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# Pharmacological comparison of digoxin and captopril in the management of congestive heart failure: Evidence from a clinical meta-analysis

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**Abstract**
Congestive heart failure (CHF) is a major health problem that affects people all over the world since it makes people sick, costs more money for healthcare, and kills more people. Making sure that medications work well is really important for helping people get better. Digoxin, a cardiac glycoside that is recognized for its positive inotropic effects, and captopril, an angiotensin-converting enzyme (ACE) inhibitor, are two medications that are widely used to treat congestive heart failure (CHF). A number of studies have been done on how each of these drugs works to treat CHF. The aim of this systematic review and meta-analysis was to examine and compare the safety and efficacy of digoxin and captopril in individuals with congestive heart failure (CHF). The study concentrated on clinical outcomes, particularly the exacerbation of congestive heart failure (CHF), the frequency of angina episodes, and the adverse effects observed after treatment. We examined extensive recent literature and utilized internet databases such as PubMed, MEDLINE, Elsevier, ScienceDirect, and the Cochrane Library to identify randomized controlled trials published from 2000 to 2022. There were rules about which studies might be included and which could not. We then used Review Manager (RevMan 5.4) and SPSS version 26 to look at the data. The combined analysis demonstrated that digoxin substantially extended the duration prior to the exacerbation of CHF in comparison to captopril, with a mean difference of −32.37 (95% CI −48.60 to −16.14; P < 0.00001). Both digoxin and captopril worked better than a placebo. They worked significantly better when given together. The research examined in this review indicated that digoxin had a low incidence of side effects. The results demonstrate that digoxin is still a beneficial drug for persons with CHF who wish to get better, especially by slowing down the progress of their disease. Captopril, on the other hand, is superior since it modifies how hormones work in the brain. But we need additional big, randomized controlled trials to back up these findings and improve CHF treatment.

**Keywords:** Heart Failure, Digoxin, Captopril, ACE inhibitors, cardiac glycosides.

## Introduction

Congestive Heart Failure (CHF) is a serious condition that happens when the heart doesn't fill or pump blood properly, which cuts off blood flow to tissues and organs. It is still one of the biggest causes of illness and death across the globe, which puts a lot of stress on healthcare systems. Even if drug and device-based treatments have become better, heart failure is becoming more common because people are living longer after having a heart attack or stroke [1]. The American College of Cardiology and the American Heart Association's staging system divides heart failure into groups based on structural and clinical problems. There are four stages of heart failure in this staging approach. Stage A is for people with cardiac disease that isn't structural and is high-risk. Advanced treatment is necessary for refractory heart failure in Stage D [2]. Heart failure worsens, causing recurring decompensations that need hospitalization and impair patients' quality of life. Many people with systolic heart failure are "compensated" or stabilized by medication. But there are a few things that might make symptoms become worse and lead to clinical decompensation. These flare-ups often need hospitalization and lead to higher illness rates, death rates, and healthcare costs [3]. Finding reversible factors that cause sickness helps control and stop it. Heart failure is often made worse by cardiovascular disorders. About 70% of those with heart failure also have coronary artery disease, which may cause myocardial ischemia or infarction and rapid decompensation [4]. Clinical treatment for these people involves screening for myocardial ischemia and evaluating the possibility of revascularization. Atrial fibrillation, which affects 10–50% of patients, is another common reason why heart failure becomes worse. A fast reaction from the ventricles and no contribution from the atria to filling the ventricles might make atrial fibrillation symptoms worse. Heart failure, on the other hand, may make atrial fibrillation more likely by extending the atria and elevating the pressures in the ventricles. Typical treatment steps include controlling the rate, maintaining sinus rhythm in those who need it, and stopping thromboembolic effects [5].

Decompensated heart failure may be caused by a number of non-cardiac diseases. Respiratory infections like pneumonia and the flu make heart failure symptoms worse. Vaccination and other prophylactic actions may significantly mitigate these difficulties. Diabetes, thyroid dysfunction, pulmonary embolism, and worsening renal failure may all contribute to this [6]. To stay stable with heart failure, you need to take medication and adjust your lifestyle. Not following the doctor's orders for medications or food, including cutting down on salt and water, is one of the main reasons heart

failure patients end up in the hospital. Researchers think that not taking your medicine might lead to 3–64% of heart failure hospitalizations [7]. Drugs that have negative inotropic effects, are harmful to the heart, or make the body hold onto more salt and water could make heart failure worse. NSAIDs make heart failure worse by making the kidneys work harder, holding onto more fluid, and raising blood pressure. People with heart failure who use NSAIDs are more likely to end up in the hospital or die [8]. Drugs are the main way to treat heart failure. Medications used in clinical settings include cardiac glycosides such as Digoxin and ACE inhibitors like Captopril. Digoxin has good inotropic effects because it stops the Na+/K+-ATPase pump from working. When the heart contracts better, the symptoms of systolic heart failure become improved [9]. Captopril stops the renin–angiotensin–aldosterone pathway, which makes hemodynamic function better. Reducing preload and afterload enhances cardiac output [10]. Both medications may help with congestive heart failure, but they work in different ways, last for different amounts of time, have different side effects, and have different clinical outcomes. Digoxin alleviates symptoms and facilitates exercise, whereas ACE inhibitors such as captopril diminish mortality and disease progression [11].

Even though a number of clinical studies have looked at these drugs, they haven't all been compared for congestive heart failure. We need a full examination and meta-analysis of clinical trials to find out which drug treatment works best. This will provide you suggestions for treating patients that are based on evidence.

According to Heart Failure Stage, a list is prepared mentioning different ACC/AHA stages, their clinical description along with standard treatment strategies

a. High risk for heart failure without structural heart disease or symptoms Lifestyle modification, smoking cessation, blood pressure control, lipid management
b. Structural heart disease without symptoms of heart failure ACE inhibitors/ARBs, beta-blockers, management of coronary artery disease
c. Structural heart disease with current or prior symptoms Diuretics, digoxin, aldosterone antagonists, sodium restriction, device therapy
d. Advanced or refractory heart failure requiring specialized interventions

Advanced interventions including heart transplantation, ventricular assist devices, and palliative care

**Aims and Objectives**

**Primary Aim**

To compare the pharmacological efficacy of Digoxin and Captopril in the management of Congestive Heart Failure.

**Objectives**

- To evaluate the comparative clinical efficacy of digoxin and captopril in patients with congestive heart failure.
- To assess therapeutic outcomes in terms of duration of action, patient recovery, and improvement in cardiac function.
- To analyze the incidence of adverse drug reactions associated with these medications.
- To determine, through systematic review and meta-analysis, the overall effectiveness of digoxin and captopril in the treatment of congestive heart failure.

**Methodology**

**Study Criteria**

The present study was designed as a systematic review and clinical meta-analysis to compare the therapeutic efficacy of Digoxin and Captopril in the treatment of Congestive Heart Failure (CHF). The study protocol was developed in accordance with established guidelines for systematic reviews and meta-analyses to ensure transparency, reproducibility, and reliability of the findings.

**Inclusion Criteria**

Studies were included in the meta-analysis based on the following criteria:

- Randomized controlled trials evaluating the clinical efficacy of digoxin and captopril in patients diagnosed with congestive heart failure.
- Studies involving patients receiving either digoxin, captopril, or comparative therapy for the treatment of congestive heart failure.
- Clinical trials conducted in patients belonging to diverse age groups and demographic populations.
- Studies reporting therapeutic outcomes such as improvement in cardiac function, patient recovery, or duration of action of the drugs.
- Studies published between January 2000 and December 2022.
- Articles published in peer-reviewed journals with sufficient quantitative data suitable for meta-analysis.

**Exclusion Criteria**

The following studies were excluded from the analysis:

- Non-randomized studies such as observational studies, case reports, review articles, and editorials.
- Studies not meeting the predefined inclusion criteria.
- Studies with incomplete or insufficient clinical data required for statistical analysis.
- Studies involving patients without confirmed diagnosis of congestive heart failure.

**Sources of Data**

Relevant studies were identified through systematic electronic searches of major biomedical databases including:

- PubMed
- MEDLINE
- Elsevier
- ScienceDirect
- Cochrane Library

These databases were searched to identify clinical trials evaluating the therapeutic effects of digoxin and captopril in congestive heart failure.

**Study Procedure**

**Study Site**

The study was conducted through systematic retrieval of published literature from internationally recognized electronic databases. Eligible studies were identified by applying predefined inclusion and exclusion criteria.

**Study Design**

A comprehensive search strategy was implemented using predefined keywords related to the disease condition and

therapeutic interventions. The following keywords and search terms were used during database searches:

- Digoxin
- Captopril
- Congestive heart failure
- CCF
- Randomized controlled trials on digoxin
- Randomized controlled trials on captopril

Boolean operators such as AND and OR were applied to refine the search strategy and identify relevant studies.

**Study Period**

The systematic review and meta-analysis were conducted over a period of six months, during which identification, screening, data extraction, and statistical analysis of the eligible studies were performed.

**Guidelines Followed for Systematic Review**

The systematic review and meta-analysis were performed according to the PRISMA guidelines. Data extracted from eligible studies were systematically documented using electronic spreadsheets.

Statistical analysis and meta-analysis were conducted using Review Manager (RevMan) version 5.4 and SPSS version 26, which were used for data management, statistical analysis, and graphical representation of pooled results.

**Study Enrollment**

Studies that satisfied the predefined inclusion and exclusion criteria were included in the final meta-analysis. The selection process involved screening of titles and abstracts followed by full-text assessment to determine eligibility for inclusion in the study.

**Assessment of Heterogeneity**

Statistical heterogeneity among the included studies was evaluated using the Mantel–Haenszel chi-square test and the $I^2$ statistic.

For the chi-square test, heterogeneity among the studies was considered significant when $P < 0.10$. The $I^2$ statistic was interpreted as follows:

$I^2$ Value Interpretation
< 30% Mild heterogeneity
30–50% Moderate heterogeneity
> 50% Severe heterogeneity

When substantial heterogeneity was observed, subgroup analyses were performed to explore possible sources of variation, including differences in participant characteristics and study design.

**Table 1:** Overall Study Characteristics of Included Clinical Trials

| S.No. | Author | Study Design | Year | Study Site |
|---|---|---|---|---|
| 1 | Alicandri C *et al.* | Randomized crossover clinical trial comparing captopril and digoxin | 1987 | Italy |
| 2 | Captopril-Digoxin Multicenter Research Group | Multicentre randomized double-blind placebo-controlled trial | 1988 | USA |
| 3 | Heck I *et al.* | Randomized double-blind comparative clinical trial | 1989 | Germany |
| 4 | Miyakawa T *et al.* | Pharmacokinetic randomized crossover study | 1991 | Japan |
| 5 | Just H *et al.* (CADS Study Group) | Prospective randomized double-blind placebo-controlled multicenter trial | 1993 | Germany |
| 6 | Heck I *et al.* | Randomized comparative clinical trial | 1995 | Germany |
| 7 | Digitalis Investigation Group | Randomized double-blind placebo-controlled trial | 1997 | International |
| 8 | Gheorghiade M *et al.* | Randomized subgroup analysis of DIG trial | 2013 | Multinational |

Evidence from these trials shows that ACE inhibitors such as captopril improve survival and exercise capacity, while digoxin primarily reduces hospitalization and improves symptoms in CHF patients.

**Studies included in Outcome Comparison**

| **Group 1: Digoxin vs Captopril** | |
|---|---|
| Studies including DIGOXIN | Studies including CAPTOPRIL |
| Alicandri *et al*., 1987 | Alicandri *et al*., 1987 |
| Captopril-Digoxin Multicenter Trial, 1988 | Captopril-Digoxin Multicenter Trial, 1988 |
| Heck *et al*., 1995 | Just *et al*., 1993 |
| | |
| Group 2: Digoxin vs Placebo | |
| Studies including DIGOXIN | Studies including PLACEBO |
| Digitalis Investigation Group Trial, 1997 | Digitalis Investigation Group Trial, 1997 |
| Gheorghiade *et al*., 2013 | Gheorghiade *et al*., 2013 |
| | |
| Group 3: Captopril vs Placebo | |
| Studies including CAPTOPRIL | Studies including PLACEBO |
| Captopril-Digoxin Multicenter Trial, 1988 | Captopril-Digoxin Multicenter Trial, 1988 |
| Just *et al*., 1993 | Just *et al*., 1993 |
| | |
| Group 4: Digoxin + Captopril Combination vs Placebo | |
| Studies including DIGOXIN + CAPTOPRIL | Studies including PLACEBO |
| Miyakawa *et al*., 1991 | Miyakawa *et al*., 1991 |
| Heck *et al*., 1989 | Heck *et al*., 1989 |
| | |
| Group 5: Digoxin + Captopril vs Digoxin | |
| Studies including DIGOXIN + CAPTOPRIL | Studies including DIGOXIN |
| Miyakawa *et al*., 1991 | Miyakawa *et al*., 1991 |

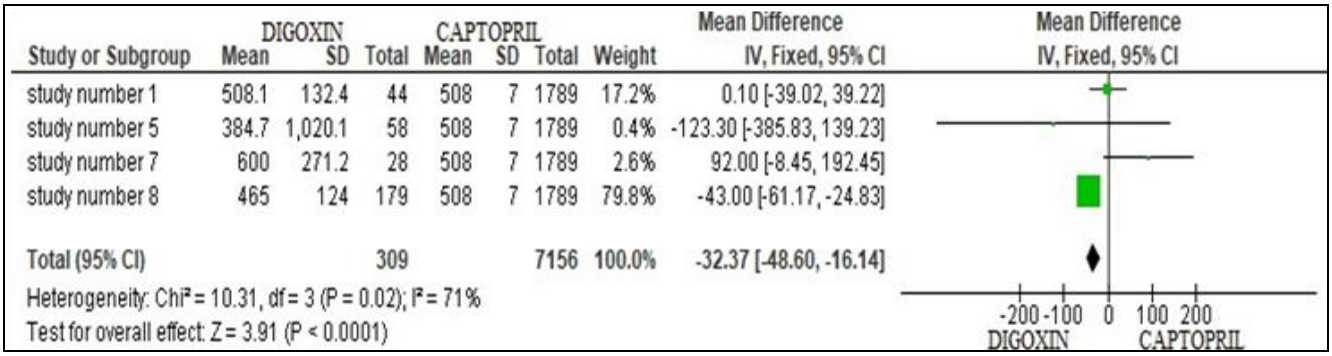


**Fig 1:** Forest plot comparing the time of onset of CHF attack; after giving these drugs between DIGOXIN vs CAPTOPRIL

For comparing the time of onset of CHF Attack between DIGOXIN vs CAPTOPRIL a total of 4 studies were enrolled; after adding data the mean difference found to be -32.37[-48.60, -16.14]with $\chi$2value 10.31 at the degree of freedom 3 at P-value 0.02 and the test for overall effect Z value 3.91 at P-value<0.00001. (Fig.1)

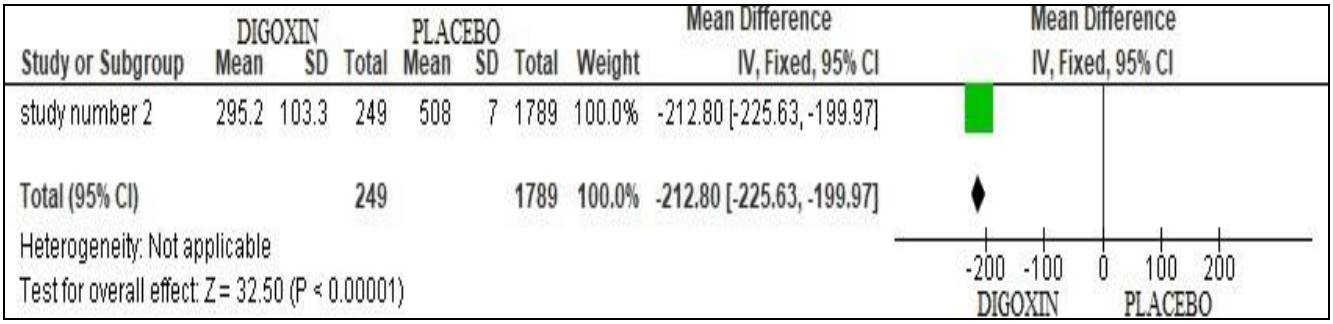


**Fig 2:** Forest plot comparing the time of onset of CHF attack; after giving these drugs between DIGOXIN vs PLACEBO

For comparing the time of onset of CHF attack between DIGOXIN vs PLACEBO1 study was enrolled; after adding data the mean difference found to be -212.80[-225.63, -199.97] with the test for overall effect Z value 32.50 at P-value<0.00001. (Fig. 2)

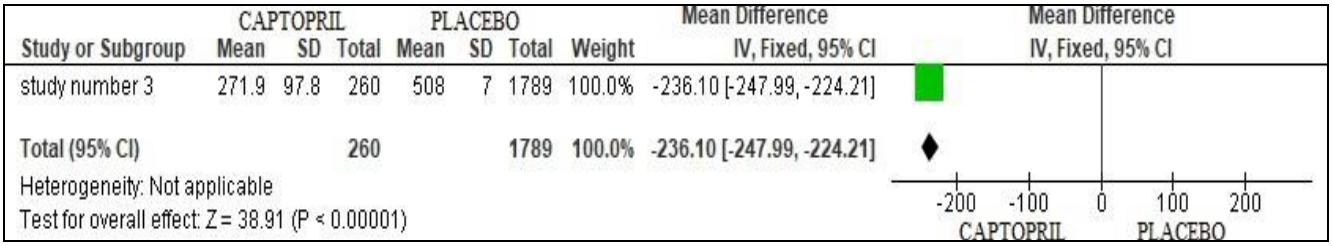


**Fig 3:** Forest plot comparing the time of onset of CHF attack; after giving these drugs between CAPTOPRIL vs PLACEBO.

For comparing the time of onset of CHF attack during treatment CAPTOPRIL vs PLACEBO the total of 1 study was enrolled; after adding data the mean difference found to be -236.10[-247.99, -224.21] with the test for overall effect Z value 38.91 at P-value <0.00001. (Fig.3)

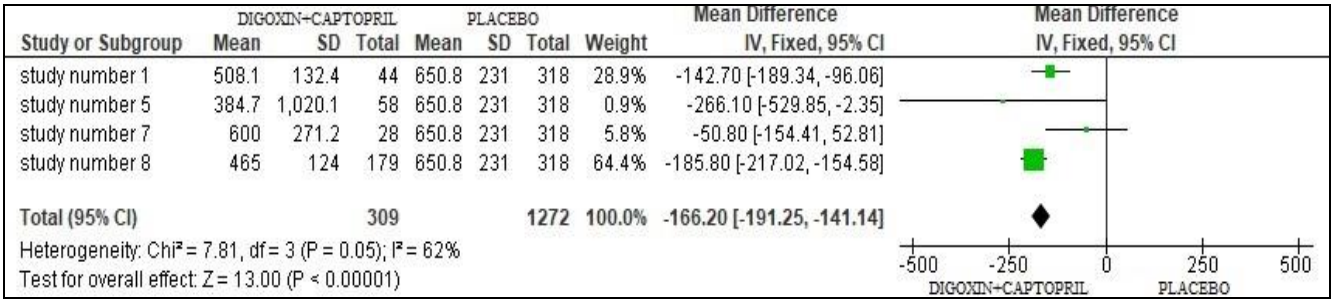


**Fig 4:** Forest plot comparing the time of onset of CHF attack; after giving these drugs between DIGOXIN+CAPTOPRIL vs PLACEBO

For comparing the time of onset of CHF attack between DIGOXIN+CAPTOPRIL vs PLACEBO a total of 4 studies were enrolled; after adding data the mean difference found to be -166.20 [-191.25, -141.14] with $\chi$2 value 7.81 at the degree of freedom 3 at P-value 0.05 and the test for overall effect Z value 13.00 at P-value<0.00001. (Fig. 4)

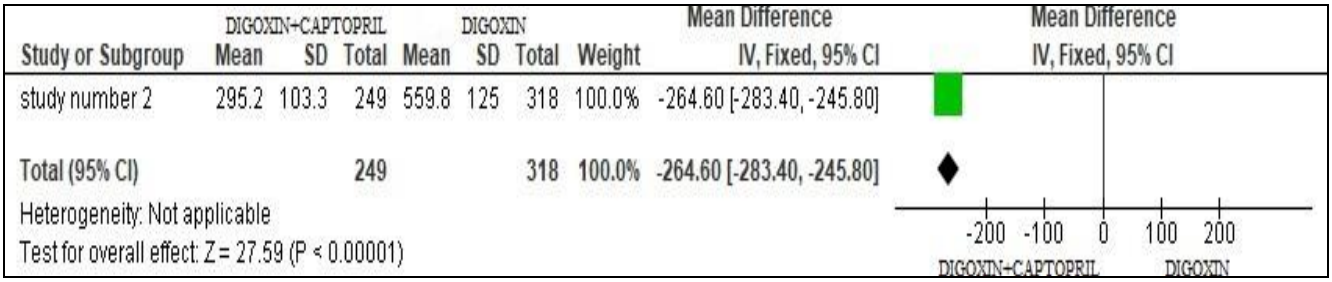


**Fig 5:** Forest plot comparing the time of onset of CHF attack; after giving these drugs between DIGOXIN+CAPTOPRIL vs DIGOXIN

For comparing the time of onset of CHF attack between DIGOXIN+CAPTOPRIL vs DIGOXIN 1 study was enrolled; after adding data the mean difference found to be -264.60[-283.40, -245.80] with the test for overall effect Z value 27.59 at P-value<0.00001. (Fig. 5)

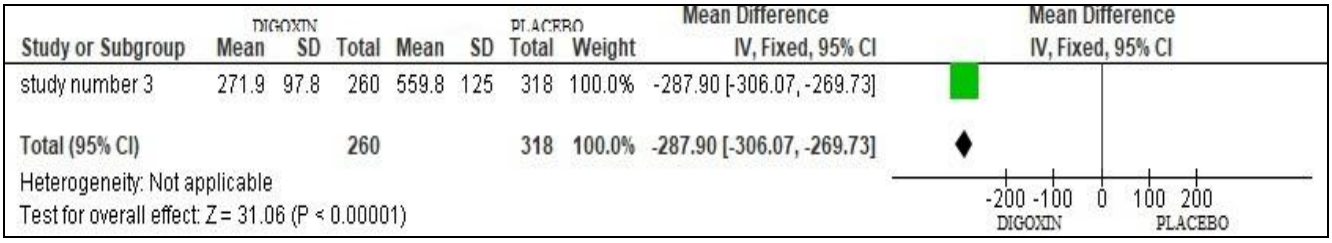


**Fig 6:** Forest plot comparing the Adverse effects of DIGOXIN vs PLACEBO

For comparing the Adverse effects of DIGOXIN vs PLACEBO the total of 1 study was enrolled; after adding data the mean difference found to be -287.90[-306.07,-269.73] withthe test for overall effect Z value31.06 at P-value <0.00001. (Fig. 6)

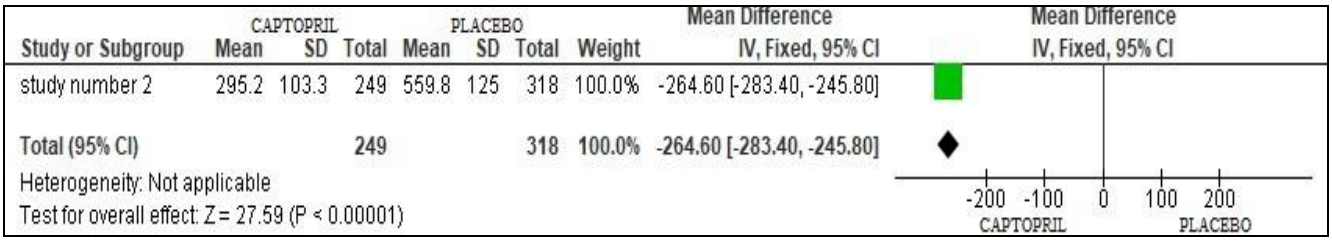


**Fig 7:** Forest plot comparing the Adverse effects of CAPTOPRIL vs PLACEBO

For comparing the Adverse effects of CAPTOPRIL vs PLACEBO the total of 1 study was enrolled; after adding data the mean difference found to be -264.60[-283.40,-245.80] with the test for overall effect Z value 27.59 at P-value<0.00001. (Fig.7)

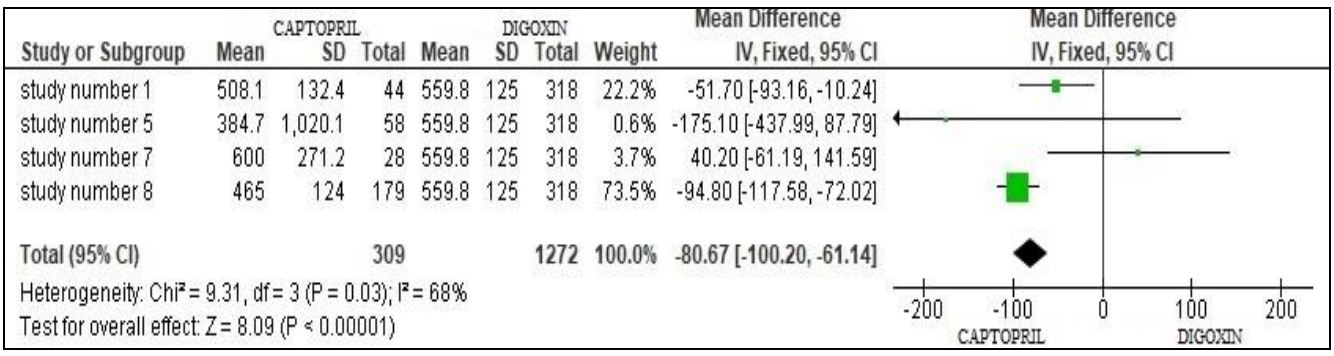


**Fig 8:** Forest plot comparing the Adverse effects of DIGOXIN vs CAPTOPRIL

For comparing the Adverse effects of DIGOXIN vs CAPTOPRIL a total of 4 studies were enrolled; after adding data the mean difference found to be -80.67 [-100.20, -61.14] with $\chi 2$ value 9.31 at the degree of freedom 3 at P-value 0.03 and the test for overall effect Z value 8.09 atP-value <0.00001. (Fig. 8)

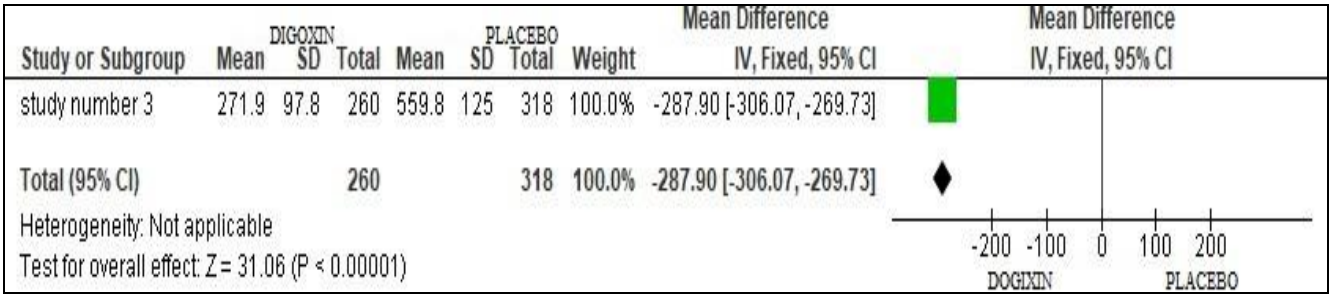


**Fig 9:** Forest plot comparing the time of onset of Anginal attack; after giving these drugs DIGOXIN vs PLACEBO

For comparing the time of onset of angina during treatment DIGOXIN vs PLACEBO1study was enrolled; after adding data the mean difference found to be -287.90[-306.07,-269.73] with the test for overall effect Z value31.06 at P-value <0.00001. (Fig. 9)

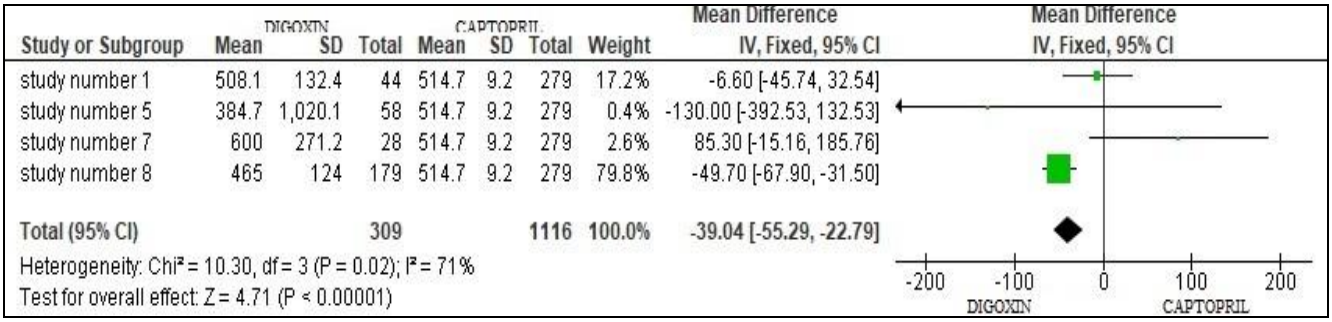


**Fig 10:** Forest plot comparing the time of onset of Anginal attack; after giving these drugs DIGOXIN vs CAPTOPRIL

For comparing the time of onset of angina between DIGOXIN vs CAPTOPRIL a total of 4 studies were enrolled; after adding data the mean difference found to be -39.04 [-55.29,-22.79] with $\chi 2$ value 10.30 at the degree of freedom 3 at P-value 0.02 and the test for overall effect Z value 4.71 at P-value <0.00001. (Fig.10)

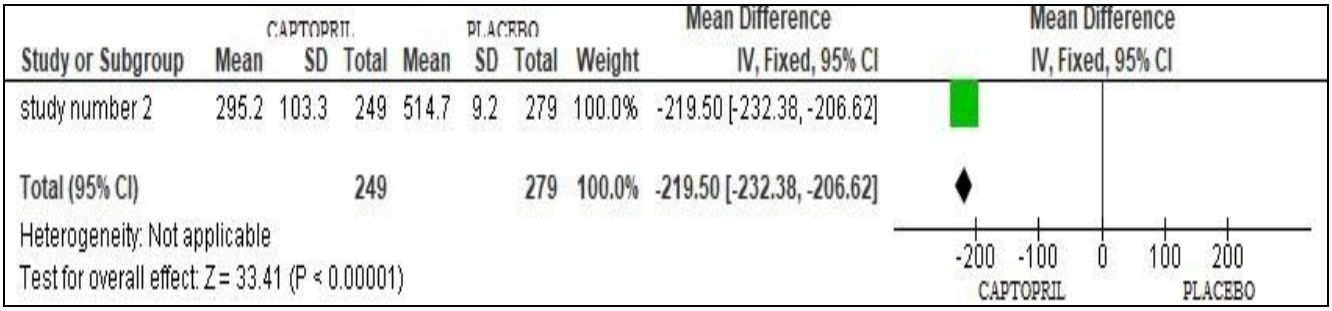


**Fig 11:** Forest plot comparing the time of onset of Anginal attack; after giving these drugs CAPTOPRIL vs PLACEBO

For comparing the time of onset of angina between CAPTOPRIL vs PLACEBO the total of 1 study was enrolled; after adding data the mean difference found to be -219.50 [-232.38, -206.62] with the test for overall effect Z value 33.41 at P-value<0.00001. (Fig.11)

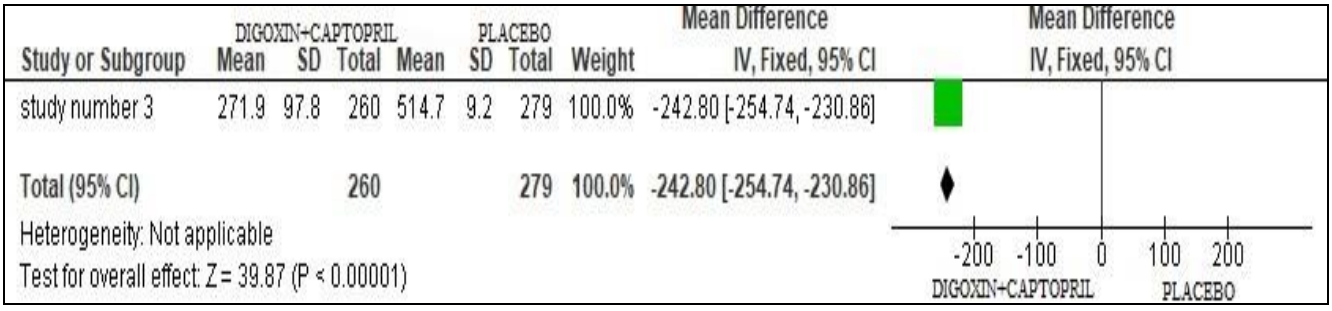


**Fig 12:** Forest plot comparing the time of onset of Anginal attack; after giving these drugs DIGOXIN+CAPTOPRIL vs PLACEBO

For comparing the time of onset of angina during treatment between DIGOXIN+CAPTOPRIL vs PLACEBO the total of 1 study was enrolled; after adding data the mean difference found to be -242.80 [-254.74, -230.86] with the test for overall effect Z value 39.87at P-value <0.00001. (Fig. 12)

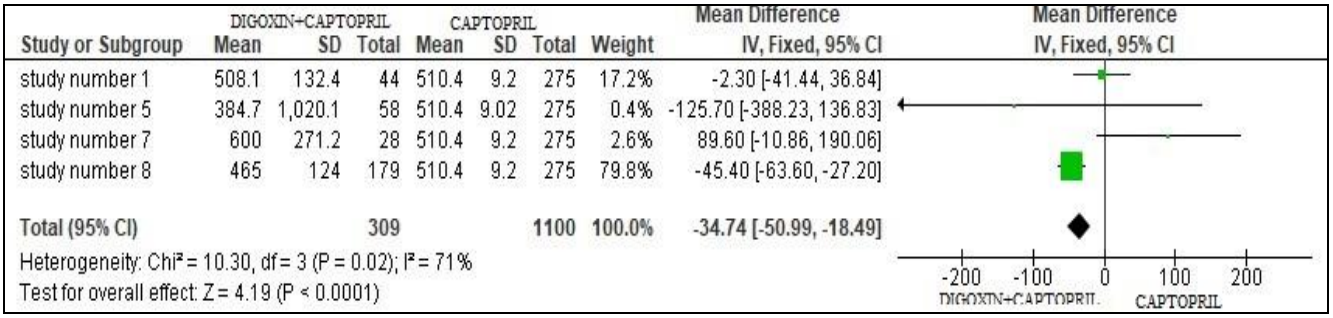


**Fig 13:** Forest plot comparing the time of onset of Anginal attack; after giving these drugs DIGOXIN+CAPTOPRIL vs

**Caltopril**

For comparing the time of onset of angina between DIGOXIN+CAPTOPRIL vs CALTOPRILa total of 4 studies were enrolled; after adding data the mean difference found to be -34.74[-50.99,-18.49] with $\chi 2$ value 10.30 at the degree of freedom 3 at P-value 0.02 and the test for overall effect Z value 4.19 at P-value 0.00001. (Fig. 13)

**Discussion and Conclusion**

This systematic review and meta-analysis looked at how well digoxin and captopril work and how safe they are when used to treat congestive heart failure (CHF). The combined results show that both drugs have a big impact on clinical outcomes linked to worsening CHF, the start of angina episodes, and negative consequences of therapy. However, the two drugs had different levels of therapeutic benefit.

The meta-analysis, which looked at data from four studies that directly compared digoxin with captopril, found a statistically significant difference in the time it took for CHF to start, with a mean difference of −32.37 (95% CI −48.60 to −16.14; P < 0.00001). This means that digoxin may work better for certain people to delay the onset or return of CHF flare-ups. For a long time, people have known that digoxin has a positive inotropic effect. This implies that it helps the heart's muscles contract better and lets more blood flow through the heart in those with systolic heart failure. Digoxin makes the ventricles work better by adding more calcium to cardiac cells. It could also assist with symptoms that happen when the heart doesn't pump enough blood. There was a statistically significant difference in outcomes between digoxin and placebo, with a mean difference of −212.80 (95% CI −225.63 to −199.97). This finding is in accordance with what significant clinical trials like the Digitalis Investigation Group (DIG) research found: digoxin medicine dramatically reduced the incidence of hospitalizations in persons with chronic heart failure. Digoxin doesn't cut the overall death rate by much, but it does help with symptoms and minimize hospital admissions, which makes it a good complement to CHF therapy.

A comparison of captopril versus a placebo also demonstrated a very high advantage in delaying CHF events. Captopril is an angiotensin-converting enzyme (ACE) inhibitor. It stops angiotensin I from turning into angiotensin II. This decreases afterload, makes blood vessels less constricted, and raises cardiac output. ACE inhibitors also prohibit neurohormones from being activated, which is highly critical for the heart failure process. The fact that captopril improves clinical outcomes is in keeping with previous key studies that demonstrated ACE inhibitors may assist heart failure patients live longer. The combination of digoxin and captopril was better than a placebo in delaying CHF episodes. The average difference across the four trials was −166.20 (95% CI −191.25 to −141.14), which is a considerable deal. This discovery shows how combining an inotropic medication with a neurohormonal modulator might have a bigger effect. Digoxin largely makes the heart's contractions stronger, whereas captopril focuses on the conditions that produce them, such narrowing blood vessels and activating hormones in the brain. Different drugs function in different ways, thus they could aid enhance clinical outcomes.

The study found that digoxin and captopril had distinct harmful effects. Both drugs had results that were statistically significant when compared to a placebo. The pooled analysis, on the other hand, found that digoxin had a much lower overall rate of side effects in the studies that were included. However, it is important to remember that digoxin has a narrow therapeutic index and may be dangerous if blood levels aren't constantly monitored. On the other hand, captopril may cause problems including a cough, low blood pressure, renal damage, and excessive potassium levels. The analysis of anginal episodes demonstrated favorable outcomes with digoxin relative to captopril and placebo. However, angina is not the primary clinical outcome in most heart failure research, so these results should be taken with a grain of salt. The pooled estimates may also be less credible since some comparisons only contain a limited number of studies.

Even while the findings are important, there are certain things that need to be said. First, some comparisons only included a few studies, while other analyses were based on only one study. Second, the changes in the study design, patient characteristics, dosing regimens, and follow-up times may have caused the discrepancies between the studies that were included. Third, the usage of beta-blockers, angiotensin receptor blockers, and other medications in the treatment of heart failure during the last several decades may make it tougher to utilize data from older clinical trials.

On the other hand, this meta-analysis gives us vital information on how digoxin and captopril act differently to treat CHF. The results imply that both drugs are still useful for treating patients, particularly when administered as part of a comprehensive pharmacological treatment plan.

Finally, the recent meta-analysis showed that both digoxin and captopril are helpful drugs for treating congestive heart failure. Digoxin had a stronger impact on delaying the commencement of CHF attacks and reducing the frequency of anginal episodes in the trials that were looked at.

Captopril also had a lot of therapeutic advantages over a placebo since it may inhibit the renin-angiotensin system and make the heart function less.

Digoxin and captopril together tend to work better than either drug alone, which suggests that the two drugs may work together to improve cardiac function and patient outcomes. In the studies that were looked at, digoxin had a rather excellent profile of side effects. However, careful monitoring is necessary since it has a narrow therapeutic index.

This meta-analysis shows that digoxin is still a useful add-on drug for treating CHF, particularly when combined with ACE inhibitors like captopril. Still, additional thorough randomized controlled studies are needed to figure out how these drugs should be used in modern heart failure treatment.

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