Study | Sources | Results
--- | --- | ---
Furberg 1995 (and correction 1996) Systematic Review Meta Analysis | Search methodology / Databases searched Not described | Relative risk of mortality Relative risk across all trials for mortality -1.16 (1.01 to 1.33) -the summary estimate fails to draw attention to an important dose-response relationship
Inclusion criteria RCT Secondary prevention trials Reporting of mortality data | Trials with doses between 30 and 50 mg/d (correction required) -30 mg/d RR for mortality = 1.01 -40 mg/d RR (corrected) for mortality = 1.08 (from 1.09) -50 mg/d RR for mortality = 1.03
Exclusion criteria Not described | Trials with 60 mg/d dose (no correction required) -RR for mortality = 1.18 (0.93 to 1.50) -2 60 mg/d trials stopped before their scheduled termination as a result of a trend toward increased mortality in one trial (Held 1994) and a doubling of the rate of reinfarction in the other (HINT 1986) -this analysis may underestimate the adverse mortality effect of the 60 mg/d dose
Evaluation Methods for Included Studies Not described | Trials with 80 mg/d dose (correction required) -RR (corrected) for mortality = 2.69 (1.16 to 6.26) (from 2.86) -significant difference from null and from the 30/40/50 mg/d RR
Outcomes considered: Nifedipine effect on mortality -within each dose category -across all trials combined | Trials with 100 mg/d dose (correction required) -RR (corrected) for mortality = 2.58 (1.03 to 6.47) (from 2.20)
N = 16 studies selected N = 8350 total participants (all studies) n = 12 trials randomized patients with MI n = 3 trials randomized patients with unstable angina n = 1 trial randomized patients with stable angina and with a history of prior infarction Dose of nifedipine ranged from 30 to 120 mg/d | The risk of mortality was strongly associated with dose of nifedipine (p = .01); risk rises sharply in trials that used ≥80 mg/d

**Studies (corrections noted below):**
- Israeli SPRINT Study Group 1988
- Gordon 1984
- Branagan 1986**
- Wilcox 1986
- Sirnes 1984
- Walker 1988
- Erbel 1988
- SPRINT Study Group 1988
- Goldbort 1993
- Muller 1984*
- Eisenberg 1985
- Gottlieb 1988
- Jaffe 1987
- Holland Interuniversity Nifedipine/Metoprolol Trial (HINT) Research Group 1986
- Gerstenbiith 1982
- Muller 1984
- Lichtlen 1990

*Muller 1984 (correction from 80 mg/d to 120 mg/d)
**Branagan 1986 (correction controls from 68 to 61)
***Two errors slightly changed RRs (reflected in this evidence table) but not the overall results or interpretation.

### Potentially harmful mechanisms

**Proischemic effect**
- increase in anginal symptoms
- most frequently observed in those with no evidence of vasospasm
- in patients with poor or no collateral flow, nifedipine reduced ischemic episodes
- in patients with good collateral flow, nifedipine significantly increased ischemic episodes
- severe proischemia may precipitate major coronary events

**Negative inotropic effect**
- calcium antagonists have a negative inotropic effect as a class; this action varies among agents
- many patients in chronic heart failure experience a worsening of their symptoms
- this adverse effect is most apparent in patients with ejection fractions <25% and 25% to 34%
- nifedipine results in a worsening of CHF and this result is not predicted by resting ejection fraction
<table>
<thead>
<tr>
<th>Results (continued)</th>
<th>Comments</th>
<th>Clinical Implications</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Effects on rhythm</strong></td>
<td>If a drug exerts a harmful effect, one would expect to see such an association most clearly with high doses of the drug. &lt;br&gt;The dose of nifedipine was directly and strongly related to the risk of mortality. &lt;br&gt;Compared with placebo, doses of &gt;60 mg/d almost tripled the risk of death and the adverse effect differed not only from the null but also from the small adverse effect seen with doses of 30 to 50 mg/d.</td>
<td>&lt;br&gt;High doses were clearly harmful.</td>
</tr>
</tbody>
</table>