Proportion of patients at HbA1c target <7% with eight classes of antidiabetic drugs in type 2 diabetes: systematic review of 218 randomized controlled trials with 78 945 patients

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CRD summary
This review showed that the attainment of HbA1c below 7% presented a huge variation among the different classes of non-insulin diabetes medications, and was strictly dependent on baseline HbA1c levels. The authors' conclusions appear to reflect the findings presented, it is uncertain whether possible error and biases in the review could have influenced the reliability of these conclusions.

Authors' objectives
To assess the efficacy of diabetes medications currently used in clinical practice for reaching the HbA1c target of less than 7% in type 2 diabetes.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and CINAHL were searched to April, 2011 with no language restrictions; search terms were reported. Prescribing information documents, relevant websites and reference lists of recovered articles were handsearched to identify further studies.

Study selection
Eligible studies for inclusion were randomised controlled trials (RCTs) published in peer-reviewed journals, that reported the effect of any non-insulin diabetes medication on HbA1c levels after a minimum of twelve weeks. Participants were non-pregnant adults (aged 18 years or over) with type 2 diabetes and were either drug naive or on background therapy with other agents. At least thirty participants were required for each arm of study. Trials were excluded if the intervention included initiation of two agents at the same time, or if doses of any antidiabetic drug (except insulin) differed from the maximum dose currently recommended in clinical practice. Reviews, editorials, comments, letters and abstracts were also excluded.

Mean age of trial participants ranged from 50.2 to 62.7 years. Mean baseline HbA1c levels ranged from 7.2 to 11.7%; length of follow-up ranged from 12 to 134 weeks. Eighty-three trials contained participants who were either drug naive or discontinued any previous drug prior to randomisation.

The authors did not state how many reviewers selected the studies for inclusion.

Assessment of study quality
Study quality was assessed according to descriptions of randomisation, blinding and withdrawals, using the Jadad Scale (scores ranged from one to five, with five being the highest quality). Trials scoring less than 3 on the Jadad Scale were deemed to have lower methodological quality.

The authors did not state how many reviewers conducted the quality assessment.

Data extraction
Proportions of participants with HbA1c levels less than 7% at endpoint were extracted, alongside the mean change in HbA1c. Study authors were contacted when necessary.

Two reviewers independently extracted the data; disagreements were resolved by consensus.

Methods of synthesis
The authors explored reasons for statistical heterogeneity between studies using meta-regression techniques. For each type of drug (antidiabetic drugs, non-insulin drugs, insulin), baseline HbA1c, change in HbA1c levels and achievement of the HbA1c target were investigated.
Results of the review
In total, 218 RCTs (approximately 78,000 participants) were included in the review; number of participants per study arm ranged from 30 to 2,493. Double-blind procedures were reported by 120 trials and triple-blind procedures reported by two trials. One trial reported a single-blind procedure; the remaining trials had open-label designs. No other quality assessment findings were reported.

The proportion of participants who achieved the HbA1c goal of less than 7% ranged from 25.9% (95% CI 18.5 to 34.9) with alpha-glucosidase inhibitors to 63.2% (95% CI 54.1 to 71.5) with exenatide long action release. Mean changes (reductions) from baseline HbA1c ranged from -0.64% (SD=0.20) for glinides to -1.91% (SD=0.63) for biphasic insulin. Significant statistical heterogeneity was found for all classes of antidiabetic drugs (all $I^2$ values exceeded 80%).

Multivariate meta-regression analysis did not indicate significant roles for drug user status, gender, mean age, year of publication, trial duration and concomitant drug use. A progressive decrease in the proportion of participants at target for each 0.5% increase in baseline HbA1c was observed.

Authors' conclusions
This review showed that the attainment of HbA1c below 7% presented a huge variation among the different classes of non-insulin diabetes medications and was strictly dependent on baseline HbA1c levels.

CRD commentary
The review question was clear and inclusion criteria appeared sufficiently replicable. Relevant data sources were accessed and efforts were made to minimise language bias. Attempts were made to reduce error and bias during data extraction, but this was unclear for the stages of study selection and quality assessment. Most trials were industry-sponsored, so it was possible that publication bias was present in the review. Adequate details of the large number of included trials were shown, the method of synthesis appeared appropriate and statistically significant heterogeneity was explored. The author's conclusions appear to reflect the findings presented, it is uncertain whether possible error and biases in the review could have influenced the reliability of these conclusions.

Implications of the review for practice and research
The authors did not state any implications for practice and further research.

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