Effect of dosing frequency on chronic cardiovascular disease medication adherence
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CRD summary
The authors concluded that patients appear to be more adherent to once-daily regimens of chronic cardiovascular disease medication than more frequently scheduled regimens. This conclusion seems to reflect the findings presented, but the likelihood of biases and the substantial heterogeneity shown mean that the reliability of this conclusion is uncertain.

Authors' objectives
To determine the effect of chronic cardiovascular disease medication dosing frequency on medication adherence.

Searching
MEDLINE and EMBASE were searched from 1986 to December 2011 for controlled trials and systematic reviews published in English. Search terms were reported. Reference lists of included articles, relevant systematic reviews and online texts from the manufacturer of the medication event monitoring systems were handsearched for further studies.

Study selection
Prospective studies that reported adherence to scheduled oral medication (administered one to four times daily) for adult patients with chronic cardiovascular disease were eligible for inclusion. Eligible studies had to follow patients for at least one month and adherence was required to be measured using electronic monitoring. Studies needed to use the definitions of taking adherence (number of bottle cap openings divided by the prescribed number of doses), regimen adherence (percentage of days with the appropriate number of doses taken) and timing adherence (percentage of near optimal inter-administration intervals). Study arms that randomised patients to interventions designed to enhance adherence (except for electronic monitoring) were excluded.

Mean participant age ranged from 46 to 79 years. The proportion of male patients per study ranged from 31% to 100%. Various disease states were reported. Drugs used varied widely and included antihyperintensives, statins, beta-blockers, nitrates, aspirin, vitamin K antagonists and warfarin. Dosing frequencies ranged from one to three times daily.

Two reviewers selected studies for inclusion; any discrepancies were resolved by a third reviewer.

Assessment of study quality
The authors assessed whether blinding had been performed in studies but did not report any other form of quality assessment.

Data extraction
Data for taking, regimen and timing adherence were extracted to calculate crude adherence estimates (%) with 95% confidence intervals (CIs). Authors were contacted for additional data or clarification when necessary.

The authors did not state how many reviewers extracted data.

Methods of synthesis
Effect estimates for adherence were pooled by frequency of daily dose using random-effects meta-analysis and controlling for other study level factors. Statistical heterogeneity was assessed using the I² statistic (>50% was defined as significant). Publication bias was assessed using Egger's weighted regression test.

Meta-regression analyses were conducted to compare frequency of dosing, year of publication, country of conduction, study design, blinding to electronic monitoring, follow-up of six months or more and disease state. A multivariate linear mixed model method was applied with the three adherence definitions as the outcomes. Both random-effects and fixed-effect (for study-level factors) models were used, weighted by the inverse of the variance of medication adherence.

Results of the review
Twenty-nine studies were included in the review (3,373 patients, sample size range 12 to 501): 18 randomised trials (2,716 patients) and 11 observational studies (657 patients). Follow-up ranged from 28 to 365 days. Two studies reported blinding of patients to the use of electronic monitoring, 20 reported that they did not blind patients and seven did not report any blinding-related information.

Crude pooled adherence estimates were highest when the lenient taking definition was assessed (dosing frequency range 80.1% to 93.1%) and lowest when the strictest timing definition was assessed (dosing frequency range 50.4% to 76.3%). Significant statistical heterogeneity ($I^2$>85%) was reported for once-daily and twice-daily regimens for all three adherence definitions and for the timing analysis of three times-daily regimens. Publication bias could not be ruled out for once-daily regimens for all three adherence definitions and for the timing analysis of twice-daily regimens.

Compared with once-daily regimens, the adjusted weighted mean percentage adherence for twice daily and three times daily regimens were significantly lower regardless of the adherence definition used (p<0.01 for all). Results were reported fully in the paper.

**Authors' conclusions**
Patients appeared to be more adherent to once-daily regimens of chronic cardiovascular disease medication than more frequently scheduled regimens; this finding was magnified when stringent definitions of adherence were employed.

**CRD commentary**
The review question was clear and inclusion criteria were sufficiently replicable. Relevant data sources were searched, but the restriction to studies in English increased the likelihood of language bias. The restricted search for published literature meant that publication bias was possible and this was suggested by results from Egger's tests. Efforts were made to minimise error and bias for study selection; it was unclear whether this also applied for data extraction. No quality assessment was reported and this made it difficult to determine levels of bias that may have confounded results. Only two of the 29 studies reported blinding to electronic monitoring, which suggested that methodological quality may not have been high for all of the studies. Study details were presented and revealed that most of the included studies had small sample sizes.

The methods of synthesis did not seem appropriate given the clinical and statistical heterogeneity and the unknown quality of the studies. There were differences in study designs but subgroup analyses of randomised and observational studies seemed to show similar results to the main analyses. It was unclear whether crossover trial data were appropriately taken account of in the analyses but as there were only two such studies was unlikely that their results majorly influenced the overall findings.

The authors conclusion seems to reflect the findings presented but the likelihood of biases and substantial differences between the included studies mean that the reliability of this conclusion is uncertain.

**Implications of the review for practice and research**
**Practice:** The authors stated that prescribers should perhaps consider the effect of dosing frequency on medication adherence when making prescribing decisions.

**Research:** The authors did not state any implications for further research.

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