

Living Friendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)

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Is there a role for digitalis in chronic heart failure?

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Abstract

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 three 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 might reduce hospitalizations and clinical deterioration. However, the certainty of the evidence is low.

Resumen

El uso de digitálicos, en pacientes con insuficiencia cardiaca crónica que persisten con síntomas moderados a graves pese al uso de terapia estándar, ha sido recomendado en las principales guías clínicas, a pesar de que existe controversia sobre su eficacia y seguridad. Utilizando la base de datos Epistemonikos, la cual es mantenida mediante búsquedas en 30 bases de datos, identificamos tres revisiones sistemáticas que en conjunto incluyen 13 estudios aleatorizados. Realizamos un metanálisis y tablas de resumen de los resultados utilizando el método GRADE. Se concluye que los digitálicos podrían no disminuir la mortalidad, pero sí el riesgo de hospitalizaciones por cualquier causa y deterioro clínico en este grupo de pacientes. Sin embargo, la certeza de la evidencia es baja.

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. Furthermore, they carry a high risk of adverse effects.

Method

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

- Use of digitalis in chronic heart failure might lead to little or no decrease in mortality. Nonetheless, they might lead to a reduction in hospitalizations and clinical deterioration.
- The conclusions of this summary are in agreement with the systematic reviews identified and with the main guidelines.

About the body of evidence for this question

What is the evidence (See evidence matrix in Epistemonikos later)	We found three systematic reviews [1],[2],[3] including 13 randomized controlled trials that are reported in 15 articles [4],[5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18].
What types of patients were included	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: < 45% [7],[18], < 40% [14] and < 35% [11],[16]. The average age was between 58 to 69 years in the different studies.
What types of interventions were included	All studies evaluated digoxin, eight using dose adjustments to reach a specific serum level [8],[9],[10],[11],[13],[14],[16],[17]. All studies compared against placebo.
What types of outcomes were measured	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.

Summary of findings

The following information is based on 13 randomized trials that included 8,304 patients. Only eight studies reported total mortality. One study reported hospitalization by any cause, four reported hospitalization from heart failure and 12 reported clinical deterioration.

- Use of digitalis in chronic heart failure might lead to little or no decrease in mortality. The certainty of the evidence is low.
- Digitalis might lead to a reduction in hospitalization and clinical deterioration, but the certainty of the evidence is low.

Digitalis in patients with chronic heart failure				
Patients	Chronic heart failure			
Intervention	Digitalis			
Comparison	Placebo			
Outcomes	Absolute effect*		Relative effect (95% CI)	Certainty of the evidence (GRADE)
	WITHOUT digitalis	WITH digitalis		
	Difference: patients per 1000			
Mortality (any cause)	312 per 1000	309 per 1000	RR 0.99 (0.93 to 1.06)	⊕⊕○○ ^{1,3} Low
	Difference: 3 patients less per 1000 (Margin of error: 22 less to 19 more)			
Hospitalization (any cause)	634 per 1000	602 per 1000	RR 0.95 (0.92 to 0.99)	⊕⊕○○ ^{2,3,4} Low
	Difference: 32 patients less per 1000 (Margin of error: 6 less to 51 less)			
Clinical deterioration	179 per 1000	63 per 1000	RR 0.35 (0.25 to 0.49)	⊕⊕○○ ^{1,3} Low
	Difference: 116 patients less per 1000 (Margin of error: 91 to 134 less)			
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 Most studies have limitations, mainly absence of blinding and incomplete follow-up.				
2 There is inconsistency between studies, I ² is 61%.				
3 We downgraded the certainty of the evidence because of indirectness, since heart failure management has changed substantially from the publication of the studies. In addition, 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.				

[Digitalis for chronic heart failure](#)

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 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

- With a low level of certainty, we can say it is an intervention that offers some benefits on hospitalization and clinical deterioration, but not on mortality. In some patients the benefit/risk balance might be in favor of the benefit, but it will not be favorable in others, like the elderly or other populations vulnerable to adverse effects, such as digitalis intoxication.
- Given that the balance will vary in different patients, and that the certainty of the evidence is low, it is particularly relevant to inform the patient and to promote shared decision-making.

Resource considerations

- Digitalis are inexpensive, and there is some benefit, so the cost/benefit ratio is probably favorable in most patients.
- In patients at risk of adverse effects, the cost derived from complications can surpass the potential benefits.

Differences between this summary and other sources

- The conclusion of this summary agrees with the systematic reviews identified and with the main guidelines [19],[20],[21],[22].

Could this evidence change in the future?

- It is highly likely that this evidence will change in the future, because the certainty of the evidence is low.
 - We did not identify ongoing studies, and the last one was conducted in 1997 [7], 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, Epistemonikos 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.

Notes

The upper portion of the matrix of evidence will display a warning of “new evidence” if new systematic reviews are published after the publication of this summary. Even though the project considers the periodical update of these summaries, users are invited to comment in *Medwave* or to contact the authors through email if they find new evidence and the summary should be updated earlier. After creating an account in Epistemonikos, users will be able to save the matrixes and to receive automated notifications any time new evidence potentially relevant for the question appears. The details about the methods used to produce these summaries are described here

<http://dx.doi.org/10.5867/medwave.2014.06.5997>.

Epistemonikos foundation is a non-for-profit organization aiming to bring information closer to health decision-makers with technology. Its main development is Epistemonikos database (www.epistemonikos.org).

These summaries follow a rigorous process of internal peer review.

Conflicts of interest

The authors do not have relevant interests to declare.

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