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[Intervention Review]

Digitalis for treatment of heart failure in patients in sinus rhythm

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ABSTRACT

Background

Digitalis glycosides have been in clinical use for the treatment of heart failure (HF) for longer than 200 years. In recent years, several trials have been conducted to address concerns about their efficacy and toxicity.

Objectives

To examine the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm. To examine the effects of digitalis in patients taking diuretics and angiotensin-converting enzyme inhibitors; in patients with varying severity and duration of disease; in patients with prior exposure to digitalis versus no prior exposure; and in patients with "HF due to systolic dysfunction" versus "HF with preserved ejection fraction."

Search methods

Searches on the following databases were updated in May 2013: The Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, and Dissertation Abstracts. Annual meeting abstracts of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were searched from 1996 to March 2013. In addition, reference lists provided by the pharmaceutical industry (GlaxoSmithKline and Covis Pharma) were searched.

Selection criteria

Included were randomized placebo-controlled trials of 20 or more adult participants of either sex with symptomatic HF who were studied for seven weeks or longer. Excluded were trials in which the prevalence of atrial fibrillation was 2% or greater, or in which any arrhythmia that might compromise cardiac function or any potentially reversible cause of HF such as acute ischemic heart disease or myocarditis was present.

Data collection and analysis

Articles selected from the searches described above were evaluated in a joint effort of the review authors. The staff of the Cochrane Heart Group ran searches on the Cochrane Central Register of Controlled Trials, MEDLINE, and EMBASE.

Main results

No new studies were identified in the updated searches. Thirteen studies (7896 participants) are included, and major endpoints of mortality, hospitalization, and clinical status, based respectively on 8, 4, and 12 of these selected studies, were recorded and analyzed. The data show no evidence of a difference in mortality between treatment and control groups, whereas digitalis therapy is associated

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with lower rates of both hospitalization and clinical deterioration. The largest study, in which most participants were taking angiotensin-converting enzyme inhibitors, showed a significant rise in “other cardiac” deaths, possibly due to arrhythmias. However collectively, these findings were based on studies done before beta-blockers, as well as angiotensin receptor blockers and aldosterone antagonists, became widely used to treat HF.

Authors' conclusions

The literature indicates that digitalis may have a useful role in the treatment of patients with HF who are in normal sinus rhythm. New trials are needed to elucidate the importance of the dosage of digitalis and its usefulness in the era of beta-blockers and other agents shown to be effective in treating HF.

PLAIN LANGUAGE SUMMARY**Digitalis for treatment of heart failure in patients in sinus rhythm**

Digitalis is a drug that is extracted from the leaves of the foxglove plant. It contains substances that stimulate heart muscle. The drug has been used for over two centuries to treat heart failure—a condition caused by inability of the injured heart to pump blood adequately. Other drugs that may be useful include diuretics, angiotensin-converting enzyme inhibitors, and beta-blockers, but digitalis may also be beneficial. The review of trials found that digitalis reduces hospitalization and can help to relieve symptoms of heart failure. More research is needed to show the full effects of digitalis.

BACKGROUND

Until the past three decades, no full-scale randomized trials of digitalis versus placebo were conducted, in part because of concerns about the use of placebo controls to replace the active agent. However, several clinical studies have appeared, showing that digitalis in many instances could be safely withdrawn in participants with HF (Dall 1970; Fonrose 1974; Gheorghide 1983; Hull 1977; Johnston 1979; McHaffie 1978; Starr 1969). At the same time, studies appeared suggesting that digitalis may have favorable short-term effects on exercise tolerance, symptoms, and cardiovascular event rates (Arnold 1980; Dobbs 1977; Firth 1980; Fleg 1991; Kirsten 1973; O'Rourke 1976; Vogel 1977). Some concern has focused on possible long-term toxicity from digitalis, as well as other inotropic agents. The latter was suggested by studies of treatment with the phosphodiesterase inhibitors milrinone (Packer 1991) and enoximone (Cowley 1994), as well as other agents such as the inodilator vesnarinone (Cohn 1998). Digitalis itself was implicated in several nonrandomized trials suggesting that patients with HF treated with digitalis might show excessive mortality rates, particularly when the underlying clinical diagnosis was ischemic heart disease (Bigger 1985; Byington 1985; Moss 1981). Thus conflicting evidence shows that some studies have suggested that digitalis might be discontinued without adverse effects, others have indicated that beneficial effects might indeed be present, and still others have suggested that digitalis might have long-term toxic effects.

Over the past 31 years, information has become available that helps to settle these points. Since 1982, 12 randomized controlled trials of digitalis in HF participants have been published (Blackwood 1990; Dig captopril 1988; Dig milrinone 1989; Dig xamoterol 1988; DIMT 1993; Fleg 1982; Guyatt 1988; Lee 1982; PROVED 1993; Pugh 1989; RADIANCE 1993; Taggart 1983), indicating that digitalis improves clinical outcomes—a conclusion reached in a meta-analysis of the first seven of these trials published in 1990 (Jaeschke 1990). In addition, a large randomized controlled trial has been published showing that digitalis, while improving hospitalization rates, has no significant effect on long-term mortality (DIG study 1997). The current review updates the 1990 meta-analysis and provides a summary statement about the current status of digitalis in treating HF. Although the utility of digitalis glycosides for controlling heart rate in patients with rapid atrial fibrillation is well recognized, the current review is restricted to the use of digitalis in patients who are in normal sinus rhythm.

OBJECTIVES

To examine the effectiveness of digitalis glycosides in treating HF in patients with normal sinus rhythm. To examine the effects of digitalis in patients taking diuretics and angiotensin-converting enzyme inhibitors; in patients with varying severity and duration of disease; in patients with prior exposure to digitalis versus no prior exposure; and in patients with "HF due to systolic dysfunction" versus "HF with preserved ejection fraction."

METHODS

Criteria for considering studies for this review

Types of studies

The central feature of this review is a consideration of the 13 randomized controlled trials selected for inclusion, particularly the data they provide on mortality, hospitalization, and clinical status. Entry criteria were based on the earlier 1990 study (Jaeschke 1990) and included only double-blind randomized trials with placebo controls, a treatment period of seven weeks or longer, and evaluation of each trial for sensibility of entry criteria, method of randomization, completeness of follow-up, and method of handling withdrawals.

Types of participants

This review includes adult participants of both sexes with HF, older than 18 years of age, and of any ethnic group. Criteria for diagnosing HF varied among the studies, but all employed clinical criteria such as presence of dyspnea, orthopnea, rales, S3 gallop, neck vein distention, or peripheral edema. In addition, ejection fraction was measured in some studies. For the purposes of this review, the presence of an ejection fraction of 0.45 or less was considered as identifying a subgroup of individuals having "HF due to systolic dysfunction." Patients with an ejection fraction greater than 0.45 were considered to have "HF with preserved ejection fraction." Duration of HF and history of prior treatment with digitalis are noted when stated.

Digitalis is effective in slowing heart rate in patients with atrial fibrillation, although the effect is a modest one (DAAF Trial 1997; Jordaens 1997). This agent was formerly thought to be of value in causing reversion of atrial fibrillation to sinus rhythm, although the latter theory has been disproved (DAAF Trial 1997; Falk 1987; Jordaens 1997). The advent of many newer antiarrhythmic agents, which are also effective in reducing the heart rate in rapid atrial fibrillation, has somewhat restricted the use of acutely administered intravenous or oral digitalis in this condition, although it still is often used as long-term oral therapy. Because atrial fibrillation is frequently present in patients with HF, exclusion of this group reduces the number of trials available for analysis in the current report. The therapeutic value of digitalis in patients with both HF and atrial fibrillation is, however, an important clinical issue and may be considered in a future review.

Types of interventions

The literature search included participants treated orally with any commonly used digitalis preparation, such as digoxin or digitoxin. For the purposes of this review, the term "digitalis" is used to refer to any of these treatments, although in practice, digoxin was the only agent employed in the 13 included studies. If the information was available, data are included on the incidence of prior treatment with digitalis, dosage levels utilized, and serum or plasma levels achieved. Use of other concurrent cardiac medications, including diuretics, angiotensin-converting enzyme (ACE) inhibitors, and beta-blocking agents, is also recorded.

Types of outcome measures

This review focuses on mortality, hospitalization, and clinical status in the 13 trials considered in the analysis. When available, data are also included on New York Heart Association (NYHA) class, quality

of life as measured by various instruments, treadmill or bicycle exercise test or walk test performance, and various measures of myocardial size or performance.

The quality of data from trials accepted for the review is assessed by ascertaining the presence of factors such as concealment of randomization, blinding to allocation and outcome assessment, comparability at baseline, and losses to follow-up. Sources of heterogeneity are identified by analyzing factors such as dose of digoxin, whether titration to blood level was employed, use of concomitant ACE inhibitor therapy, and whether the trial was a withdrawal trial.

Search methods for identification of studies

The searches, originally run in 2008 ([Appendix 1](#)) and re-run for the previous update in April 2011 ([Appendix 2](#)), were updated in May 2013 ([Appendix 3](#)). The Cochrane Central Register of Controlled Trials (CENTRAL; 2013, Issue 4 of 12), MEDLINE (Ovid) (1946 to May 2013 Week 2), EMBASE (Ovid) (1947 to 2013 Week 20), and Dissertation Abstracts (to February 2013) were searched. For this update, we also searched PubMed (<http://www.ncbi.nlm.nih.gov/pubmed>) on 21 May 2013 to identify any new records not available through MEDLINE.

Annual meeting abstracts of the American Heart Association, the American College of Cardiology, and the European Society of Cardiology were searched from 1996 to March 2013.

The analysis in MEDLINE was restricted to clinical trials for the period 1966 to 1984. Both clinical trials and reviews from 1985 to 2013 were examined. In addition, reference lists provided by the pharmaceutical industry (GlaxoSmithKline and Covis Pharma) were searched. We also searched the clinical study register of GlaxoSmithKline (<http://www.gsk-clinicalstudyregister.com/>). Reference lists of identified studies and reviews were checked.

No language restrictions were applied.

Data collection and analysis

Quantitative information concerning mortality, hospitalization, and clinical deterioration was obtained directly from the articles. Each of these endpoints is presented as a separate meta-analysis, using the algorithms supplied by [Review Manager](#). The meta-analyses are based on a fixed-effect model, and data are presented using the Peto odds ratio.

RESULTS

Description of studies

Previous searches up to April 2011 identified a total of 1854 articles of possible interest. From these, 19 papers were selected for further examination. Four papers were excluded (see [Characteristics of excluded studies](#)). Thirteen studies, reported in 15 papers, were included (see [Characteristics of included studies](#) and references for [Included studies](#)). Updated searches from May 2013 retrieved 383 new records, for a total of 2237 records examined to date. No new studies were identified.

The 13 studies included a total of 7896 participants. Of these, 7755 contributed to information on mortality, 7262 to information on the incidence of hospitalization due to worsening HF during the course of the study, and 1096 to information on clinical

status. The 13 trials varied in size, characteristics of participant populations, duration, drug dosage, ancillary therapy for HF, and experimental design. The largest trial—the one of longest duration—is the study of the Digitalis Investigation Group ([DIG study 1997](#)), a multicenter parallel trial in which 6800 participants with "HF due to systolic dysfunction" were randomly assigned to digoxin or placebo and were followed over a period of three to five years. The primary endpoint of this study was mortality, but information was also provided on the incidence of hospitalization. Because of its size, the DIG study provided 87.7% of the participants included in the mortality analysis and 93.6% of those included in the hospitalization analysis. The DIG study also provided 98.0% of the weight to the meta-analysis for mortality and 97.9% of the weight for hospitalization. However, the DIG study did not provide information on symptoms; these data were derived from the other 12 studies, all of which included this information.

Of the 13 studies, six had a parallel design with drug treatment provided to the active group ([Blackwood 1990](#); [Dig captopril 1988](#); [Dig milrinone 1989](#); [DIG study 1997](#); [Dig xamoterol 1988](#); [DIMIT 1993](#)), two were drug withdrawal studies ([PROVED 1993](#); [RADIANCE 1993](#)), and five had a cross-over design ([Fleg 1982](#); [Guyatt 1988](#); [Lee 1982](#); [Pugh 1989](#); [Taggart 1983](#)). Information derived from withdrawal studies should perhaps be viewed with circumspection ([De Bono 1994](#)) because all participants by definition were previously treated with digitalis and were able to tolerate the agent ([RADIANCE 1993](#)). Therefore they may represent a group that benefits from the use of digitalis, and this could create some bias in favor of the drug. In fact, this type of bias could also be encountered in parallel trials in which digitalis was initially withdrawn from all participants before randomization ([Dig captopril 1988](#); [DIG study 1997](#)). Nonetheless, for the purposes of this review, withdrawal study data are lumped together with data from other groups. Of the 13 studies, eight were multicenter—six with a parallel design and two with a withdrawal design. Each of the other five studies, all with a cross-over design, was carried out at a single institution. Taken together, data on mortality were derived from eight of the 13 studies, data on hospitalization from four, and data on clinical outcomes from 12. Thus no single study provided information on all three endpoints.

With exclusion of the study of the Digitalis Investigation Group ([DIG study 1997](#)), trial duration varied from seven weeks to six months; therefore much of the information reported is relatively short-term. The size of these smaller trials ranged from 20 to 213 participants, with larger numbers recruited into the multicenter trials. Although in most instances, study duration was clearly specified by the protocol, in one study, it varied somewhat ([Lee 1982](#)). Participant characteristics included mean or median age (three studies reported only median age, i.e. [Blackwood 1990](#); [Dig xamoterol 1988](#); [Pugh 1989](#)), which ranged from 58 to 69 years, and with three exceptions ([Blackwood 1990](#); [Dig xamoterol 1988](#); [Fleg 1982](#)), all showed a predominance of male participants. All studies but two ([Lee 1982](#); [Pugh 1989](#)) provided information about NYHA functional class, and most of the participants studied were NYHA Class II or III. Knowledge about severity of illness is of importance in assessing whether the effects of digitalis are dependent on this factor, and comments on this were made in several studies ([Guyatt 1988](#); [Lee 1982](#)). On the other hand, inclusion of less severely ill participants, as may have been the case in one of the relevant studies ([Dig xamoterol 1988](#)), could limit the value of the study in contributing information on endpoints such as mortality, which

clearly is higher in more advanced degrees of HF (CONSENSUS 1987).

All of the 13 studies provided information on the use of diuretics, which were being received by most participants in all but one trial (Dig xamoterol 1988). Five of the thirteen trials provided information on ACE inhibitors, and eight on beta-blocking agents. Seven of the eight studies published before 1990 did not comment on the use of ACE inhibitors, most likely reflecting the fact that these agents were not yet widely available, and that the benefits of treatment with ACE inhibitors (CONSENSUS 1987; SOLVD 1991) had not yet been recognized. More recently, two trials have provided specific information on the actions of digoxin in the presence or absence of concurrent administration of ACE inhibitors. In the trial reported by Uretsky et al, participants taking ACE inhibitors were deliberately excluded, and the trial was ended in part because of growing evidence that treatment with ACE inhibitors was of value in HF (PROVED 1993). In the trial reported by Packer et al, participants taking ACE inhibitors were intentionally enrolled (RADIANCE 1993). In the large study conducted by the Digitalis Investigation Group, use of ACE inhibitors was encouraged, and 94% of participants were receiving this type of agent (DIG study 1997). However, comparable information is not available concerning the concurrent use of beta-blocking agents and digoxin. Of the eight trials in which information about use of beta-blocking agents was given, these agents were not being taken at all in five, and rates of administration in the remaining three trials were low, ranging from 9% to 20% (Fleg 1982; Pugh 1989; Taggart 1983).

The incidence of prior treatment with digitalis, reported in 10 of the 13 studies including by definition the two withdrawal studies, ranged from 46% to 100%. Duration of HF (range 16 months to 3.3 years) was reported in only three of the 13 studies (Dig captopril 1988; DIG study 1997; PROVED 1993). The etiology of HF, which was well characterized in all but one study (Dig xamoterol 1988), was predominantly ischemic. However, the cause was cardiomyopathy in one-third or more of participants in three series (Lee 1982; PROVED 1993; RADIANCE 1993). The incidence of valvular disease was generally low, and such cases were excluded in three series (DIMIT 1993; Guyatt 1988; PROVED 1993), whereas in two studies, the incidence was as high as 34% (Pugh 1989) and 17% (Fleg 1982). Patients with atrial fibrillation were excluded in all but two studies. One study (Dig xamoterol 1988) included a small number of participants with this arrhythmia (four of 213, or 1.9%), and in another, a single participant (one of 108, or 0.9%) had atrial fibrillation (DIMIT 1993). It may also be noted that one study, which otherwise might have qualified for inclusion, was excluded because 13 of the 46 participants in the study (28.3%) had atrial fibrillation (Dobbs 1977). The mean or median dose of digoxin employed (one study reported only the median dose, i.e. PROVED 1993) ranged from 0.25 to 0.435 mg/d in the seven studies that provided this information, and mean serum or plasma levels ranged from 0.87 to 1.15 mg/mL in the six studies that provided these data.

Some information is also provided in the study conducted by the Digitalis Investigation Group on the subgroup of participants with "HF with preserved ejection fraction," who have an ejection fraction in the normal or low normal range (DIG study 1997). The cause of HF in this group may relate to restricted diastolic inflow into the left ventricle. The etiology, treatment, and prognosis for this group were less well defined than for participants with low ejection fraction who display "HF due to systolic dysfunction."

Although it was thought previously that digitalis might be relatively contraindicated in "HF with preserved ejection fraction" (Gaasch 1994), this hypothesis was put to the test by random assignment of an additional 988 participants with HF who had an ejection fraction greater than 0.45 to treatment with digoxin versus placebo (DIG study 1997).

Risk of bias in included studies

Concealment of randomization was employed in all 13 of the studies included in this review, but blinding of outcome assessment is commented on in only five studies. Baseline comparability between control and treatment groups appeared to be achieved in all eight of the non-cross-over studies. Losses to follow-up were small (less than 2%) in the three studies that provided these data. Titration to the level of the dose of digoxin was carried out in six of the trials. These data, plus information presented earlier, suggest that some heterogeneity in clinical characteristics was present among these trials. However, the χ^2 and I^2 values that accompany the meta-analyses (Analysis 1.1, Analysis 1.2, and Analysis 1.3) do not suggest that the degree of statistical heterogeneity was great.

Effects of interventions

Meta-analyses on mortality, hospitalization, and clinical deterioration

A meta-analysis of mortality figures for the eight studies that provided these data clearly showed that treatment with digoxin had no effect on death rate (Analysis 1.1). This observation is based almost entirely on findings in the trial conducted by the Digitalis Investigation Group (DIG study 1997). Although the number of deaths in the other seven studies was quite small, the results appear to be in accord with those of the DIG study (Analysis 1.1). Additional information is available from the study conducted by the Digitalis Investigation Group concerning the causes of mortality, which were assigned by investigators to the categories of "worsening heart failure" and "other cardiac" (DIG study 1997), the latter possibly including many deaths attributable to arrhythmia. The group treated with digoxin showed a trend toward a lower death rate due to "worsening heart failure" (P value 0.06) and a significant increase in death due to "other cardiac" causes (P value 0.04), although the latter was not a prespecified endpoint of the study. These two opposite directional changes tended to counterbalance one another, so that the overall effect on survival was neutral. However, the changes are consistent with a small beneficial effect of digoxin in preventing death directly caused by deterioration in cardiac function, which may have been offset by a small increase in mortality resulting from arrhythmias, observations of which are plausible in view of the known pharmacologic and electrophysiologic actions of digitalis. These findings may provide a basis for future investigations of factors that predispose to "other cardiac" death, although none are described in the report (DIG study 1997).

Four studies provided data on hospitalization for worsening HF (Analysis 1.2). The figure shows that hospitalization for worsening HF was significantly less common among participants taking digoxin than in the control group. Point estimates in terms of odds ratios are shown in the figure, with an overall relative risk reduction (RRR) of 23.4%. The baseline risk of hospitalization in the control groups in these four studies, if constant hazard over the study duration is assumed, ranged from 9.7% to 34.7%, with the larger

figure a function of the much longer duration of the DIG study. Values for calculated numbers needed to treat for an additional beneficial outcome (NNTB) ranged from 13 to 17 (Table 1).

Twelve trials presented data on cardiac symptoms (Analysis 1.3). The figure shows that the clinical status of participants taking digoxin was better than that of participants assigned to placebo therapy. Because these 12 smaller trials had many fewer participants than the DIG study, less than 15% of the entire study population was available to contribute to this meta-analysis. Comparable data were not collected in the DIG study, although the group has published in abstract form a retrospective analysis suggesting that digoxin does ameliorate symptoms in HF (DIG study 1999). Point estimates in terms of odds ratios are shown in the figure, with an overall RRR of 64.5%. The baseline risk of clinical deterioration in the control groups in 11 of these studies in which this calculation could be made, assuming constant hazard over the study duration, ranged from 3.8% to 46.9%, and calculated NNTB from 3 to 61 (Table 2).

Other observations

The total series of 13 studies included several other observations (see Characteristics of included studies). One of these is the result of treadmill or bicycle exercise testing and of the six-minute walk test. Unfortunately, these data were not presented in a consistent manner, and no meta-analysis could be done. However of the 10 studies using exercise testing (Blackwood 1990; Dig captopril 1988; Dig milrinone 1989; Dig xamoterol 1988; DIMT 1993; Fleg 1982; Guyatt 1988; PROVED 1993; Pugh 1989; RADIANCE 1993), functional capacity was significantly improved by digoxin in four (Dig milrinone 1989; DIMT 1993; PROVED 1993; RADIANCE 1993). Of the three studies in which a six-minute walk test was carried out (Guyatt 1988; PROVED 1993; RADIANCE 1993), one showed a beneficial effect of digoxin (RADIANCE 1993). Of the eight studies in which assessment of NYHA class or evaluation of a "heart failure score" was performed (Dig captopril 1988; DIMT 1993; Guyatt 1988; Lee 1982; PROVED 1993; Pugh 1989; RADIANCE 1993; Taggart 1983), the results were significantly better with digoxin in four (Guyatt 1988; Lee 1982; Pugh 1989; RADIANCE 1993), whereas no significant change was noted in the other four studies. Quality of life was assessed in four studies (Blackwood 1990; Guyatt 1988; PROVED 1993; RADIANCE 1993) and in a substudy of the trial conducted by the Digitalis Investigation Group (Lader 2003), but a significant result favoring digoxin was noted in only one (RADIANCE 1993). Ejection fraction as a treatment endpoint was measured in five studies (Dig captopril 1988; Dig milrinone 1989; Lee 1982; PROVED 1993; RADIANCE 1993), and the measurement was significantly better with digoxin than placebo therapy in four of them (Dig captopril 1988; Dig milrinone 1989; PROVED 1993; RADIANCE 1993). Cardiothoracic ratio was an endpoint in four studies (Fleg 1982; Guyatt 1988; Lee 1982; Taggart 1983), with a result favoring digoxin noted in two of these studies (Guyatt 1988; Lee 1982). Left ventricular end-diastolic dimension was measured in six studies (Fleg 1982; Guyatt 1988; Lee 1982; PROVED 1993; Pugh 1989; RADIANCE 1993), with a result favoring digoxin therapy in three of them (Fleg 1982; Lee 1982; RADIANCE 1993). In general, these findings suggest a beneficial effect from digitalis treatment, although the results were by no means uniform or consistent. One may conclude that digitalis does have favorable effects, but that they are not very pronounced and may not be observed in all patients. This point has been made in several of the publications

included in this review (Dig xamoterol 1988; Fleg 1982; Guyatt 1988; Taggart 1983).

Additional observations were made in the ancillary study conducted by the Digitalis Investigation Group in 988 participants with "HF with preserved ejection fraction" (DIG study 1997). The pathophysiologic mechanism in this group of participants may relate to restricted diastolic inflow into the left ventricle. Concern has been expressed about whether treatment with digoxin is relatively contraindicated, as the agent could reduce ventricular diastolic compliance (Gaasch 1994). However, findings of the study conducted by the Digitalis Investigation Group do not support this concept (Ahmed 2006; DIG study 1997), as no difference in mortality was seen in participants with "HF with preserved ejection fraction" who received digoxin (N = 492) versus placebo (N = 496). In addition, a trend toward reduction in the combined outcome of death or hospitalization due to worsening heart failure was observed (risk ratio 0.82, 95% confidence interval 0.63 to 1.07).

DISCUSSION

Use of digitalis in the treatment of HF has been considerably attenuated by the widespread acceptance of ACE inhibitors (CONSENSUS 1987; SOLVD 1991) and beta-blocking agents (Carvedilol 1996; CIBIS II 1999; MERIT-HF 1999; Packer 2001) for treating this syndrome. Use of ACE inhibitors and beta-blocking agents is based on randomized clinical trials that conclusively show that both agents decrease mortality. Failure of digoxin to reduce mortality suggests that agents with a mortality benefit—ACE inhibitors and beta-blocking agents—should be offered to patients in preference to the older drug. However, the present review does show that digoxin therapy can have beneficial effects, even in patients already treated with ACE inhibitors, and most participants in the trials that demonstrated benefits of digoxin for clinical status were also receiving diuretics. Based on these findings, clinicians can offer digoxin to patients who remain symptomatic despite treatment with ACE inhibitors and to those at appreciable risk of hospitalization, with reasonable expectation of benefit. Whether these findings generalize to patients receiving beta-blockers is unknown at the present time, although a retrospective study showed no benefit of digoxin therapy in a group of predominantly male participants receiving contemporary therapy that included beta-blockers (Dhaliwal 2008).

Beta-blocking agents are now, in conjunction with ACE inhibitors, the cornerstone of treatment for HF (CIBIS II 1999; COPERNICUS 2002; MERIT-HF 1999; SENIORS 2005). Any information yet to be derived in future trials about treatment of HF with digoxin will be obtained in the setting of concurrent treatment with ACE inhibitors plus beta-blocking agents. Also of note are findings that the aldosterone inhibitors spironolactone (RALES 1999) and eplerenone (Zannad 2011) and the angiotensin receptor blockers valsartan (Cohn 2001) and candesartan (CHARM 2003) have beneficial long-term effects in HF. All of these agents appear to be effective in groups of participants with substantial levels of digoxin usage: 73% in the spironolactone trial (RALES 1999), 27% in the eplerenone study (Zannad 2011), 67% in the valsartan trial (Cohn 2001), 43% in the candesartan trial (CHARM 2003), and more than 50% in some beta-blocker trials (CIBIS II 1999; Packer 2001), with demonstrable continuing effectiveness in participants already receiving digitalis.

Although the DIG study showed no reduction in mortality among participants receiving digoxin, the overall effect on reduction of HF hospitalization of 7.9% was substantial (DIG study 1997). This effect occurred within one month of the start of therapy (Bourge 2013) and was sustained (Ahmed 2009). Regarding the use of digitalis in patients with HF of varying severity, individuals with impaired cardiac function who have few or no symptoms (NYHA Class I) and are at low risk for exacerbations or hospitalizations, as occurred in 25% of participants in one of the trials reported here (Dig xamoterol 1988), are very unlikely to receive important benefit from digoxin. The bulk of information available for digoxin therapy pertains to patients whose status is NYHA Class II or III, and this is the group in which digoxin improves symptoms and decreases exacerbations. Some evidence suggests that patients with more advanced symptoms may respond better to digoxin than those with less severe HF (Adams 1998; DIG study 1997; DIMT 1993; Gheorghiade 2013; Guyatt 1988; Lee 1982). In one study it was noted that participants with an S3 gallop and a dilated and poorly functioning ventricle may tend to respond most favorably to digoxin (Lee 1982). Other investigators have sought to confirm this observation but with somewhat less striking results (Guyatt 1988).

The issue of dosage of digitalis and its use in various subgroups has also been explored, with several publications based on retrospective analyses of the large trial carried out by the Digitalis Investigation Group (DIG study 1997). Such findings must be interpreted cautiously and need to be confirmed in prospective studies. Lower doses appear to be associated with beneficial effects (ACC/AHA Guidelines 2005; Adams 2002; ESC Guidelines 2008; HFSA Guideline 2006), as demonstrated in the large DIG study, in which the median baseline dosage of digoxin was 0.25 mg/d (DIG study 1997). A post-hoc analysis of the DIG study suggested that lower doses and serum digoxin levels were associated with reduced mortality and hospitalization in comparison with the placebo group (Ahmed 2009), and another post-hoc analysis of the results in the DIG study suggested that higher serum digoxin levels were associated with an increase in mortality (Rathore 2003). On the other hand, evidence shows that larger doses of digoxin are associated with improved efficacy (RADIANCE 1993; Slatton 1997). Furthermore, results from two of the trials (PROVED 1993; RADIANCE 1993) suggest that clinical efficacy was independent of the digoxin dosage (Adams 2002). In summary, results indicate that patients may receive comparable benefits from digoxin dosage regimens that are in current use, although some caution may be required when higher doses are employed.

With regard to differential effects in men and women, a post-hoc analysis of the DIG study observed that digoxin therapy was associated with an increase in mortality in women, but not in men (Rathore 2002)—an observation supported by a recent cluster analysis of the DIG study data (Ather 2011). The difference was more pronounced in those with higher serum digoxin levels (Adams 2005). This gender differentiation is not, however, consistent (Domanski 2005). No evidence suggests that age (Rich 2001) or duration of HF is important in the decision of who should receive digoxin, and evidence from yet another DIG study post-hoc analysis suggests that the drug is effective in low doses and with low serum digoxin levels in a geriatric population (Ahmed 2007). No evidence suggests a selective advantage for digoxin therapy in patients whose HF is of ischemic or cardiomyopathic origin.

Based on yet another post-hoc analysis in a subset of participants in the DIG study (DIG study 1997), evidence that digoxin improves renal function has been observed (Testani 2011). In addition, beneficial effects of digoxin on the combined endpoint of cardiovascular death and hospitalization for worsening HF in the DIG study were comparable to those occurring in HF patients receiving the sinus node I_f inhibitor ivabradine (Castagno 2012). These findings are perhaps attributable to the bradycardic action of ivabradine comparable to heart rate slowing by digoxin resulting from its known effects on vagal tone. This observation may stimulate further studies to determine the importance of heart rate reduction in treating HF patients.

Although the emphasis in this review is on the beneficial effects of digitalis, it provides more valid data on effectiveness than on harm. However, toxic effects of digitalis therapy are well known and include adverse interactions with other drugs, electrolytes, and various disease states, as well as induction of proarrhythmias. In addressing the issue of postmarketing surveillance, the US Food and Drug Administration (FDA) archives provide an extensive list of these adverse effects but are lacking long-term follow-up in large numbers of patients analogous to the RCT approach used to evaluate beneficial effects.

Findings in the ancillary study of the Digitalis Investigation Group in patients having "HF with preserved ejection fraction" raise new questions about this entity (DIG study 1997). Although it is evident that a substantial fraction of patients with HF may share this pathophysiology (Jones 2004; Vasani 1999), the etiology, treatment, and prognosis for this group are less well defined than for patients having "HF due to systolic dysfunction." Some investigators have suggested that the prognosis may be more favorable in patients having "HF with preserved ejection fraction" than in those with "HF due to systolic dysfunction" (Vasani 1999), as was the case in the ancillary study (DIG study 1997). Although the DIG study ancillary trial showed a trend toward better outcomes in the group receiving digoxin for the combined endpoint of death or hospitalization due to worsening heart failure (DIG study 1997), it is still possible that digoxin is not beneficial or may even be harmful in several conditions in which "HF with preserved ejection fraction" is present. These may include such conditions as hypertrophic cardiomyopathy and amyloid infiltration of the myocardium (Chew 1975). Four participants in one of the series included in this review (Lee 1982) had a diagnosis of hypertrophic cardiomyopathy, but none of these participants responded positively to digoxin therapy.

The mechanism of action of digoxin is also of interest. Digitalis has multiple effects on cardiac function at the cellular level (Wasserstrom 2005), but the mechanism by which beneficial effects on the failing heart are produced is not fully understood. The traditional view has been that the drug exerts beneficial inotropic effects on the failing heart, but more recent evidence suggests that reduction of augmented adrenergic tone and renin-angiotensin system activation in HF may also play a role (Packer 1992; Packer 1999). Evidence indicates that digoxin treatment of patients with HF can reduce sympathetic tone (Ferguson 1989; Gheorghiade 1991), as exemplified in one study among the 13 included in this report that demonstrated a reduction in circulating catecholamine levels in the digoxin-treated group (DIMT 1993). Digoxin therapy may also inhibit the renin-angiotensin system (Covit 1983) and augments vagal tone, as evidenced by an increase in heart rate variability (DIMT 1995) and frequent occurrence of sinus node

slowing (Castagno 2012). These observations may relate to the question raised earlier regarding the effects of digoxin therapy in patients who are already taking beta-blocking agents because the latter could abrogate the sympatholytic effects of digoxin (Hauptman 1999). However, ACE inhibitors also reduce sympathetic tone, yet digoxin is known to be effective in this group of patients (RADIANCE 1993).

The key question is whether digoxin added to a treatment regimen that already includes ACE inhibitors and beta-blocking agents, or some combination of these agents with spironolactone or the angiotensin receptor blockers valsartan or candesartan, produces additional gains. The preferable sequence for adding digoxin, spironolactone, or an angiotensin receptor blocker to established treatment with ACE inhibitors and beta-blockers remains uncertain at the present time. However currently available data indicate that spironolactone (RALES 1999), candesartan (CHARM 2003), and eplerenone (Zannad 2011) may reduce mortality and morbidity in patients with HF, and both digoxin (DIG study 1997) and valsartan (Cohn 2001), as well as candesartan (CHARM 2003), reduce hospitalization. Digoxin is at least as efficacious as valsartan and candesartan in this respect. Another issue is whether there are different indications for these agents in NYHA Class IV HF. Finally, there is the question of whether digoxin truly has a different mechanism of action in patients having "HF due to systolic dysfunction" versus "HF with preserved ejection fraction," and whether this is dependent on the underlying cause of the two syndromes. In patients having "HF with preserved ejection fraction," does digoxin actually have any therapeutic potential?

AUTHORS' CONCLUSIONS

Implications for practice

The results of the present meta-analyses further strengthen the concept that digoxin may have beneficial effects in treating patients with HF who remain symptomatic despite therapy with ACE inhibitors, diuretics, and possibly beta-blockers. The agent has been shown to improve clinical status and to reduce hospitalizations. Although some authors have stated that the agent is of limited value, and its ultimate role in the current era of

improved pharmacotherapy for HF remains untested, the agent may still have value as adjunctive therapy. The significant rise in "other cardiac" deaths possibly due to arrhythmias warrants cautious use in patients at risk for such events.

Implications for research

Several unanswered questions may ultimately deserve further investigation. Concerns about dosage and specific indications for digoxin therapy in different subgroups have led to the suggestion that additional clinical trials in the future may be warranted (Ahmed 2009; van Veldhuisen 2002). It has also been recommended that studies of the drug be carried out in acute heart failure syndromes (Gheorghiu 2009). Of considerable interest is the question whether there is truly a slight decrease in mortality due to "worsening heart failure" and an increase in mortality due to "other cardiac" causes in patients taking digoxin (DIG study 1997), but further studies on the point are lacking.

Despite more than two centuries of use, up-to-date information about digitalis is still not available in the current era, when several newer first-line agents have been identified for the treatment of HF. The DIG study is now 16 years old, and although most of the study participants were taking ACE inhibitors, definitive information about interactions with beta-blockers and with angiotensin receptor blockers and aldosterone inhibitors is lacking. Perhaps in the future, studies will be carried out to address these unknowns.

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van Veldhuisen DJ. Low-dose digoxin in patients with heart failure. Less toxic and at least as effective?. *Journal of the American College of Cardiology* 2002;**39**:954-6.

Vasan 1999

Vasan RS, Larson MG, Benjamin EJ, Evans JC, Reiss CK, Levy D. Congestive heart failure in subjects with normal versus reduced left ventricular ejection fraction: prevalence and mortality in a population-based cohort. *Journal of the American College of Cardiology* 1999;**33**:1948-55.

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Vogel R, Frischknecht J, Steele P. Short- and long-term effects of digitalis on resting and posthandgrip hemodynamics in patients with coronary artery disease. *American Journal of Cardiology* 1977;**40**:171-6.

Wasserstrom 2005

Wasserstrom JA, Aistrup GL. Digitalis: new actions for an old drug. *American Journal of Physiology, Heart and Circulatory Physiology* 2005;**289**:H1781-93.

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Zannad F, McMurray JJV, Krum H, Van Veldhuisen DJ, Swedberg K, Shi H, et al. Eplerenone in patients with systolic heart failure and mild symptoms. *New England Journal of Medicine* 2011;**364**:12-21.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES
Characteristics of included studies [ordered by study ID]
Blackwood 1990

Methods	three-mo multicenter parallel trial with third xamoterol arm; endpoints—ET, QOL
Participants	61 pts; *median age 60; 50% male; 94% Class II, 6% Class III; 56% on diuretics; dx—~67% ischemic *Note: Figures shown in "Participants" section show composite data from all three study arms, except for number of pts
Interventions	dig dosage 0.25 mg/d
Outcomes	for dig vs pla, no significant difference in ET, QOL
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—yes loss to follow-up—?

Blackwood 1990 (Continued)

dig titrated to level—no

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Dig captopril 1988

Methods	six-mo multicenter parallel trial with third captopril arm; primary endpoint—ET; secondary endpoints—NYHA class, hospitalization, EF
Participants	196 pts; mean age 58; 83% male; 80% Class II; 87% on diuretics, none on beta-blockers; mean EF 0.25; mean duration of HF 3.0 yrs; prior dig Rx in 68%; dx—61% ischemic, 31% cardiomyopathic
Interventions	dig dosage of 0.125 to 0.375 mg/d titrated to serum levels of 0.7 to 2.5 ng/mL
Outcomes	for dig versus pla, ET +10% & +6% (P value NS), EF +17% & +3% (P < 0.01); NYHA class improved in 31% of dig versus 22% of pla (P value NS)
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—yes loss to follow-up—? dig titrated to level—yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Dig milrinone 1989

Methods	12-wk multicenter parallel trial with third milrinone arm & fourth dig + milrinone arm; endpoints—ET, EF
Participants	111 pts; mean age 60; 76% male; 32% Class II, 66% Class III; 100% on diuretics, none on beta-blockers; mean EF 0.25; dx—53% ischemic, 32% idiopathic
Interventions	dig dosage 0.125 to 0.5 mg/d
Outcomes	ET +14% for dig (P < 0.03 compared with pla); EF +6.7% for dig, -8.2% for pla (P < 0.01)
Notes	blind allocation—yes blinded to outcomes—yes baselines comparable—yes loss to follow-up—? dig titrated to level—no

Dig milrinone 1989 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

DIG study 1997

Methods	Three- to five-yr (mean follow-up 37 mo) multicenter parallel trial; primary endpoint—mortality; secondary endpoint—hospitalization for HF
Participants	6800 pts with EF \leq 0.45 in main trial; mean age 63; 88% male; 54% Class II, 31% Class III; 82% on diuretics, 94% on ACEI; EF 0.29 & 0.28 (dig & pla); median duration of HF 17 & 16 mo (dig & pla); prior dig Rx in 44%; dx—71% ischemic, 15% idiopathic. Note: ancillary trial carried out in 988 additional pts with EF > 0.45
Interventions	dig dosage at investigators' discretion; median baseline dosage in main trial of 0.25 mg/d
Outcomes	main trial mortality, dig versus pla: overall 34.8% & 35.1% (P value 0.80), from "worsening heart failure" 11.6% & 13.2% (P value 0.06), from "other cardiac" 15.0% & 13.0% (P value 0.04); main trial hospitalization, dig versus pla: 26.8% & 34.7% (P < 0.001); ancillary trial mortality 23.4% in both groups
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—yes main trial loss to follow-up—1.4% dig titrated to level—no

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Dig xamoterol 1988

Methods	Three-mo multicenter parallel trial with third xamoterol arm; endpoints—EX, symptoms, signs
Participants	213 pts; median age 62; 38% male; 25% Class I, 62% Class II, 13% Class III; 22% on diuretics, none on ACEI or beta-blockers; prior dig Rx in 46%; dx—unspecified in 76% of pts
Interventions	dig dosage 0.25 mg/d, mean plasma dig level 0.87 ng/mL
Outcomes	for dig versus pla, no significant difference in EX; symptoms: Likert but not VAS improved by dig; signs: edema & rales improved by dig, but not JVP or hepatomegaly
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—yes loss to follow-up—? dig titrated to level—no

Digitalis for treatment of heart failure in patients in sinus rhythm (Review)

Dig xamoterol 1988 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

DIMT 1993

Methods	Six-mo multicenter parallel trial with third ibopamine arm; primary endpoint—EX; secondary endpoints—"heart failure score," change in plasma norepinephrine
Participants	108 pts; mean age 61; 86% male; 80% Class II, 20% Class III; 100% on diuretics, none on ACEI or beta-blockers; dx—69% ischemic, 31% idiopathic; valvular disease excluded
Interventions	dig dosage 0.25 mg/d, mean plasma level 0.94 ng/mL
Outcomes	for dig versus pla, EX +1.6% & -5.8% (P value 0.008); no significant difference in "heart failure score;" plasma norepinephrine values changed by -106 pg/mL for dig & +62 pg/mL for pla (P < 0.001)
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—yes loss to follow-up—? dig titrated to level—no

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Fleg 1982

Methods	Three-mo cross-over trial; endpoints—ET, CT ratio, LVED, FS, Vcf
Participants	30 pts; mean age 69; 47% male; 53% Class II, 43% Class III; 77% on diuretics, 13% on beta-blockers; prior dig Rx in 87%; dx—63% ischemic, 17% valvular
Interventions	dig dosage titrated to serum dig level of 1.0 to 2.0 ng/mL
Outcomes	for dig versus pla, no difference in ET, CT ratio, FS; LVED 55.8 & 57.6 mm (P < 0.001), Vcf 0.90 & 0.82 circ/s (P < 0.05)
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—NA loss to follow-up—? dig titrated to level—yes

Risk of bias
Digitalis for treatment of heart failure in patients in sinus rhythm (Review)

Fleg 1982 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Guyatt 1988

Methods	Seven-wk cross-over trial; endpoints—"heart failure score," six-minute walk test, CT ratio, QOL, LVED, FS, EX	
Participants	20 pts; mean age 63; 90% male; 50% Class II, 40% Class III; 90% on diuretics; prior dig Rx in 85%; dx—85% ischemic; valvular disease excluded	
Interventions	dig dosage titrated to serum level of 1.54 to 2.56 nmol/L (1.2 to 2.0 ng/mL), mean dig dosage 0.391 mg/d	
Outcomes	for dig versus pla, "heart failure score" 2.3 & 4.4 (P value 0.001), six-minute walk test 411 & 392 m (P value 0.055), CT ratio 0.53 & 0.58 (P value 0.04), FS 21% & 17% (P value 0.04); no significant difference in QOL profile, LVED, EX	
Notes	blind allocation—yes blinded to outcomes—yes baselines comparable—NA loss to follow-up—? dig titrated to level—yes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Lee 1982

Methods	cross-over trial, mean treatment duration 53 days for both dig & pla; endpoints—"heart failure score," CT ratio, LVED, EF	
Participants	25 pts; mean age 61; 72% male; 88% on diuretics; mean EF 0.29; prior dig Rx in 96%; dx—60% ischemic, 24% cardiomyopathic, 16% hypertrophic cardiomyopathy	
Interventions	dig dosage titrated to mean serum level of 1.15 ng/mL, mean dig dosage 0.435 mg/d	
Outcomes	for dig versus pla, "heart failure score" 2.0 & 3.6 (P < 0.05), CT ratio 0.51 & 0.53 (P value 0.00027), LVED 31 & 33 mm/sq m (P value 0.0026), EF 0.30 & 0.29 (P value NS)	
Notes	blind allocation—yes blinded to outcomes—yes baselines comparable—NA loss to follow-up—? dig titrated to level—yes	

Risk of bias
Digitalis for treatment of heart failure in patients in sinus rhythm (Review)

Lee 1982 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

PROVED 1993

Methods	12-wk multicenter withdrawal trial; primary endpoint—ET, six-minute walk test; secondary endpoints—QOL, "heart failure score," global evaluation of progress, LVED, EF	
Participants	88 pts; mean age 64; 85% male; 83% Class II or III; 100% on diuretics, none on ACEI or beta-blockers; mean EF 0.28; mean duration of HF 3.3 yrs; prior dig Rx in 100%; dx—64% ischemic, 36% cardiomyopathic; valvular disease excluded	
Interventions	dig dosage titrated to mean serum level of 1.2 ng/mL, median digoxin dosage 0.375 mg/d	
Outcomes	for dig versus pla, median ET change +1% & -18% (P value 0.003); no significant difference in six-minute walk test, QOL profile, "heart failure score," global evaluation of progress, LVED; EF +7% for dig & -10% for pla (P value 0.016)	
Notes	blind allocation—yes blinded to outcomes—yes baselines comparable—yes loss to follow-up—1.1% dig titrated to level—yes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Pugh 1989

Methods	Eight-wk cross-over trial; endpoints—clinical score, systolic time intervals (LVET, PEP, PEP/LVET, LVED, FS, Vcf, ET)	
Participants	44 pts; median age 62; 73% male; 75% on diuretics, 20% on beta-blockers; prior dig Rx in 100%; dx—61% ischemic, 34% valvular	
Interventions	dig dosage was "the patient's usual dose"	
Outcomes	for dig versus pla, worsened clinical score in 11% versus 25% of pts (P < 0.04); borderline decrease in PEP (P ≤ 0.08), no significant differences in LVED, PEP/LVET, FS, Vcf, ET	
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—NA loss to follow-up—? dig titrated to level—no	

Risk of bias
Digitalis for treatment of heart failure in patients in sinus rhythm (Review)

Pugh 1989 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

RADIANCE 1993

Methods	Three-mo multicenter withdrawal trial; primary endpoints—clinical deterioration, ET, six-minute walk test; secondary endpoints—symptoms, QOL, functional class, LVED, EF
Participants	178 pts; mean age 60; 76% male; 73% Class II, 27% Class III; 100% on diuretics & ACEI; mean EF 0.27; prior dig Rx in 100%; dx—60% ischemic, 38% cardiomyopathic
Interventions	dig dosage titrated to mean serum level of 1.2 ng/mL, mean dig dosage 0.38 mg/d
Outcomes	for dig versus pla, ET 43 seconds greater (P value 0.033), six-minute walk test 41 m further (P value 0.01), better self-assessed symptoms (P value 0.007) & QOL profile (P value 0.04), less deterioration in class (10% vs 27%, P value 0.019); LVED -1.4% versus +3.0% (P value 0.04), EF -3.7% versus -13.3% (P value 0.001)
Notes	blind allocation—yes blinded to outcomes—yes baselines comparable—yes loss to follow-up—1.7% dig titrated to level—yes

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Taggart 1983

Methods	Three-mo cross-over trial; endpoints—"heart failure score," CT ratio, systolic time intervals (LVET, PEP, PEP/LVET)
Participants	22 participants; mean age 65; 64% male; 82% Class II; 95% on diuretics, 9% on beta-blockers; prior dig Rx in 100%; dx—77% ischemic, 9% valvular
Interventions	mean plasma dig level 1.2 ng/mL
Outcomes	for dig versus pla, no significant difference in "heart failure score," CT ratio; LVET 388 & 403 msec (P < 0.001), PEP 128 & 138 msec (P < 0.001), PEP/LVET 0.39 & 0.41 (P < 0.02)
Notes	blind allocation—yes blinded to outcomes—? baselines comparable—NA loss to follow-up—? dig titrated to level—no

Risk of bias
Digitalis for treatment of heart failure in patients in sinus rhythm (Review)

Taggart 1983 (Continued)

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A—Adequate

Abbreviations:

ET = treadmill exercise time.

class = NYHA functional class.

EF = ejection fraction.

pts = participants.

HF = heart failure.

dig = digoxin.

Rx = treatment.

dx = diagnosis.

pla = placebo.

ACEI = angiotensin-converting enzyme inhibitors.

EX = bicycle exercise.

VAS = visual analogue scale.

JVP = jugular venous pulse.

CT ratio = cardiothoracic ratio.

QOL = quality of life.

LVED = left ventricular end-diastolic dimension.

FS = fiber-shortening fraction.

Vcf = circumferential fiber shortening velocity.

LVET = left ventricular ejection time.

PEP = pre-ejection period.

mo = month.

wk = week.

yr = year.

Note: For studies of dig versus pla with additional arms, all data shown are for the dig and pla groups only.

Characteristics of excluded studies [ordered by study ID]

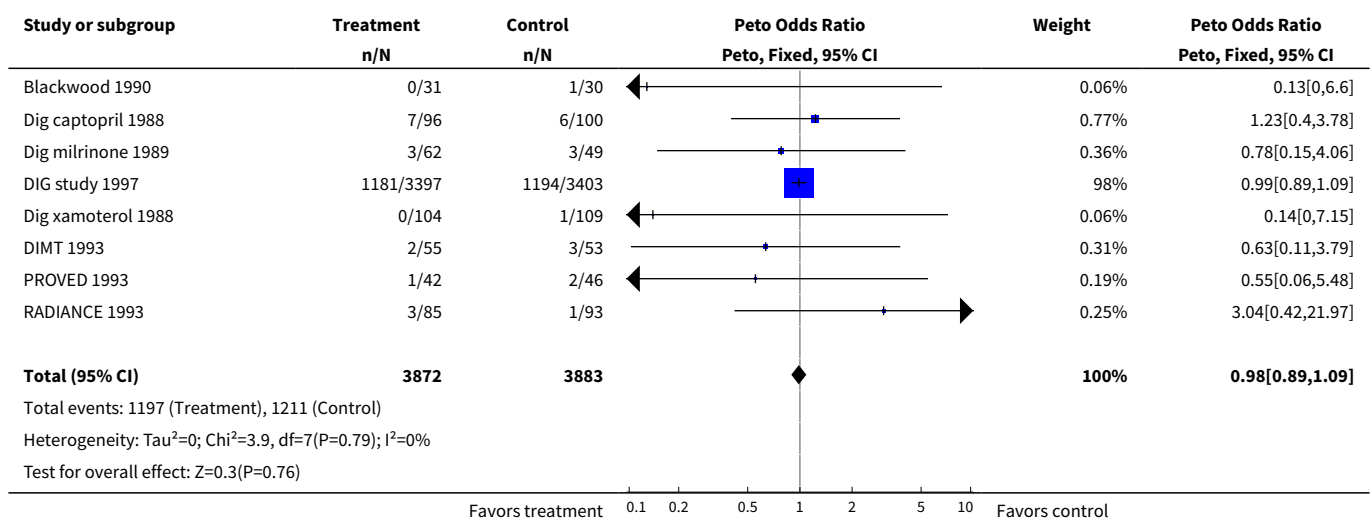
Study	Reason for exclusion
Dobbs 1977	Atrial fibrillation in 28.3% of participants
Fleg 1991	Ten participants, studied using cross-over design over two four-week periods
Just 1993	Study in 133 participants directed at individuals "without significantly reduced ejection fraction at rest"
Kostis 1994	Seven participants randomly assigned to digitalis and six to placebo

DATA AND ANALYSES

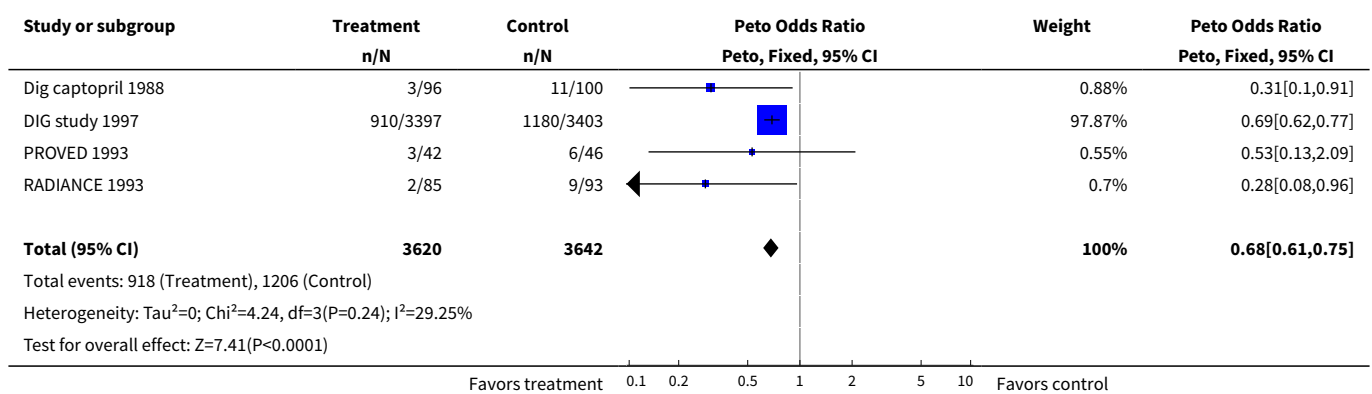
Comparison 1. Digitalis versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Figure 1—Mortality	8	7755	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.98 [0.89, 1.09]
2 Figure 2—Hospitalization	4	7262	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.68 [0.61, 0.75]
3 Figure 3—Clinical deterioration	12	1234	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.31 [0.21, 0.43]

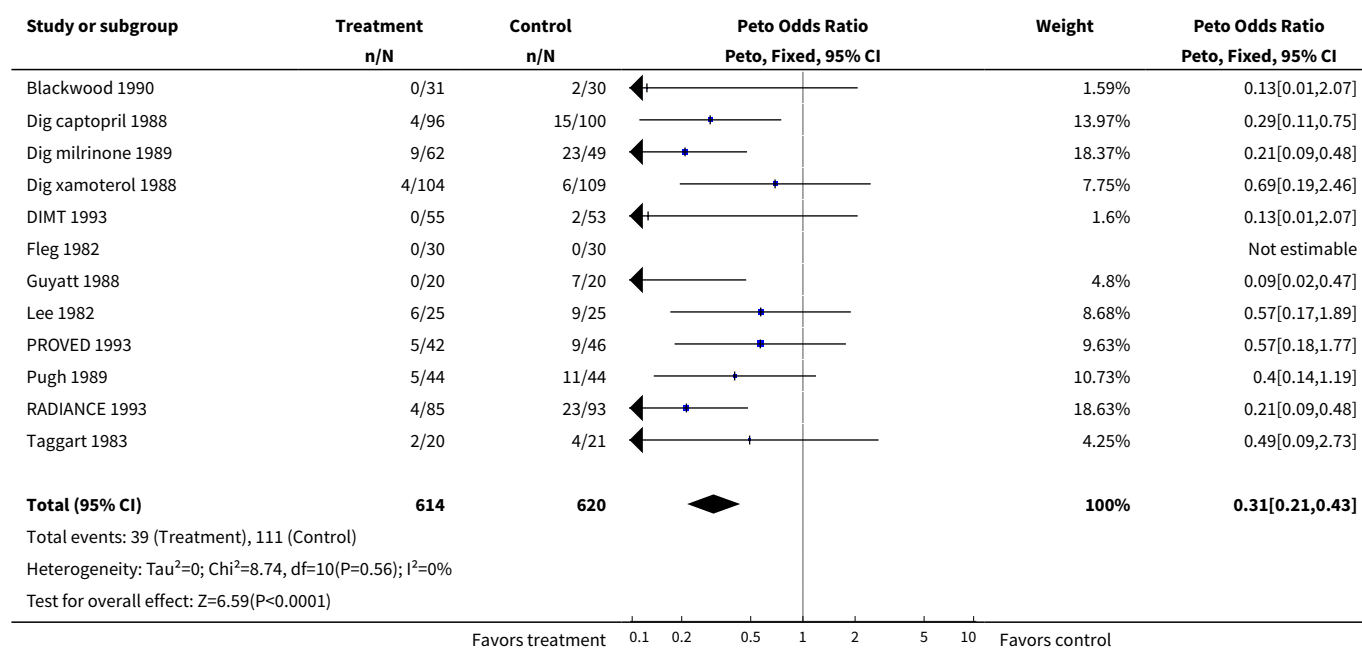
Analysis 1.1. Comparison 1 Digitalis versus control, Outcome 1 Figure 1—Mortality.



Analysis 1.2. Comparison 1 Digitalis versus control, Outcome 2 Figure 2—Hospitalization.



Analysis 1.3. Comparison 1 Digitalis versus control, Outcome 3 Figure 3—Clinical deterioration.



ADDITIONAL TABLES

Table 1. Hospitalization

Study	Baseline risk	Odds ratio	NNTB	Study duration	Comment
Dig captopril 1988	11.0%	0.31	13	six months	
DIG study 1997	34.7%	0.69	13	mean 37 months	Note NNTB similar despite longer study duration
PROVED 1993	13.0%	0.53	17	three months	
RADIANCE 1993	9.7%	0.28	14	three months	

Table 2. Clinical deterioration

Study	Baseline risk	Odds ratio	NNTB	Study duration
Blackwood 1990	6.7%	0.13	15	three months
Dig captopril 1988	15.0%	0.29	10	six months
Dig milrinone 1989	46.9%	0.21	4	12 weeks
Dig xamoterol 1988	5.5%	0.69	61	three months
DIMT 1993	3.8%	0.13	27	six months

Table 2. Clinical deterioration (Continued)

Guyatt 1988	35.0%	0.09	3	seven weeks
Lee 1982	36.0%	0.57	9	mean 53 days
PROVED 1993	19.6%	0.57	14	12 weeks
Pugh 1989	25.0%	0.40	8	eight weeks
RADIANCE 1993	24.7%	0.21	5	three months
Taggart 1983	19.0%	0.49	12	three months

APPENDICES

Appendix 1. Search strategies 2008

CENTRAL

- #1 DIGITALIS-GLYCOSIDES*:ME
- #2 DIGITALIS
- #3 DIGOXIN
- #4 DIGITOXIN
- #5 (#1 or #2 or #3 or #4)
- #6 HEART-FAILURE-CONGESTIVE*:ME
- #7 (HEART near FAILURE)
- #8 (CARDIAC near FAILURE)
- #9 (#6 or #7 or #8)
- #10 (#5 and #9)

MEDLINE on Ovid (2008 November 13)

- 1 Digitalis/
- 2 exp Digitalis Glycosides/
- 3 digitalis.tw.
- 4 digoxin.tw.
- 5 digitoxin.tw.
- 6 or/1-5
- 7 exp Heart Failure, Congestive/
- 8 heart failure.tw.
- 9 cardiac failure.tw.
- 10 or/7-9
- 11 6 and 10
- 12 randomized controlled trial.pt.
- 13 controlled clinical trial.pt.
- 14 Randomized controlled trials/
- 15 random allocation/
- 16 double blind method/
- 17 single-blind method/
- 18 or/12-17
- 19 exp animal/ not humans/
- 20 18 not 19
- 21 clinical trial.pt.
- 22 exp Clinical Trials as Topic/
- 23 (clin\$ adj25 trial\$).ti,ab.
- 24 ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
- 25 placebos/
- 26 placebo\$.ti,ab.

27 random\$.ti,ab.
28 research design/
29 or/21-28
30 29 not 19
31 30 or 20
32 11 and 31

EMBASE on Ovid (2008 week 44)

1 Digitalis Glycoside/
2 Digoxin/
3 Digitalis/
4 Digitoxin/
5 digitalis.tw.
6 digoxin.tw.
7 digitoxin.tw.
8 or/1-7
9 exp Heart Failure/
10 heart failure.tw.
11 cardiac failure.tw.
12 or/9-11
13 8 and 12
14 controlled clinical trial/
15 random\$.tw.
16 randomized controlled trial/
17 follow-up.tw.
18 double blind procedure/
19 placebo\$.tw.
20 placebo/
21 factorial\$.ti,ab.
22 (crossover\$ or cross-over\$).ti,ab.
23 (double\$ adj blind\$).ti,ab.
24 (singl\$ adj blind\$).ti,ab.
25 assign\$.ti,ab.
26 allocat\$.ti,ab.
27 volunteer\$.ti,ab.
28 Crossover Procedure/
29 Single Blind Procedure/
30 or/14-29
31 (exp animals/ or nonhuman/) not human/
32 30 and 13

Appendix 2. Search strategies 2011**CENTRAL**

#1 MeSH descriptor Digitalis Glycosides explode all trees
#2 digitalis
#3 digoxin
#4 digitoxin
#5 (#1 OR #2 OR #3 OR #4)
#6 MeSH descriptor Heart Failure explode all trees
#7 heart near failure
#8 cardiac near failure
#9 (#6 OR #7 OR #8)
#10 (#5 AND #9)

MEDLINE on Ovid (2011 March week 5)

1. Digitalis/
2. exp Digitalis Glycosides/
3. digitalis.tw.
4. digoxin.tw.
5. digitoxin.tw.

6. or/1-5
7. exp Heart Failure/
8. heart failure.tw.
9. cardiac failure.tw.
10. or/7-9
11. 6 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. Randomized controlled trials/
15. random allocation/
16. double blind method/
17. single-blind method/
18. or/12-17
19. exp animal/ not humans/
20. 18 not 19
21. clinical trial.pt.
22. exp Clinical Trials as Topic/
23. (clin\$ adj25 trial\$.ti,ab.
24. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj (blind\$ or mask\$)).ti,ab.
25. placebos/
26. placebo\$.ti,ab.
27. random\$.ti,ab.
28. research design/
29. or/21-28
30. 29 not 19
31. 30 or 20
32. 11 and 31
33. ("20081114" or "20081115" or "20081116" or "20081117" or "20081118" or "20081119" or 2008112* or 2008113* or 2009* or 2010* or 2011*).ed.
34. 32 and 33

EMBASE on Ovid (2011 Week 14)

1. digitalis glycoside/
2. digoxin/
3. digitalis/
4. digitalis/
5. digitalis.tw.
6. digoxin.tw.
7. digitoxin.tw.
8. or/1-7
9. exp heart failure/
10. heart failure.tw.
11. cardiac failure.tw.
12. or/9-11
13. 8 and 12
14. random\$.tw.
15. factorial\$.tw.
16. crossover\$.tw.
17. cross over\$.tw.
18. cross-over\$.tw.
19. placebo\$.tw.
20. (doubl\$ adj blind\$).tw.
21. (singl\$ adj blind\$).tw.
22. assign\$.tw.
23. allocat\$.tw.
24. volunteer\$.tw.
25. crossover procedure/
26. double blind procedure/
27. randomized controlled trial/
28. single blind procedure/
29. 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28

30. (animal/ or nonhuman/) not human/
31. 29 not 30
32. 13 and 31
33. ("200845" or "200846" or "200847" or "200848" or "200849" or "200850" or "200851" or "200852" or 2009* or 2010* or 2011*).em.
34. 32 and 33
35. limit 34 to embase

Appendix 3. Search strategies 2013

CENTRAL

- #1MeSH descriptor: [Digitalis Glycosides] explode all trees
- #2MeSH descriptor: [Digitalis] this term only
- #3digitalis
- #4digoxin
- #5digitoxin
- #6#1 or #2 or #3 or #4 or #5
- #7MeSH descriptor: [Heart Failure] explode all trees
- #8heart near/6 failure
- #9cardiac near/6 failure
- #10#7 or #8 or #9
- #11#6 and #10
- #12((cardi* or heart* or myocard*) near/2 (failure* or incompet* or insufficien* or decompensat*))
- #13#7 or #12
- #14#13 and #6
- #15#11 or #14

MEDLINE

1. Digitalis/
2. exp Digitalis Glycosides/
3. digitalis.tw.
4. digoxin.tw.
5. digitoxin.tw.
6. or/1-5
7. exp Heart Failure/
8. heart failure.tw.
9. cardiac failure.tw.
10. or/7-9
11. 6 and 10
12. randomized controlled trial.pt.
13. controlled clinical trial.pt.
14. randomized.ab.
15. placebo.ab.
16. drug therapy.fs.
17. randomly.ab.
18. trial.ab.
19. groups.ab.
20. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19
21. exp animals/ not humans.sh.
22. 20 not 21
23. 11 and 22
24. (201104* or 201105* or 201106* or 201107* or 201108* or 201109* or 201110* or 201111* or 201112* or 2012* or 2013*).ed.
25. 23 and 24
26. ((heart or cardia* or myocard*) adj2 (fail* or insufficienc*)).tw.
27. 7 or 26
28. 6 and 22 and 27
29. 28 not 23
30. 25 or 29

EMBASE

1. digitalis glycoside/
2. digoxin/

3. digitalis/
4. digitalis.tw.
5. digoxin.tw.
6. digitoxin.tw.
7. or/1-6
8. exp heart failure/
9. heart failure.tw.
10. cardiac failure.tw.
11. or/8-10
12. 7 and 11
13. random\$.tw.
14. factorial\$.tw.
15. crossover\$.tw.
16. cross over\$.tw.
17. cross-over\$.tw.
18. placebo\$.tw.
19. (doubl\$ adj blind\$).tw.
20. (singl\$ adj blind\$).tw.
21. assign\$.tw.
22. allocat\$.tw.
23. volunteer\$.tw.
24. crossover procedure/
25. double blind procedure/
26. randomized controlled trial/
27. single blind procedure/
28. 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27
29. (animal/ or nonhuman/) not human/
30. 28 not 29
31. 12 and 30
32. ("201115" or "201116" or "201117" or "201118" or "201119" or 20112* or 20113* or 20114* or 20115* or 2012* or 2013*).em.
33. 31 and 32
34. ((heart or cardia* or myocard*) adj2 (fail* or insufficienc*)).tw.
35. 8 or 34
36. 7 and 30 and 35
37. 36 not 31
38. 33 or 37
39. limit 38 to embase

PubMed

#4 #3 Filters: Publication date from 2011/01/01 to 2013/05/21

#3 #1 not #2

#2 (digitalis or digoxin or digitoxin) and (heart failure) Filters: MEDLINE

#1 (digitalis or digoxin or digitoxin) and (heart failure)

WHAT'S NEW

Date	Event	Description
12 April 2016	Review declared as stable	No new studies since 2006

HISTORY

Protocol first published: Issue 2, 1999

Review first published: Issue 1, 2001

Date	Event	Description
30 July 2013	New citation required but conclusions have not changed	No new studies were identified by the updated search. Minor changes were made to the Discussion. Conclusions have not changed.
30 July 2013	New search has been performed	Searches were re-run in May 2013.
13 April 2011	New search has been performed	The search was re-run in April 2011. No new studies were identified. Minor changes were made to the Discussion. Conclusions not changed.
17 December 2008	New search has been performed	The search was updated to November 2008. No new studies were identified. Minor changes were made to discussion. Conclusions not changed.
7 September 2008	Amended	Converted to new review format.
3 October 2006	Amended	The search was updated to August 2006. No new studies were found. Minor changes have been made to the discussion to take account of newly identified references.
1 February 2004	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

All review authors participated in preparation of the final review by preparing critiques of the protocol and of various drafts of the review. Statistical input was also provided (GHG and RJ).

DECLARATIONS OF INTEREST

None.

SOURCES OF SUPPORT

Internal sources

- University of Washington, USA.
- College of Medicine, University of the Philippines, Philippines.
- McMaster University, Canada.
- University of Glasgow, Western Infirmary Glasgow, UK.

External sources

- University of Rochester, USA.

INDEX TERMS

Medical Subject Headings (MeSH)

*Heart Rate; Cardiotonic Agents [*therapeutic use]; Cross-Over Studies; Digitalis Glycosides [*therapeutic use]; Disease Progression; Double-Blind Method; Heart Failure [*drug therapy] [mortality] [physiopathology]; Hospitalization [statistics & numerical data]; Randomized Controlled Trials as Topic

MeSH check words

Humans