Glycemic effectiveness and medication adherence with fixed-dose combination or coadministered dual therapy of antihyperglycemic regimens: a meta-analysis
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CRD summary
This review concluded that use of fixed-dosed combinations with antihyperglycaemic agents was associated with lower HbA\textsubscript{ic} and higher medication possession ratio values compared with co-administered dual therapy use in patients with type 2 diabetes. These conclusions may not be reliable given the moderate to high level of heterogeneity of pooled outcomes and low methodological rigour of the included studies.

Authors' objectives
To compare the efficacy of fixed-dosed combinations and co-administered dual therapy of antihyperglycaemic agents on glycaemic control and medication adherence.

Searching
PubMed, EMBASE, Web of Knowledge and The Cochrane Library were searched from inception to 2011 for studies in English. Search terms were reported. Reference lists of retrieved articles were screened.

Study selection
Prospective or retrospective studies that compared equivalent oral drug components in fixed-dosed combinations and co-administered dual therapy of antihyperglycaemic agents in patients diagnosed with type 2 diabetes were eligible for inclusion. Eligible trials had to evaluate the same drug class of oral antihyperglycaemic drugs. The review outcomes of interest were changes in HbA\textsubscript{ic} and medication adherence (measured as medication possession ratio).

The vast majority of included studies evaluated the efficacy of metformin plus thiazolidinedione or sulphonylurea. Most of the included studies were based on USA cohorts and one used a cohort from Greece. Where reported, patients’ mean ages ranged from 52 to 63 years. From 27% to 97% of patients were male. Where reported, length of follow-up ranged from two to 21 months. The timing of the measurement of HbA\textsubscript{ic} varied between studies.

Two reviewers independently assessed studies for inclusion.

Assessment of study quality
The authors stated that they assessed study quality. No further details were reported.

The authors did not state how many reviewers performed quality assessment.

Data extraction
Data were extracted on means and standard deviations to enable calculation of mean differences with 95% confidence internals (CIs).

Two reviewers independently performed data extraction. Extracted data were cross-checked. Any disagreements were resolved by discussion.

Methods of synthesis
The studies were combined in a meta-analysis. Weighted mean differences (WMDs) with 95% CIs were calculated using a random-effect model. Statistical heterogeneity was assessed using the Q and I\textsuperscript{2} statistics. Subgroup analyses were performed by types of study designs.

Results of the review
Ten studies were included in the review (70,573 participants). All studies were of retrospective design: seven studies used a cohort comparison and three studies used a cohort before-after design.

Compared with co-administered dual therapy, fixed-dosed combination therapy was significantly associated with a
greater reduction in HbA\textsubscript{ic} (WMD -0.53%, 95% CI -0.78 to -0.28; five studies). Moderate heterogeneity was found in this outcome ($I^2$ = 52.4%).

There was a significantly higher medication possession ratio in patients who received fixed-dosed combination therapy when compared with those who received co-administered dual therapy (WMD 8.6%, 95% CI 1.6% to 15.6%; five cohort comparisons). Significant heterogeneity was observed in this outcome ($I^2$ = 98.7%).

For those patients who switched from monotherapy to fixed-dosed combinations or co-administered dual therapy, there was a significantly higher medication possession ratio for patients who switched to fixed-dosed combination therapy (WMD 7.7%, 95% CI 5.7% to 9.6%; four cohort comparisons). For patients who switched from co-administered dual therapy to fixed-dosed combination therapy or remained on co-administered dual therapy, a significantly higher medication possession ratio was found in patients who switched to fixed-dosed combination therapy (WMD 5.0%, 95% CI 3.1% to 6.8%; three cohort comparisons). No significant heterogeneity was found for both outcomes.

Results for subgroup analyses were reported.

**Authors' conclusions**

Use of fixed-dosed combinations with antihyperglycaemic agents was associated with lower HbA\textsubscript{ic} and higher medication possession ratio values compared with co-administered dual therapy use in patients with type 2 diabetes.

**CRD commentary**

This review's inclusion criteria were clear. Several relevant databases were searched. Efforts were made to find both published and unpublished studies, which minimised the risk of publication bias. The searches were restricted to studies in English, which increased the risk of language bias. Steps were made to minimise errors and biases during study selection and data extraction; it was unclear whether quality assessment was performed in duplicate. The authors stated that they assessed study quality but reported no further details. All included studies were observational studies, which were of low methodological rigour. Statistical heterogeneity was assessed and appropriate methods were used to pool the results.

The high level of clinical heterogeneity related to the timing of the measurement of HbA\textsubscript{ic} between included studies, the moderate to high level of statistical heterogeneity of the pooled outcomes and low methodological rigour of the included studies mean that the authors' conclusions may not be reliable.

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

The authors did not state any implications for practice and research.

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