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Living FRIendly Summaries of the Body of Evidence using Epistemonikos (FRISBEE)
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Are beta-blockers effective in heart failure with preserved ejection fraction?

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Abstract

Beta-blockers constitute standard therapy for heart failure with reduced ejection. However, their role in patients with preserved ejection fraction is not clear. Searching in Epistemonikos database, which is maintained by screening multiple databases, we identified four systematic reviews covering 19 primary studies, including seven randomized trials answering the question of this summary. We combined the evidence using meta-analysis and generated a summary of findings table following the GRADE approach. We concluded the use of beta-blockers probably leads to little or no difference in the risk of death or hospitalization in patients with heart failure with preserved ejection fraction.

Problem

Around 50% of patients with heart failure have preserved ejection fraction, with or without diastolic dysfunction, and there is no treatment that is clearly effective.

Beta-blockers constitute standard therapy for heart failure with reduced ejection fraction. As they reduce heart rate it has been postulated they can also improve diastolic function, so constituting an alternative for patients with preserved ejection fraction. However, their clinical role is not clear.

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
- Use of beta-blockers probably leads to little or no difference in the risk of death or hospitalization in patients with heart failure with preserved ejection fraction

About the body of evidence for this question

What is the evidence. See evidence matrix in Epistemonikos later	We found four systematic reviews [1],[2],[3],[4] including 19 primary studies, reported in 20 references [5],[6],[7],[8],[9],[10],[11],[12],[13],[14],[15],[16],[17],[18],[19],[20],[21],[22],[23],[24]. Seven correspond to randomized controlled trials, reported in eight references [8],[9],[10],[11],[13],[16],[17],[24], but four of them did not report any patient-important outcome (echocardiographic and hemodynamic measures only) [11],[13],[16],[24]. This table and the summary in general are based on the three trials reporting important outcomes for decision making; J-DHF [8], SWEDIC [10] and SENIORS [9].
What types of patients were included	Ejection fraction was defined as >35% in one trial [9], > 40% in one trial [8] and > 45% in one trial [10]. Mean ejection fraction in the trials ranged from 49% to 63%. Even though trials did not restrict inclusion by functional class, most patients were NYHA II or III. All of the trials included adults. SENIORS trial restricted inclusion to patients over 70 years [9]. Mean age ranged from 66 to 76 years across studies. Between 66 and 86% of patients were hypertensive in the different trials, 3 to 24% had diabetes and 37 to 41% had atrial fibrillation. The latter were excluded in SWEDIC trial [10]. Etiology was ischemic in 77% of patients in SENIORS [9], 15% in J-DHF [8] and it was not reported in SWEDIC [10].
What types of interventions were included	Two trials used carvedilol [8],[10] and one nebivolol [9]. In one trial carvedilol was initiated at 2.5 mg per day, then increasing up to 20 mg per day [8]; in the other trial initial dose was not reported, but the target dose was 25 or 50 mg depending on body weight [10]. Nebivolol starting dose was 1.25 mg per day, increasing up to 10 mg per day [9]. All of the trials compared against placebo.
What types of outcomes were measured	The different systematic reviews identified groups outcomes as follows: • All-cause mortality • All-cause hospitalization • Cardiovascular-cause hospitalization • Cardiovascular mortality

Summary of findings

The information on the effects of beta-blockers for heart failure with preserved ejection fraction is based on three randomized trials including 1094 participants. All of the trials reported mortality, but one did not have any event [10]. Only one trial reported all-cause hospitalization [9]. The summary of findings is the following:

- Use of beta-blockers probably leads to little or no difference in the risk of death in patients with heart failure with preserved ejection fraction. The certainty of the evidence is moderate.
- Use of beta-blockers probably leads to little or no difference in the risk of hospitalization in patients with heart failure with preserved ejection fraction. The certainty of the evidence is moderate.

Beta-blockers for heart failure with preserved ejection fraction

Patients	Heart failure with preserved ejection fraction (defined as EF > 35 to >45 in the different trials)
Intervention	Beta-blockers
Comparison	Placebo

Outcomes	Absolute effect*		Relative effect (IC 95%)	Certainty of the evidence (GRADE)
	WITHOUT Beta-blockers	**WITH Beta-blockers**		
	Difference: patients per 1000			
Mortality	153 per 1000	141 per 1000	RR 0.92 (0.68 to 1.24)	⨁⨁⨁◯[1,2] Moderate
	Difference: 12 patients less per 1000 (Margin of error: 49 less to 37 more)			
All-cause hospitalization	349 per 1000	335 per 1000	RR 0.96 (0.78 to 1.17)	⨁⨁⨁◯[1,2] Moderate
	Difference: 14 patients less per 1000 (Margin of error: 77 less to 59 more)			

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 beta-blockers** is based on the risk in the control group of the trials. The risk **WITH beta-blockers** (and this margin of error) is calculated from relative effect (and this margin of error)

[1] Notwithstanding some trials have methodological flaws, the study contributing more data had low risk of bias. We did not downgrade the certainty of the evidence for this aspect.
[2] We downgraded the certainty of the evidence for imprecision because the confidence interval contemplates the possibility of both clinically relevant benefit and risk.

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.

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Other considerations for decision-making

To whom this evidence does and does not apply

- The evidence presented in this summary applies to patients with heart failure with preserved ejection fraction, defined as >35%, typically of advanced age, symptomatic and hypertensives. Only two beta-blockers have been assessed: carvedilol and nebivolol.

About the outcomes included in this summary

- The outcomes selected for the summary of findings table are those considered critical for decision-making by the authors of this summary. They coincide with those mentioned in the systematic reviews and guidelines identified in this report.

Balance between benefits and risks, and certainty of the evidence

- Considering it is probable there is no benefit, and beta-blockers are associated to important adverse effects, the risk/benefit balance is not favorable.

What would patients and their doctors think about this intervention

- When confronted to existing evidence, most patients and their clinicians should be inclined against using this intervention.
- However, given there are no effective drugs for these cases, some might opt for using it anyway. It is particularly important to inform about existing evidence in these cases.

Resource considerations

- Beta-blockers are accessible and not expensive, so this factor should not be determinant for decision-making.

Differences between this summary and other sources

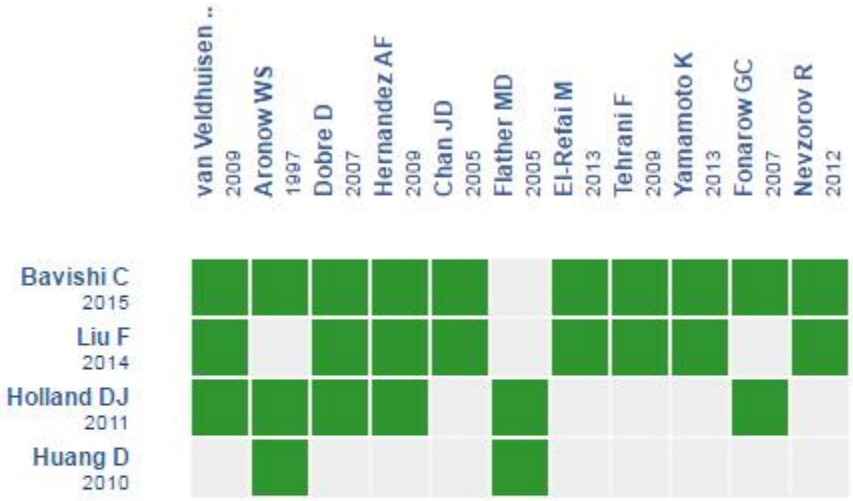
- The conclusions of this summary agree with the systematic reviews identified that base their conclusions on randomized trials [1] and disagree with those using non-randomized studies as their main source of information [3].
- This summary is partially concordant with the main guidelines. Some of them state pharmacological therapy has not demonstrated any role in heart failure with preserved ejection fraction [25], and others recommend it in patients with comorbidities such as recent myocardial infarction, atrial fibrillation or hypertension [26]. This summary disagrees with the recommendation for hypertensive patients since the risk/benefit of beta-blockers in this case is probably not favorable. It is important to consider none of the guidelines incorporate the evidence analyzed in this summary.

Could this evidence change in the future?

- The likelihood that future evidence changes the conclusion of this summary is low, because of the certainty of the evidence.
- There are no ongoing trials, at least according to the World Health Organization's International Controlled Trials Registry Platform.

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 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:** Beta-blockers for heart failure with preserved ejection fraction.

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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