
Anticoagulation Therapy In Heart Failure Patients With Normal Heart Rhythm: A Review Of The Evidence

M Edwards

Citation

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Abstract

Purpose: The purpose of this review is to explore the current clinical trial data to determine if the use of anticoagulants in heart failure patients with systolic dysfunction and without demonstrated rhythm disturbances results in decreased mortality or a reduction in thromboembolic events. **Data Sources:** A literature search was conducted using Pub Med, CINAHL, and the Cochrane Library databases. The literature review was limited to randomized control trials with primary and secondary end points of all causes of mortality, embolic events (including stroke and myocardial infarction), and frequency of hospitalization that compared oral anticoagulants to control or placebo in patients with left ventricular systolic heart failure. **Conclusions:** Limited evidence exists to support the use of oral anticoagulation in heart failure patients without the presence of additional risk factors such as atrial fibrillation, severely depressed left ventricular contractility with known history of previous embolic event, or evidence of mural thrombus. Current studies established no significant difference in the primary endpoints for study participants, but demonstrated a trend toward increased risk of bleeding for those patients receiving warfarin therapy. **Implications for practice:** Health care practitioners should not contribute to the polypharmacy of this vulnerable patient population without clear evidence of benefit. Until more definitive data are available, clinicians should assess the use of oral anticoagulation in heart failure on a case by case basis. The use of oral anticoagulants should be limited to those heart failure patients with additional risk factors.

INTRODUCTION

The decision whether or not to initiate oral anticoagulation for patients with chronic left ventricular systolic heart failure (HF) who have a normal heart rhythm and no prior history of thromboembolic event can be complex. The use of anticoagulation in this patient population has been the subject of numerous debates with many opinions for a number of years, and has been based primarily on conflicting data from retrospective trials and observational studies. Until recently, no prospective randomized control trial data were available that could speak to the risks and benefits of embracing such practice. This review examines the outcomes of three recently published randomized control trials (RCTs) that attempted to shed some light on the subject: 1) the Warfarin/ Aspirin Study in Heart Failure (WASH), 2) the Heart Failure Long-term Antithrombotic Study (HELAS), and 3) the Warfarin and Antiplatelet Therapy in Heart Failure (WATCH).

BACKGROUND

Heart failure is a disease of epidemic proportions. More than

5.7 million people in the United States are currently living with heart failure and nearly 670,000 new cases are diagnosed each year.¹ Prognosis is poor and is associated with limited functional capacity and decreased quality of life. Despite the significant advances in the medical management of heart failure, this condition remains a major cause of morbidity and mortality, with an overall 5 year mortality rate of 50%.¹ While the leading cause of death is often attributed to sudden cardiac arrest from an acute arrhythmia, thromboembolic events including cerebral vascular accident (CVA), myocardial infarction (MI), and pulmonary embolism (PE) are known to be contributors to death and disability. In fact, some researchers suggest that thromboembolism as a cause death in these patients may be under appreciated. One study that evaluated the cause of death of patients with moderate to severe heart failure caused by systolic dysfunction (originating from various etiologies, including ischemic and non-ischemic heart disease), found that a significant number of patients' deaths ($p < 0.0001$) adjudicated as sudden cardiac death or progressive pump failure were reclassified at autopsy as

acute MI or coronary thrombus.²

Pathophysiologically, chronic heart failure with left ventricular systolic dysfunction demonstrates an environment representative of a prothrombotic or hypercoagulable state, and is viewed often within the context of fulfilling Virchow's triad of thrombogenesis.³ The triad involves three broad categories of factors known to contribute to the development of thrombosis: 1) endothelial injury/ dysfunction (changes in the vessel wall), 2) hemodynamic changes resulting in an disruption or decreased blood flow (stasis), and 3) changes in blood composition causing hypercoagulability. Dilated ventricles and suppressed contractility, characteristics of systolic heart failure, result in abnormal changes in vessel wall morphology, decreased blood flow, and abnormal blood constituents which may account for the higher incidence of thrombosis-related complications in this patient population.³ While the actual risk may be higher or lower depending upon the severity of heart failure disease, the annual risk of thromboembolic events in the general heart failure population is estimated to be in the range of 1- 4.5%, representing up to a four-fold increase as compared to the general populace.⁴

In theory, the use of anticoagulant therapy in this patient group seems to be a logical approach to preventing thrombosis. However, while the benefit of long term use of anticoagulant therapy in heart failure patients with atrial fibrillation, a previous thromboembolic event, or known ventricular thrombus is well established, its use in patients with a normal heart rhythm (and without the aforementioned conditions) remains controversial and varies broadly in clinical practice. A Cochrane review of anticoagulation for heart failure in sinus rhythm concluded that the evidence from earlier trials, some of which were conducted over fifty years ago, established a reduction in mortality and cardiovascular events with anticoagulants when compared to control groups, but urged that this evidence be interpreted with caution as many of the early trials would not meet modern day trial standards.⁵

METHODS

SEARCH STRATEGY

A comprehensive literature search was conducted using three databases (Cochrane Library, PubMed, and CINAHL). The following key words were used in the search: heart failure, systolic heart failure, chronic heart failure, cardiomyopathy, dilated cardiomyopathy, anticoagulation,

thromboembolism, thromboembolic events, thrombus, sinus rhythm, and normal heart rhythm. Although, the search strategy was initially limited to include only the evidence published in the past 15 years, a Cochrane Review published in 2000 was identified. As a result, a publication date range of 2000 – 2010 was imposed for subsequent searches.

STUDY SELECTION

The study design was limited to RCTs. Only those studies in which oral anticoagulant therapy was evaluated in heart failure patients with left ventricular systolic dysfunction in normal sinus rhythm were eligible for inclusion in the review. Patients with heart failure due to any underlying cause were included. Eligible outcomes included death, thrombotic events, hospitalizations, and adverse events related to treatment therapy. Studies that did not include anticoagulation as a treatment arm, and those that included HF patients with mechanical valves or a high percentage of (>10%) concomitant atrial fibrillation were excluded.

The search strategy resulted in 986 references; 982 were excluded after checking the title and abstract against the inclusion criteria because they were either not relevant or did not meet the standards for research design. Six references, including the Cochrane Review, were initially included. The Cochrane Review was retained for the primary purpose of establishing a historical background. The WARCEF (Warfarin Versus Aspirin in Patients with Reduced Cardiac Ejection Fraction) was excluded because the study is unreported, and at the time of this writing is still recruiting patients. Of the 5 remaining clinical trials, one was later excluded (EPICAL 2002) after determining the study was observational in design and 24% of the study participants had concomitant atrial fibrillation. These findings were not clearly evident in the initial abstract review.

ANALYSES AND FINDINGS

Three RCTs met the trial selection criteria for review (Table 1): The Warfarin/ Aspirin Study in Heart Failure (WASH), the Heart Failure Long-term Antithrombotic Study (HELAS), and the Warfarin and Antiplatelet Therapy in Heart Failure Trial (WATCH).

WASH

WASH was a small feasibility study leading up to the larger WATCH trial. WASH was a multi-center trial, and used a Prospective Randomized Open-label Blinded Endpoint (PROBE) design. WASH randomized 279 New York Heart Association (NYHA) class III and IV heart failure patients

with left ventricular systolic dysfunction and an ejection fraction (EF) of < 35% to no antithrombotic treatment, aspirin (300 mg), or warfarin (target INR 2.5). The mean patient follow up was 27 months (627 patient years). The percentage of patients with atrial fibrillation (AF) in the study was relatively low, with 4% in the placebo group and 7% in both the aspirin and warfarin groups. Because the study was intended to be a pilot, no sample size power calculations were performed. Statistical analyses were conducted using the log-rank tests and quantified by hazard ratios and 95% confidence intervals (CI).

The WASH trial demonstrated no significant difference in the composite primary end points of death from any cause, non-fatal MI, and nonfatal stroke between the treatment groups, with 26%, 32%, and 26% of patients randomized to placebo, aspirin, and warfarin respectively. However, significantly more hospitalizations, especially for worsening heart failure, were evident in patients randomized to the aspirin group (P=0.44). In addition, (although not statistically significant), patients in the warfarin group spent approximately 200 less days in the hospital compared to those in the placebo and aspirin groups.⁸

HELAS

The HELAS study was a multicenter, double-blind, placebo controlled trial of 197 NYHA class II – IV heart failure patients with EF < 35%. Patients with Ischemic Heart Disease (IHD) were randomized to either aspirin (325 mg) or warfarin (target INR 2-3), and patients with dilated cardiomyopathy (DCM) were randomized to receive either warfarin or placebo. Patients with mitral valve disease, reversible ischemia, hypertrophic cardiomyopathy, atrial fibrillation or known left ventricular thrombi were excluded from the study. Based on the original power calculations, the study was designed for 6000 patients (1500 per treatment arm), but suffered from poor enrollment causing it to be significantly underpowered.

The primary endpoints for the HELAS study were non-fatal stroke, peripheral or pulmonary embolism, MI, hospitalization, and exacerbation of heart failure. However, because the study was considerably underpowered, differences in efficacy among treatment groups could not be statistically evaluated.⁹ Nonetheless, the study demonstrated a low embolic rate overall (2.2 per 100 patient years). Only five strokes and two MIs were recorded. No difference between aspirin and warfarin in the IHD group could be appreciated, but a favorable trend was evident toward

warfarin versus placebo in the DCM group (8.9 events per 100 patient years with warfarin versus 14.8 events per 100 patient years with placebo). Even so, major hemorrhage only occurred in the warfarin group at an average rate of 4.6 per 100 patient years.⁹

WATCH

The latest reported and largest trial to date is the WATCH trial. This study was a prospective, multi-national, multi-center (142 centers), open-label warfarin, double-blind aspirin and clopidogrel trial that randomized 1587 NYHA class II – IV heart failure patients with an EF < 35% (mean EF 24%) to receive warfarin (target INR 2.5 – 3.0), aspirin (162mg) or clopidogrel (75 mg). Patients were followed up for an average of 23 months (median follow up, 21 months). The trial was originally designed to include 4500 patients, but was terminated early (N= 1587) due to poor enrollment. Like the HELAS study, WATCH suffered from significant power reduction to distinguish differences in treatment arms.^{6,7} Statistical analyses was conducted using the adjusted odds ratio and 95% CI.

As a consequence of being underpowered, the study failed to outline significant differences between treatment groups for the composite primary endpoints (all cause mortality, MI or stroke): 20.5%, 19.8% and 21.8% for aspirin, warfarin and clopidogrel respectively. Still, a strong trend toward warfarin over aspirin was demonstrated with decreasing non-fatal strokes, and significantly fewer HF-related hospitalizations (P= 0.001) was seen with warfarin as compared to aspirin. However, these favorable occurrences were offset by a considerably higher incidence of bleeding in the warfarin group (5.5%, 3.6% and 2.5% for warfarin, aspirin, and clopidogrel respectively).⁷

CONCLUSION

To date, no clear evidence exists to indicate anticoagulation therapy in left ventricular systolic heart failure patients with a normal heart rhythm and no prior history of thromboembolic events is beneficial. While some data demonstrated a favorable trend toward warfarin with reducing patient hospitalizations, significantly higher incidences of bleeding were common in these patient groups. Likewise, the perceived beneficial effect of antiplatelet therapy with aspirin has not been fully supported either. In fact, the WASH study showed significantly more hospitalizations from worsening heart failure in patients randomized to the aspirin group.

The highly anticipated WARCEF (Warfarin versus Aspirin in Patients with Reduced Cardiac Ejection Fraction) trial promises to provide a clearer understanding for this ongoing discussion. WARCEF is a randomized, double-blind, multi-center study whose purpose is to define optimal antithrombotic therapy for patients with heart failure and low ejection fraction (EF). The study will randomize 2860 heart failure patients at all stages of illness (NYHA class I – IV) with EF < 35% and normal heart rhythm. Patients with the presence of any of the following unequivocal cardiac sources of embolism will be excluded: paroxysmal atrial fibrillation, mechanical valve, intracardiac thrombus, endocarditis and valvular vegetation. The study will determine which of the two commonly used treatments, warfarin (an anticoagulant) or aspirin (drug affecting platelet function) is better for preventing death and strokes in patients with low EF.¹⁰

IMPLICATIONS FOR PRACTICE

Current data are insufficient to provide an evidence-based recommendation for clinical practice at this time. As a result, the author provides the following approach and precautions based on the trial findings and clinical expertise. While warfarin anticoagulation merits consideration in some heart failure patients, careful assessment of the risks and benefits of such therapy should be undertaken in individual patients on a case by case basis. Until further evidence is available, the author suggests that anticoagulation in HF patients with normal heart rhythm be reserved primarily for those patients with severely depressed ventricular contraction (< 35%), history of stroke or thromboembolism, or evidence of cardiac thrombus.

Additionally, even though aspirin is generally recommended for patients with ischemic heart disease (the cause of heart failure in many patients), the author cautions against generalized use of aspirin in all heart failure patients, especially those patients with moderate to severe illness and/or no evidence of ischemia, until further trial data can be obtained. Not only has clear benefit for aspirin therapy not been established, but also concern for potential harm does exist. Several studies have suggested that there may be an interaction between aspirin therapy and angiotensin-converting enzyme (ACE) inhibitors, a known survival-enhancing treatment for systolic heart failure. The cyclooxygenase inhibition achieved with aspirin (its mode of action for preventing platelet aggregation and clot formation) may be responsible for blunting the beneficial effects of ACE inhibition.^{11, 12} Also aspirin (like other non-steroidal anti-inflammatory drugs [NSAIDs]) is known to

inhibit the synthesis of vasodilating prostaglandins which can result in increased vasoconstriction and decreased renal blood flow. This hemodynamic alteration may account for the worsening heart failure and increased hospitalization seen in the WASH study. With this in mind, the author proposes that the use of aspirin therapy be limited to those HF patients with known IHD, recent MI, or current angina. Given the risk of worsening heart failure, a lower dosage of 81mg may be more appropriate, and even avoided, in refractory heart failure.

Figure 1

TABLE 1. Randomized Clinical Trials

Source	Trial	Sample	LVEF	Intervention	Follow-up	End points	Results	Study Limitations
Cleveland et al., 2004	WASH	279	≤35%	No antithrombotic vs. Aspirin 300mg vs. Warfarin (INR 2.5)	27 months	Primary: - Death, - Nonfatal MI, - Nonfatal stroke Secondary: - Hospitalization - other thrombotic events - hemorrhage	No significant difference in primary endpoints Increased HF hospitalizations in aspirin group	Underpowered Not blinded
Cokkinos et al., 2006	HELAS	197	<35%	Ischemic: Aspirin 325mg or warfarin (INR 2-3) Nonischemic: warfarin or placebo	24 months	- Non-fatal stroke - Peripheral or pulmonary embolism - MI - Re-hospitalization - Heart failure exacerbation - All cause mortality Secondary: - Hemorrhage	No difference in primary endpoints (both groups) Trend toward benefit with warfarin vs. placebo Hemorrhage occurred only in warfarin group	Underpowered
Masnie et al., 2009	WATCH	1587	≤35% (mean 24%)	Warfarin (INR 2.5 – 3.0) vs. Aspirin 162mg vs. Clopidogrel 75mg	23 months	Primary: - All cause mortality - Non-fatal MI - Non-fatal stroke Secondary: - Hospitalizations - Bleeding	No difference in primary endpoints Significantly more HF hospitalizations with Aspirin compared to warfarin (P=0.01) Greater incidence of bleeding in warfarin group	Underpowered

LVEF- Left ventricular ejection fraction; HELAS- Heart Failure Long-term Antithrombotic Study; MI- myocardial infarction; WASH- Warfarin/ Aspirin Study in Heart Failure; WATCH- Warfarin and Antiplatelet Therapy in Chronic Heart Failure

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Author Information

Michelle L. Edwards, MSN, APRN, FNP-BC, ACNP-BC

Doctor of Nursing Practice Candidate, The University of Texas Health Science Center at Houston School of Nursing