Verapamil use in patients with cardiovascular disease: an overview of randomized trials

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Authors' objectives
To present an overview of randomised trials investigating the use of verapamil in patients with cardiovascular disease.

Searching
MEDLINE was searched from January 1966 to April 1997) using the keyword 'verapamil' alone and in combination with the following terms: 'clinical trial', 'MI', 'angina', and 'hypertension'. Further searches of the Science Citation Index and Current Contents were carried out (search dates unclear). All of the searches were limited to publications in the English language. The bibliographies of retrieved articles and other reviews were also examined for additional studies. Three investigators knowledgeable with the verapamil literature reviewed the final list of publications for completeness.

Study selection

Study designs of evaluations included in the review
Prospectively randomised clinical studies comparing verapamil with either placebo or other therapies were included in the review.

Specific interventions included in the review
The review included verapamil (various regimens) and verapamil plus trandolapril, compared with either placebo or other therapies, such as metoprolol. The duration of the treatment varied from 48 hours to 75 months.

Participants included in the review
Patients with acute myocardial infarction (MI), angina, or hypertension were included in the review.

Outcomes assessed in the review
The clinical outcomes assessed included all-cause mortality and nonfatal reinfarction or infarction, and combinations of these two events.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The specific validity criteria were not identified. However, studies were excluded from the meta-analyses and results section on the basis of problems with their design, e.g. short treatment duration and small sample size. The authors do not state how the papers were assessed for validity, or how many of the authors performed the validity assessment.

Data extraction
The data were extracted by one co-author, then cross-checked by two other co-authors to arrive at a final set of studies and data elements for pooling. Any differences were resolved by consensus.

Methods of synthesis
How were the studies combined?
The studies were grouped according to the patient population (MI, angina or hypertension). The data were then combined using meta-analyses where appropriate. The percentage risk reduction, relative risk and 95% confidence intervals (CIs) were calculated. Where meta-analyses were inappropriate, the results were combined in a narrative summary.
How were differences between studies investigated?
Heterogeneity tests were performed to examine whether the relative risks varied significantly among the different studies.

Results of the review
In total, 66 reports of studies were identified and extracted, although some were multiple publications of the same clinical trial; only a limited number of the studies were reported in detail and included in the statistical analyses. Seven RCTs (n=4,516) involving patients with MI, and 3 RCTs (n=1,020) involving patients with angina, were included in the analyses. None of the 17 identified RCTs involving patients with hypertension were analysed or reported in detail, due to their limited treatment duration and size.

The relative risks and 95% CIs were presented diagrammatically; the absolute values were not reported.

Acute MI (7 of the 7 studies analysed).

The combined relative risks (three combinations of the 7 studies) for nonfatal reinfarction ranged from 0.79 to 0.80 in favour of verapamil. This corresponded to a 20 to 21% risk reduction for nonfatal reinfarction associated with verapamil. The effect on mortality associated with verapamil ranged from a 5.6% increase to an 18.5% reduction in mortality. The combined odds reduction (using three different combinations of the 7 studies) ranged from 7 to 14% in favour of verapamil. There was no evidence of marked between-study differences in the relative risk (p=0.50). The combined relative risk (5 studies) of a combined adverse outcome (death or reinfarction) in patients taking verapamil, compared with controls, was estimated to be 0.82 (95% CI: 0.70, 0.97).

Angina (3 of the 43 studies analysed).

Forty of the 43 studies identified were short-term crossover studies with a treatment duration of less than 4 weeks; these studies were not included in the analysis (no further details provided). The remaining 3 studies were double-blind parallel group studies (2 placebo and 1 versus metoprolol), which were discussed in detail. The paucity of the data from the 3 trials was such that no results were reported for the formal pooled analysis. Examining the 3 studies individually, no significant associations with verapamil were identified with respect to the incidence of nonfatal infarction.

No deaths or nonfatal infarctions were observed in the 17 trials (12 short-term crossover trials; 5 parallel, randomised double-blind studies). However, the studies were described as uninformative by the authors as they were limited in both treatment duration and size (no further details provided).

Authors' conclusions
For patients with MI, the aggregate of existing data presented here does not support the hypothesis that verapamil use is associated with harm. In patients with MI, the risks of both nonfatal reinfarction and the combined outcome of death or nonfatal MI were reduced over intermediate-term follow-up among patients treated with verapamil, compared with controls, (p=0.024 and p=0.016, respectively). In patients with angina, no evidence for harm was noted, but in hypertension the data were too limited to draw conclusions. These findings support the need to distinguish between different calcium-antagonist compounds, and emphasise the need for more data in patients with hypertension.

CRD commentary
This review used clearly defined inclusion criteria for study design and outcome assessment, to investigate the use of verapamil in cardiovascular disease. A clearly outlined search strategy was used to locate relevant information, and the terms used in the retrieval were listed to enable other researchers to repeat the search strategy. Although the authors appear to have made a valid attempt to locate all of the relevant studies, the search was limited to English language publications, which may exclude useful data.

No details were provided as to how the validity of the studies was assessed and on what criteria. However, the studies do appear to have been subject to some form of quality assessment, as the authors only report in detail those studies which they believe to be of adequate quality. Where there were a sufficient number of good-quality studies, the authors
pooled the data in a meta-analysis. The results of the analyses were presented diagrammatically, but no absolute values were presented either in the figure or the accompanying text. A summary table of the relative risks, combined relative risks and CIs would have been useful.

In view of the data presented, the authors would appear to be justified in their conclusions and recommendations for further research. However, the review only considers the 'average' verapamil effect and the authors highlight that caution should be taken when extrapolating their findings to other patient groups, such as those with MI and left ventricular systolic dysfunction.

**Implications of the review for practice and research**

Research: The authors state 'these findings support the need to distinguish among different calcium-antagonist compounds and to emphasise the need for more data in patients with hypertension'.

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