Living friendly summaries of the body of evidence using Epistemonikos (FRISBEE)

Is there a role for digitalis in chronic heart failure? – First update

Authors: Carmen Rain[1], Gabriel Rada[1,2,3,4,5]

Affiliation:
[1] Programa de Salud Basada en Evidencia, Facultad de Medicina, Pontificia Universidad Católica de Chile
[2] Departamento de Medicina Interna, Facultad de Medicina, Pontificia Universidad Católica de Chile
[3] GRADE working group
[5] Fundación Epistemonikos

E-mail: radagabriel@epistemonikos.org

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Abstract

This Living FRISBEE (Living FRIendly Summary of the Body of Evidence using Epistemonikos) is an update of the summary published in April 2015, based on a new systematic review published in May 2015.

The main clinical guidelines recommend the use of digitalis for chronic heart failure when moderate to severe symptoms persist after standard therapy, even though there is controversy about its efficacy and security. Searching in Epistemonikos database, which is maintained by screening 30 databases, we identified four systematic reviews including 13 randomized trials. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded the use of digitalis for chronic heart failure probably leads to little or no decrease in mortality, but they might reduce hospitalizations and clinical deterioration. However, the certainty of the evidence is low.
About the update
The article updates the April 2015 Living FRISBEE (Living FRISBEE: Living FRIendly Summary of the Body of Evidence using Epistemonikos) (doi: 10.5867/medwave.2015.03.6129) by including one new systematic review appeared after publication of the original article [1].

The new evidence incorporated in this summary led to a downgrade in the certainty of the evidence from low to very low, and the corresponding changes on key messages and considerations for decision-making.

Problem
Digitalis have been in use for treatment of heart failure for more than two centuries. However, their effects on heart failure are controversial. On one hand they would improve symptoms and exercise tolerance. On the other hand they might increase mortality, especially when there is underlying ischemic heart disease, and they carry a high risk of adverse effects.

Methods
We used Epistemonikos database, which is maintained by screening more than 30 databases, to identify systematic reviews and their included primary studies. With this information we generated a structured summary using a pre-established format, which includes key messages, a summary of the body of evidence (presented as an evidence matrix in Epistemonikos), meta-analysis of the total of studies, a summary of findings table following the GRADE approach and a table of other considerations for decision-making.

Key messages
- Digitalis in chronic heart failure might lead to a reduction in hospitalizations and clinical deterioration, however there is uncertainty if they decrease or increase mortality because the certainty of the evidence is very low.
- The conclusions of this summary partially agree with the systematic reviews identified and with the main guidelines, since these do not clearly recognize the uncertainty about the effect on mortality.

Acerca del conjunto de evidencia para esta pregunta

<table>
<thead>
<tr>
<th>What is the evidence. See evidence matrix in Epistemonikos later</th>
<th>We found four systematic reviews [1],[2],[3],[4] including 13 randomized controlled trials that are reported in sixteen articles [5-20].</th>
</tr>
</thead>
<tbody>
<tr>
<td>What types of patients were included</td>
<td>All studies considered heart failure of any etiology, being the most frequent ischemic. All studies included patients in sinus rhythm. Only five studies included patients with reduced ejection fraction: &lt; 45% [14],[15], &lt; 40% [5] y and &lt; 35% [17],[18]. One publication reported the outcomes of patients with preserved ejection fraction [20] from the largest trial (DIG). The average age was between 58 to 69 years in the different studies.</td>
</tr>
<tr>
<td>What types of interventions were included</td>
<td>All studies evaluated digoxin, eight using dose adjustments to reach a specific serum level [5],[9],[10],[14],[16-19]. All studies compared against placebo.</td>
</tr>
<tr>
<td>What types of outcomes were measured</td>
<td>Total mortality or heart failure mortality; hospitalization for any cause or for heart failure, emergency room visits, clinical deterioration, quality of life, walking test, neurohumoral markers and echocardiographic parameters.</td>
</tr>
</tbody>
</table>
Summary of findings
The following information is based on 13 randomized trials that included 9022 patients. Only eight studies reported total mortality. One study reported hospitalization by any cause, four heart failure hospitalization and 12 reported clinical deterioration.

- There is uncertainty if digitalis decrease or increase mortality in chronic heart failure because the certainty of the evidence is very low.
- Digitalis in chronic heart failure might lead to a reduction in hospitalizations and clinical deterioration. The certainty of the evidence is low.

<table>
<thead>
<tr>
<th>Patients</th>
<th>Chronic heart failure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention</td>
<td>Digitalis</td>
</tr>
<tr>
<td>Comparison</td>
<td>Placebo</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>WITHOUT digitalis</th>
<th>WITH digitalis</th>
<th>Relative effect (95% CI)</th>
<th>Certainty of the evidence (GRADE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality (any cause)</td>
<td>303 per 1000</td>
<td>300 per 1000</td>
<td>RR 0.99 (0.93 to 1.06)</td>
<td>⧵⧵⧵⧵1,2,4 Very low</td>
</tr>
<tr>
<td></td>
<td>Difference: 3 patients less per 1000</td>
<td>(Margin of error: 21 less to 15 more)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hospitalization (any cause)</td>
<td>634 per 1000</td>
<td>612 per 1000</td>
<td>RR 0.96 (0.93 to 0.99)</td>
<td>⧵⧵⧵⧵3,4,5 Low</td>
</tr>
<tr>
<td></td>
<td>Difference: 26 patients less per 1000</td>
<td>(Margin of error: 6 to 45 less)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical deterioration</td>
<td>179 per 1000</td>
<td>63 per 1000</td>
<td>RR 0.35 (0.25 to 0.49)</td>
<td>⧵⧵⧵⧵2,4 Low</td>
</tr>
<tr>
<td></td>
<td>Difference: 116 patients less per 1000</td>
<td>(Margin of error: 91 to 134 less)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

RR: Risk ratio.
Margin of error = 95% confidence interval (CI).
GRADE: evidence grades of the GRADE Working Group (see later in this article).

The risk WITHOUT digitalis is based on the risk in the control group of the trials. The risk WITH digitalis (and its margin of error) is calculated from relative effect (and its margin of error).
1 The confidence interval included both the possibility of an important increase or decrease in mortality.
2 Most studies have limitations, mainly absence of blinding and incomplete follow-up.
3 There is inconsistency between studies, I² is 61%.
4 We downgraded the certainty of the evidence because of indirectness, since heart failure management has changed substantially from the publication of the studies. Also, most of the studies performed dose adjustment to reach a specific serum digoxin concentration, a circumstance that is rare in clinical practice nowadays.
4 Three of four studies did report the results of hospitalization for heart failure, and not by any cause. However, we did not downgrade by indirectness because these studies represent 1.1% of participants.
Other considerations for decision-making

To whom this evidence does and does not apply

- All studies included patients with heart failure in sinus rhythm with no restriction on etiology or ejection fraction, so the evidence can be applied to the totality of patients with this condition.

About the outcomes included in this summary

- The outcomes presented in this summary are those considered as critical for decision-making by the authors of this summary, and they agree with those used by the main clinical guidelines.

Balance between benefits and risks, and certainty of the evidence

- There is uncertainty about the effects of digitalis on mortality, the more important outcome for this particular decision-making, because the certainty of the evidence is very low. Considering the biological plausibility of the increase in digitalis-associated mortality and the observation of this risk in patients with atrial fibrillation [1], more certainty is needed in order to conduct an adequate benefit/risk balance.

What would patients and their doctors think about this intervention

- Most patients and doctors would not accept this level of uncertainty on the main outcome.
- However, this intervention might be considered in some patients with important symptoms and low risk of adverse effects, especially if other therapeutic alternatives are not available. It is particularly relevant to promote shared decision-making in these cases.

Resource considerations

- Digitalis are inexpensive, but it is not possible to estimate the cost/benefit because of the existing uncertainty on the main outcome.

Differences between this summary and other sources

- The systematic reviews identified partially disagree, since all except one conclude there is no effect on mortality and more evidence is needed. The more recent review suggest a substantial increase in mortality [1]. This review has several important differences with previous works. The first is on inclusion criteria, since it incorporates observational studies which increases the risk of bias but increases the number of available studies, specially those where the management of heart failure is similar to the current treatment. Additionally, it uses a criteria based on statistical analysis which leaves out many old studies. The second is it included an ancillary study of the DIG trial, which is not considered in the other reviews. The third is it combines the effect of digitalis in patients with different conditions, mainly atrial fibrillation.
- Our summary also disagrees with the main guidelines, which recommend the use of digitalis in non-responsive patients [21],[22],[23],[24]. None of the guidelines consider all the evidence or the more recent systematic review.

Could this evidence change in the future?

- The probability of this evidence to change in the future is high, because the certainty of the evidence is low.
- We did not identify ongoing studies, and the last one was conducted in 1997 [15], so it is unlikely that new evidence relevant for this question would appear in the future.
How we conducted this summary

Using automated and collaborative means, we compiled all the relevant evidence for the question of interest and we present it as a matrix of evidence.

Starting from any systematic review, Epistemonekon builds a matrix based on existing connections in the database (the review from which the matrix is built, appears highlighted). The author of the matrix can select relevant information for a specific health question (typically in PICO format) in order to display the information set for the question. The rows represent systematic reviews that share at least one primary study, and columns display the studies. The boxes in green correspond to studies included in the respective reviews.

Follow the link to access the interactive version Digitalis for chronic heart failure

About the certainty of the evidence (GRADE)*

⭐⭐⭐⭐
**High:** This research provides a very good indication of the likely effect. The likelihood that the effect will be substantially different† is low.

⭐⭐⭐⭐
**Moderate:** This research provides a good indication of the likely effect. The likelihood that the effect will be substantially different† is moderate.

⭐⭐⭐⭐
**Low:** This research provides some indication of the likely effect. However, the likelihood that it will be substantially different† is high.

⭐⭐⭐⭐
**Very low:** This research does not provide a reliable indication of the likely effect. The likelihood that the effect will be substantially different† is very high.

*This concept is also called ‘quality of the evidence’ or ‘confidence in effect estimates’. † Substantially different = a large enough difference that it might affect a decision.
The authors do not have relevant interests to declare.

References


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Correspondencia a:
Facultad de Medicina
Pontificia Universidad Católica de Chile
Lira 63,
Santiago Centro
Chile

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