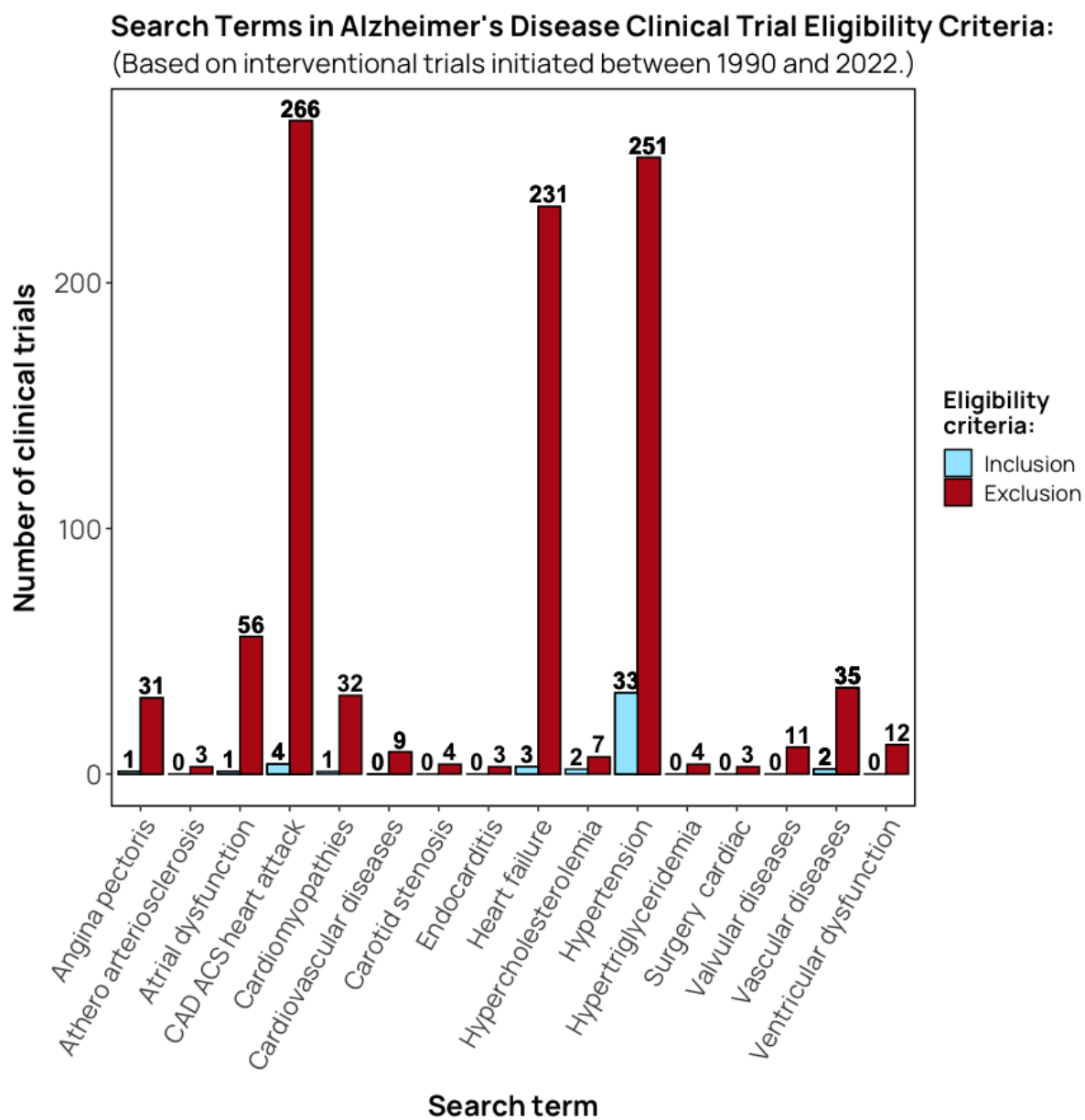
Table 1. Inclusion and exclusion frequencies of cardiovascular terms in Alzheimer's clinical trials.

Search Term	Inclusion criteria	Exclusion criteria	Term groups
Angina pectoris	1	20	Angina pectoris
Angina pectoris unstable	0	11	
Athero arteriosclerosis	0	3	Ather/ arteriosclerosis
Atrial fibrillation	1	53	Atrial dysfunction
Atrial flutter	0	3	
Acute coronary syndrome	0	14	Coronary disease/Heart attack
ACS			
Cardiac arrest	2	197	
Coronary artery disease CAD	2	55	
Cardiomyopathy	1	32	Cardiomyopathies
Cardiovascular diseases	0	6	Cardiovascular diseases
Heart diseases	0	3	
Carotid stenosis	0	4	Carotid stenosis
Endocarditis	0	3	Endocarditis
Congestive heart failure CHF	0	5	Heart failure
Heart failure	3	226	
Hypercholesterolemia	2	7	Hypercholesterolemia
Hypertension	33	248	Hypertension
Intracranial hypertension	0	2	
Pulmonary hypertension	0	1	
Hypertriglyceridemia	0	4	Hypertriglyceridemia
Surgery cardiac	0	3	Surgery cardiac
Heart valve diseases	0	11	Valvular diseases
Aortic aneurysm	0	4	
Arteritis	0	3	
Deep vein thrombosis	1	13	Vascular diseases
Giant cell arteritis	0	1	
Peripheral arterial disease	0	1	

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PAD			
Vascular diseases	1	13	
Ventricular fibrillation	0	12	Ventricular dysfunction
TOTAL:	47 (4.68%)	958 (95.32%)	

Figure 1. Comparison of inclusion and exclusion frequencies of cardiovascular terms in Alzheimer's disease clinical trials.



(Source: www.clinicaltrials.gov)

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INSERT FIGURE HERE

Results and Discussion

This study identified a total of 52 cardiovascular terms within 2686 AD clinical trials. Collectively, these terms were identified 1005 times and 958 (95.32%) were found within the exclusion section compared to 47 (4.68%) in the inclusion section of AD clinical trials. Hypertension, stroke, heart failure, myocardial infarction (MI), transient ischemic attack (TIA), and arrhythmia were found and excluded the most frequently. Of these terms, only stroke and hypertension yielded inclusion rates exceeding 10%. Heart failure, MI, TIA, and arrhythmia did not exceed inclusion rates of 2%. One-way ANOVA indicated statistically significant differences between the inclusion and exclusion frequencies ($p < .05$).

These results indicate two primary findings. First, AD clinical trials commonly consider cardiovascular conditions when determining patient eligibility. Second, cardiovascular conditions are almost exclusively prohibited in AD clinical trials with the exception of hypertension and stroke. Even arrhythmia was excluded from AD clinical trials at disproportionate rates despite no significant relationship between atrial fibrillation and AD (Proietti et al., 2020, 106). Based on these data and the correspondence between AD and cardiovascular dysfunction, it's necessary to explore the cotreatment of these conditions in clinical trials to understand the potential for reduced cognitive impairment and cardiovascular function, amongst other potential benefits. Future clinical trials should target AD patients with comorbid cardiovascular conditions.

References

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