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Computerized advice on drug dosage to improve prescribing practice (Review)

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[Intervention Review]

Computerized advice on drug dosage to improve prescribing practice

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ABSTRACT

Background

Maintaining therapeutic concentrations of drugs with a narrow therapeutic window is a complex task. Several computer systems have been designed to help doctors determine optimum drug dosage. Signicant improvements in health care could be achieved if computer advice improved health outcomes and could be implemented in routine practice in a cost-effective fashion. This is an updated version of an earlier Cochrane systematic review, first published in 2001 and updated in 2008.

Objectives

To assess whether computerized advice on drug dosage has beneficial effects on patient outcomes compared with routine care (empiric dosing without computer assistance).

Search methods

The following databases were searched from 1996 to January 2012: EPOC Group Specialized Register, Reference Manager; Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Ovid; EMBASE, Ovid; and CINAHL, EbscoHost. A "top up" search was conducted for the period January 2012 to January 2013; these results were screened by the authors and potentially relevant studies are listed in Studies Awaiting Classification. The review authors also searched reference lists of relevant studies and related reviews.

Selection criteria

We included randomized controlled trials, non-randomized controlled trials, controlled before-and-after studies and interrupted time series analyses of computerized advice on drug dosage. The participants were healthcare professionals responsible for patient care. The outcomes were any objectively measured change in the health of patients resulting from computerized advice (such as therapeutic drug control, clinical improvement, adverse reactions).

Data collection and analysis

Two review authors independently extracted data and assessed study quality. We grouped the results from the included studies by drug used and the effect aimed at for aminoglycoside antibiotics, amitriptyline, anaesthetics, insulin, anticoagulants, ovarian stimulation, anti-rejection drugs and theophylline. We combined the effect sizes to give an overall effect for each subgroup of studies, using a random-effects model. We further grouped studies by type of outcome when appropriate (i.e. no evidence of heterogeneity).

Main results

Forty-six comparisons (from 42 trials) were included (as compared with 26 comparisons in the last update) including a wide range of drugs in inpatient and outpatient settings. All were randomized controlled trials except two studies. Interventions usually targeted doctors, although some studies attempted to influence prescriptions by pharmacists and nurses. Drugs evaluated were anticoagulants, insulin, aminoglycoside antibiotics, theophylline, anti-rejection drugs, anaesthetic agents, antidepressants and gonadotropins. Although all studies used reliable outcome measures, their quality was generally low.

This update found similar results to the previous update and managed to identify specific therapeutic areas where the computerized advice on drug dosage was beneficial compared with routine care:

1. it increased target peak serum concentrations (standardized mean difference (SMD) 0.79, 95% CI 0.46 to 1.13) and the proportion of people with plasma drug concentrations within the therapeutic range after two days (pooled risk ratio (RR) 4.44, 95% CI 1.94 to 10.13) for aminoglycoside antibiotics;

2. it led to a physiological parameter more often within the desired range for oral anticoagulants (SMD for percentage of time spent in target international normalized ratio +0.19, 95% CI 0.06 to 0.33) and insulin (SMD for percentage of time in target glucose range: +1.27, 95% CI 0.56 to 1.98);

3. it decreased the time to achieve stabilization for oral anticoagulants (SMD -0.56, 95% CI -1.07 to -0.04);

4. it decreased the thromboembolism events (rate ratio 0.68, 95% CI 0.49 to 0.94) and tended to decrease bleeding events for anticoagulants although the difference was not significant (rate ratio 0.81, 95% CI 0.60 to 1.08). It tended to decrease unwanted effects for aminoglycoside antibiotics (nephrotoxicity: RR 0.67, 95% CI 0.42 to 1.06) and anti-rejection drugs (cytomegalovirus infections: RR 0.90, 95% CI 0.58 to 1.40);

5. it tended to reduce the length of time spent in the hospital although the difference was not significant (SMD -0.15, 95% CI -0.33 to 0.02) and to achieve comparable or better cost-effectiveness ratios than usual care;

6. there was no evidence of differences in mortality or other clinical adverse events for insulin (hypoglycaemia), anaesthetic agents, anti-rejection drugs and antidepressants.

For all outcomes, statistical heterogeneity quantified by I^2 statistics was moderate to high.

Authors' conclusions

This review update suggests that computerized advice for drug dosage has some benefits: it increases the serum concentrations for aminoglycoside antibiotics and improves the proportion of people for which the plasma drug is within the therapeutic range for aminoglycoside antibiotics.

It leads to a physiological parameter more often within the desired range for oral anticoagulants and insulin. It decreases the time to achieve stabilization for oral anticoagulants. It tends to decrease unwanted effects for aminoglycoside antibiotics and anti-rejection drugs, and it significantly decreases thromboembolism events for anticoagulants. It tends to reduce the length of hospital stay compared with routine care while comparable or better cost-effectiveness ratios were achieved.

However, there was no evidence that decision support had an effect on mortality or other clinical adverse events for insulin (hypoglycaemia), anaesthetic agents, anti-rejection drugs and antidepressants. In addition, there was no evidence to suggest that some decision support technical features (such as its integration into a computer physician order entry system) or aspects of organization of care (such as the setting) could optimize the effect of computerized advice.

Taking into account the high risk of bias of, and high heterogeneity between, studies, these results must be interpreted with caution.

PLAIN LANGUAGE SUMMARY

Computerized advice on drug dosage to improve prescribing practice

Background

Physicians and other healthcare professionals often prescribe drugs that will only work at certain concentrations. These drugs are said to have a narrow therapeutic window. This means that if the concentration of the drug is too high or too low, they may cause serious side effects or not provide the benefits they should. For example, blood thinners (anticoagulants) are prescribed to thin the blood to prevent clots. If the concentration is too high, people may experience excessive bleeding and even death. In contrast, if the concentration is too low, a clot could form and cause a stroke. For these types of drugs, it is important that the correct amount of the drug be prescribed.

Calculating and prescribing the correct amount can be complicated and time-consuming for healthcare professionals. Sometimes determining the correct dose can take a long time since healthcare professionals may not want to prescribe high doses of the drugs initially because they make mistakes in calculations. Several computer systems have been designed to do these calculations and assist healthcare professionals in prescribing these types of drugs.

Study characteristics

We sought clinical trial evidence from scientific databases to evaluate the effectiveness of these computer systems. The evidence is current to January 2012. We found data from 42 trials (40 randomized controlled trials (trials that allocate people at random to receive one of a number of drugs or procedures) and two non-randomized controlled trials).

Key results

Computerized advice for drug dosage can benefit people taking certain drugs compared with empiric dosing (where a dose is chosen based on a doctor's observations and experience) without computer assistance. When using the computer system, healthcare professionals prescribed appropriately higher doses of the drugs initially for aminoglycoside antibiotics and the correct drug dose was reached more quickly for oral anticoagulants. It significantly decreased thromboembolism (blood clotting) events for anticoagulants and tended to reduce unwanted effects for aminoglycoside antibiotics and anti-rejection drugs (although not an important difference). It tended to reduce the length of hospital stay compared with routine care with comparable or better cost-effectiveness. There was no evidence of effects on death or clinical side events for insulin (low blood sugar (hypoglycaemia)), anaesthetic agents, anti-rejection drugs (drugs taken to prevent rejection of a transplanted organ) and antidepressants.

Quality of evidence

The quality of the studies was low so these results must be interpreted with caution.

SUMMARY OF FINDINGS FOR THE MAIN COMPARISON [Explanation]

Computerized advice on drug dosage for leading serum concentrations within therapeutic range

Patient or population: patients with leading serum concentrations within therapeutic range
Settings: outpatient/inpatient
Intervention: computerized advice on drug dosage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Computerized advice on drug dosage				
Serum concentrations - aminoglycoside antibiotics: peak concentration Follow-up: 2 days	-	The mean serum concentrations - aminoglycoside antibiotics: peak concentration in the intervention groups was **0.79 standard deviations higher** (0.46 to 1.13 higher)	-	372 (4 studies)	⊕⊕◯◯ **low**[1,2,3]	SMD 0.79 (95% CI 0.46 to 1.13)
Serum concentrations - theophylline	-	The mean serum concentrations - theophylline in the intervention groups was **0.41 standard deviations higher** (0.2 lower to 1.02 higher)	-	201 (4 studies)	⊕⊕◯◯ **low**[3,4,5]	SMD 0.41 (95% CI -0.2 to 1.02)

Proportion of participants within therapeutic range - aminoglycoside antibiotics: % of participants with peak concentrations adequate after 2 days Follow-up: 2 days	**Study population**		**RR 4.44** (1.94 to 10.13)	72 (2 studies)	⊕⊕⊕○ **moderate**[3,6]	-
	135 per 1000	**600 per 1000** (262 to 1000)				
	Moderate					
	151 per 1000	**670 per 1000** (293 to 1000)				
Proportion of participants with toxic drug levels - theophylline	**Study population**		**RR 0.53** (0.25 to 1.13)	109 (2 studies)	⊕⊕⊕○ **moderate**[3,7]	-
	273 per 1000	**145 per 1000** (68 to 308)				
	Moderate					
	217 per 1000	**115 per 1000** (54 to 245)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Lack of blinding of participants and personnel in all studies. Incomplete outcome data in three studies. Random sequence generation and allocation concealment unclear in one study.
[2] I^2 = 51%.
[3] No funnel plot was performed since the validity conditions were not met.
[4] No blinding of participants and personnel in the two studies. Random sequence generation and allocation concealment unclear in one study.
[5] I^2 = 76%

[6] Lack of blinding of participants and personnel, incomplete outcome data in all studies. Participants were not similar at baseline in one study.

[7] No blinding of participants and personnel in the two studies. Random sequence generation and allocation concealment unclear in one study.

BACKGROUND

Medication mistakes still represent 20% of all medical errors although many efforts have focused in recent years on reducing the risk of drug errors (Brennan 1991). Maintaining therapeutic concentrations of drugs is a complex task requiring knowledge of evidence-based clinical guidelines, clinical pharmacology and skills in dose calculation. The potential for error is great since many of the drugs commonly used have a narrow 'window' within which therapeutic benefits can be obtained with a low risk of unwanted effects.

Description of the condition

Monitoring drug therapy to optimize effects and minimize dangers can be very time consuming. Practitioners may need access to a large amount of information to make an appropriate dose adjustment in situations such as prevention of deep vein thrombosis or management of people with renal insufficiency (Durieux 2005). Under these conditions, healthcare professionals make errors of judgement because their ability to process information is finite (McDonald 1976a).

For example, in ambulatory settings, general practitioners (GP) reported difficulties with drug dosing, especially for children, elderly people and people with renal impairment (Franke 2000). Moreover, physicians' computational abilities are often insufficient to perform calculations for drug dosage (Baldwin 1995). For example, 82 out of 150 hospital doctors were unable to calculate how many milligrams of lidocaine were in a 10 mL ampoule of 1% solution (Rolfe 1995).

Description of the intervention

Clinical decision support systems (CDSS), either computerized or not, have been proposed to improve clinical practice (Kawamoto 2005). Ideally, decision support, integrated in the electronic medical record as the platform, can provide physicians with tools making it possible to improve practice and patient safety (Bates 2003). An effective decision support system would anticipate needs and deliver information quickly in real time, adapted to the user's workflow (Bates 2003).

How the intervention might work

Computers are very good at collecting information and performing repetitive calculations. Moreover, the drugs that cause the most problems have often been in use for many years. The pharmacology of the drugs is, therefore, well understood and thus computer models can be used to generate advice on dosage. Several types of computer systems have been designed to help doctors in the task of determining the optimum dosage of drugs. Significant improvements in health could be achieved if computer advice was shown to be beneficial and was provided by the computers that clinicians now use for their everyday work.

In addition, the logistics by which the advice on drug dosage is delivered to the healthcare professional is critical to its effectiveness and to the transferability of this effectiveness in other settings. Computer physician order entry (CPOE) systems, which allow physicians to enter orders directly into a computer rather than hand writing them, have the potential to incorporate CDSS into daily practice (Kuperman 2003). According to three systematic reviews (Garg 2005; Kawamoto 2005; Nieuwlaat 2011a), CDSSs are more often associated with improvement of practice when the decision aid is automatically prompted, integrated in clinicians' workflow, and provided at time and location of decision making. This review focuses on advice with a personalized dosage for a specific participant. Two other Cochrane systematic reviews were interested in computer-generated reminders: one evaluated the effects of on-screen computer reminders delivered to clinicians at the point of care (Shojania 2009), and one considered reminders delivered on paper to healthcare professionals (Arditi 2012).

Why it is important to do this review

This is an updated version of two earlier Cochrane systematic reviews (Walton 2001; Durieux 2008).Those earlier reviews provided some evidence to support the use of computer assistance in determining drug dosage but concluded that further clinical trials were necessary to confirm those results.

OBJECTIVES

The primary objective of this systematic review was to examine whether computerized advice on drug dosage given to healthcare professionals is beneficial when compared with routine care (empiric dosing without computer assistance). The secondary objective was to determine whether any technical features of computerized systems or organizational aspects concerning their implementation influence their effectiveness.

Hypothesis tested

In previous versions of this review, we tested the benefit in terms of effects on process of care (healthcare professional oriented) and on outcome of care (patient oriented). The effect on process of care was any change in drug dose as a process measure. However, there are problems with this approach since a higher dose may, in some circumstances, be beneficial and, in others, be disadvantageous. Thus, in this review we have removed this outcome and

only reported effects on dosage where we judged the changes to be meaningful. We examined six hypotheses on patient-oriented outcomes (most of them measuring surrogate outcomes).

Effect on outcome of care (patient-oriented outcomes)

1. Decisions on drug dosage based on computer advice lead more often to drug levels within the therapeutic range.
2. Decisions on drug dosage based on computer advice lead more often to a physiological parameter being maintained within the desired range (e.g. blood pressure or prothrombin (PT) time).
3. Decisions on drug dosage based on computer advice lead to more rapid therapeutic control, assessed by a physiological parameter.
4. Decisions on drug dosage based on computer advice lead to greater clinical effectiveness, assessed by clinical improvement.
5. Decisions on drug dosage based on computer advice lead to fewer unwanted effects than conventional dose adjustment.
6. Computer advice reduces the cost of health care or the use of resources (e.g. length of hospital stay).

Unlike the previous update of this review, we decided to analyze the results individually for each drug because of a high clinical and statistical heterogeneity between drugs (each drug has its specific outcomes).

Other hypotheses address our secondary objectives and reflect a series of subgroup analyses.

Effect of decision support logistics and organization of care

1. Computer advice given in real time is more effective than that given by delayed feedback.
2. Computer advice integrated in CPOE system is more effective than other systems.
3. System-initiated computer advice is more effective than user-initiated computer advice.
4. Direct intervention (system delivers advice directly to the provider) is more effective than indirect intervention (advice is made available to the provider by the intermediate of a third party actor, i.e. system is not directly used by the provider).
5. The impact of computer advice depends on the setting where it is implemented (inpatient versus outpatient care).
6. Computer advice given as a recommendation is more effective than a calculated dose proposed without possibility of change and which does not take into account the healthcare professional's experience).

METHODS

Criteria for considering studies for this review

Types of studies

We considered for inclusion all types of study designs that met Effective Practice and Organization of Care Group (EPOC) inclusion criteria:

- Randomized controlled trials (RCTs) where the unit of randomization was:

1. the participant or
2. the cluster: healthcare professionals (doctors, nurses or pharmacists) or groups of professionals (practices or hospitals);

- Non-randomized controlled trials (NRCTs);
- Controlled before-and-after (CBA) studies with:

1. the same pre- and postintervention periods for study and control sites;
2. comparable study and control sites with respect to level of care, setting of care and baseline characteristics;
3. two intervention sites and two control sites;

- Interrupted time series (ITS) studies with:

1. a clearly defined point in time when the intervention occurred;
2. at least three data points before and three after the intervention.

See the EPOC checklist for definition of designs (EPOC 2012).

Types of participants

The participants were healthcare professionals with responsibility for patient care.

Types of interventions

We sought to identify all comparative studies comparing computerized advice on drug dosage given to routine care (empiric dosing without computer assistance). We defined computerized advice on drug dosage as a recommendation provided to the healthcare professional on the drug dosage needed for a specific participant and a specific drug and calculated by a computer.

Computer program

The computer program was a software model or an application integrated into a laptop, a smartphone, a tablet computer, the CPOE, or a website (online calculator). We did not consider interventions where the recommended drug dose was not calculated by a computer, for example an equation or a nomogram not implemented in a computer device.

Nature of advice

The advice included a dosage personalized for a specific participant. We did not include studies reporting a popup with general advice on the dosage required for a specific condition (most frequently dose of medication, dose interval, maximum total daily dose).

Content of recommendation and calculation of drug dose

The recommendation could be evidence-based, a clinical practice guideline developed by expert bodies (government, professional) or local clinicians, or population pharmacokinetic/pharmacodynamic models. The participant's drug dose was computed using an equation including participant's characteristics (participant's age, weight, previous drug levels…). Alternatively, a more complex mathematical model was used, which was generally a pharmacokinetic model of the relationship between administered doses of the drug and observed concentrations in the participant's body.

Advice delivery and timing

The computerized advice could be delivered to clinicians when they are writing their prescription (point of care delivery) or it could be delivered at a later time. In addition, the computerized advice could be delivered to another healthcare professional (e.g. a pharmacist or a pharmacokinetic unit) and passed to the clinician. Unlike the review on the effect of point-of-care computer reminders on physician behaviour (Shojania 2009), we included systems that were not encountered during routine performance of the activities of interest, for example a dedicated computer used only for performing dose calculation for anticoagulants. These systems require clinicians to depart from their usual workflow in order to avail themselves of the reminder or decision support.

Control of the healthcare professional

We included studies where advice was given as a recommendation so that the healthcare professional was able to accept or refuse it. We did not include studies reporting non-specific advice given to a healthcare professional to adjust drug dosage or when the healthcare professional was not in charge of every adjustment of the drug, for example studies reporting the direct administration of a drug to the participant by means of a computer supervised device (closed-loop system) or through self dosing devices (one Cochrane review addresses the evaluation of anticoagulant self management (Garcia-Alamino 2010)).

Starter

The advice could be system-initiated (advice appears without user intervention) or user-initiated (the computer program must be started by the user to obtain an advice).

Control group

The control group included empiric dosing without computer assistance, in general routine care.

Types of outcome measures

All outcome measures included were patient-oriented outcomes.

1. Proportion of participants or time for which the plasma drug concentrations was within the therapeutic range.
2. Proportion of participants or time for which the studied physiological parameter was maintained within the target range.
3. Time to achieve therapeutic control.
4. Proportion of participants with toxic drug levels.
5. Proportion of participants with clinical improvement.
6. Proportion of participants with adverse effects of drug therapy.
7. Proportion of deaths.
8. Length of hospital stay.
9. Total cost per participant.

We excluded the outcomes for which reporting was incomplete (e.g. no numerical values reported, no measure of dispersion) and excluded studies whose only relevant outcomes were death or adverse effects requiring monitoring and which did not explicitly report such outcomes as primary.

For serum concentrations, we also considered peak, trough and steady-state concentrations. The measurement of drug levels in the blood, called therapeutic drug monitoring (TDM), is required for some drugs to ensure that the participants maintain the concentration of drug within the established therapeutic range (drug effective without toxicity). Blood for peak level is collected at the drug's highest concentration within the dosing period. Trough levels (occasionally called residual levels) are measured just prior to administration of the next dose, and are the lowest concentration in the dosing interval. Most therapeutic drugs have a narrow trough to peak difference (therapeutic range), and, therefore, only trough levels are needed to detect blood levels that are too low or too high. Peak levels are needed for some drugs, especially aminoglycoside antibiotics: a concentration below the therapeutic range will not resolve the bacterial infection so high peak concentrations are necessary for optimal efficacy; however, too high a level can cause damage such as nephrotoxicity so it is important that the trough concentration be allowed to fall in order to avoid accumulation. The steady-state concentration is defined as the point at which the amount of drug administered (drug intake) and the amount of drug excreted (drug elimination) reach an equilibrium. The goal of TDM is to optimize the drug dose so that the participant's drug concentrations remain within the therapeutic range.

Search methods for identification of studies

Updates to Cochrane systematic reviews usually entail executing previously used search strategies for the update period or, in other

words, from the date of the last search, to present. In some cases, however, search strategies must be assessed and revised in order to optimize the identification of evidence. When this occurs, it is advisable to search retrospectively--that is, to re-search previously searched time periods, in order to discover whether or not studies have been missed. This update represents a review where search strategies have been revised significantly (by M. Fiander, Information Scientist, and Trials Search Co-ordinator for the EPOC Group) and where, consequently, searching has been conducted not only from the date of last search in 2006, but retrospectively from 1996 to January 2012, where 1996 to 2006 represents a previously searched time period.

The revised search strategies had an impact on the review since the strategies identified a number of studies which should have been found during previous searches: Ageno 2000, Claes 2005, Claes 2006, Mitra 2005, Plank 2006, Poller 2002, Poller 2003.

For the initial review, the databases listed below were searched from database start date to 1996; for the first update, the search period was 1996 to 2006; for this, the second, update, searches were run from 1996 to January 2012. Two methodological search filters were used to limit retrieval to appropriate study designs: the Cochrane Highly Sensitive Search Strategy (sensitivity- and precision-maximizing version, 2008 revision) to identify randomized trials; and an EPOC methodology filter (Appendix 1) to identify non-RCT designs. Related reviews were identified by searching the Database of Abstracts of Reviews (DARE). All databases were searched from their start date forward; start date represents the date the database began to index journals. Note that database start dates vary by database (Medline, EMBASE, etc.) and provider (OVID, Ebsco, etc.). Start dates are provided in the list of databases, below.

A top-up search was conducted for the period January 2012 to January 2013; the authors screened the titles and abstracts of these results and added potentially relevant studies to Studies awaiting classification.

The original MEDLINE search strategies used until 2006 are in Appendix 2. The revised search strategies used for this update are in Appendices 2 to 6 as follows: MEDLINE, Appendix 3; EMBASE, Appendix 4; CINAHL, Appendix 5; Cochrane Central Register of Controlled Trials, Appendix 6; EPOC Specialised Register, Appendix 7.

Databases searched

- Cochrane Central Register of Controlled Trials (CENTRAL), Issue 12, 2012, OvidSP EBM Reviews
- MEDLINE, including In-Process & Other Non-Indexed Citations, OvidSP, 1946-January 2013
- EMBASE, 1947 to January 2013, OvidSP
- CINAHL (Cumulative Index to Nursing and Allied Health Literature), 1980-January 2013, EbscoHost
- EPOC Group, Specialised Register

Searching other resources

The review authors handsearched reference lists from primary articles and relevant reviews identified, and conference proceedings. We contacted experts in the field.

We also:

- Screened (hand searched) the following journals:
  - *Therapeutic Drug Monitoring* journal (1979 to December 2006).
  - *Journal of the American Medical Informatics Association* (January 1996 to March 2007).
- Reviewed reference lists of all included studies, relevant systematic reviews and primary studies.
- Contacted authors of relevant studies/ reviews to clarify reported published information and to seek unpublished results/ data.
- Contacted researchers with expertise relevant to the review topic/ EPOC interventions.

Data collection and analysis

Selection of studies

We merged the search results using Reference Manager 5 (RevMan 2011), and removed duplicate records. We examined all titles and abstracts.

Two review authors (FG, PD) examined independently each title and abstract to exclude obviously irrelevant reports (mainly therapeutic trials and genetic research). We retrieved full texts, which were independently screened. We then randomly allocated each selected study to two pairs of review authors (IC and FG, MR and PD) who reviewed it and extracted data independently. We resolved disagreements by group discussion with the four review authors. We reported reasons for excluding full papers.

Data extraction and management

We reviewed the data abstraction form for the previous update of the review. We adapted a checklist to the specific subject to extract the decision support technical features by which the advice on drug dosage was delivered to the healthcare professional.

- Was the computerized advice delivered in real time (at the moment of the practitioners decision making) or by delayed feedback?
- Was the computerized advice integrated in a CPOE?
- Was the computerized advice user-initiated or system-initiated?
- Was the intervention direct or indirect (a third party brought advice from computer and transfers it to user)?

An additional feature was added:

- Was the information of the calculated dose given as a recommendation to the healthcare professional who prescribed

through the computer or through another healthcare professional (the healthcare professional had the possibility to accept or refuse the advice)?

The review authors abstracted the data independently and resolved disagreements by discussion. A statistician (FG) reviewed all data and contacted authors of included studies for additional information.

Assessment of risk of bias in included studies

We assessed the risk of bias of the studies using the 'Risk of bias' criteria described by the EPOC group and extracted data using the EPOC checklist (EPOC 2009; Higgins 2011). We used nine standard criteria for RCTs, NRCTs and CBAs: allocation sequence adequately generated; allocation adequately concealed; baseline outcome measurements similar; baseline characteristics similar; incomplete outcome data adequately addressed; knowledge of the allocated interventions adequately prevented during the study; study adequately protected against contamination; study free from selective outcome reporting; study free from other risks of bias. We scored studies using cluster randomization to be adequate on concealment of allocation (if the sequence generation was adequate) and on protection against contamination. Baseline characteristics were considered for similarity at the unit of analysis level. Risk of bias on baseline outcome measurements was only evaluated for insulin. For the other drugs, the baseline measurement was not relevant since there was no drug intake before the intervention. Therefore, we considered risk of bias on baseline outcome measurements to be 'low risk' for these drugs.

The risk of bias for ITS studies can be evaluated using seven standard criteria but we found no ITS studies.

We included all the 'Risk of bias' criteria in the data abstraction form and independently scored criteria as 'yes' (adequate), 'no' (inadequate) or 'unclear'. We resolved disagreements by discussion and, where necessary, with a third review author. The risk of bias of included studies is summarized in the text and presented in the 'Risk of bias' section within the Characteristics of included studies table.

Two review authors (EC, PD) assessed the quality of evidence for each main outcome - that is the extent of confidence in the estimate of effect across studies (high, moderate, low or very low) - using the GRADE approach (Guyatt 2008).

Measures of treatment effect

For dichotomous variables, we used the risk ratio (RR).

When the outcomes were continuous variables, we calculated standardized mean differences (SMD) with 95% confidence intervals (CI). The SMD is a statistical measure of the impact of the intervention, which is independent of the units used to measure study outcomes. This measure allows studies of the same intervention using different outcomes to be compared. For example, measurement of drug concentrations in blood in different studies may use different assays in several laboratories and results may be reported in different units. The SMD compares differences between experimental and control groups to the standard deviation of the outcome for each study. Hence, a quantitative approximation can be made of the overall effect of decision support on plasma levels. Because SMD can be difficult to interpret (as it is reported in units of standard deviation), we also presented mean difference (MD), that is the absolute difference between the mean value in two groups, in relevant cases (when measurements were made on the same scale).

Clinical adverse events were expressed as RRs or rate ratios. In a randomized trial, rate ratios may often be very similar to RRs obtained after dichotomizing the participants, since the mean period of follow-up should be similar in all intervention groups. Rate ratios and RRs will differ, however, if an intervention affects the likelihood of some participants experiencing multiple events.

The effect sizes were combined to give an overall effect for each subgroup of studies, using a random-effects model. The random-effects model was chosen because it does not assume that all interventions have the same underlying effect.

Unit of analysis issues

Analyses of studies using cluster randomization that do not account for the design effect risk inflating the type 1 error-rate resulting in artificially narrow CIs (Ukoumunne 1999). We have reported potential errors and did not attempt to reanalyze data unless standard errors were correctly stated with number of clusters allowing the calculation of appropriate CIs.

Dealing with missing data

When the mean and standard deviation were missing, we estimated the mean from the median and standard deviation from the interquartile range or range (Hozo 2005). Missing data on outcomes or estimated data are explicitly indicated in the tables and text. We did not attempt to impute or model other missing data.

Assessment of heterogeneity

We explored heterogeneity using tests of heterogeneity and examinations of direction, magnitude and variability of effects. The statistical test for heterogeneity (Chi^2 test) tests the null hypothesis that all studies in a meta-analysis have the same underlying magnitude of effects. The I^2 statistic quantifies the proportion of the variation in point estimates due to among-study differences but is influenced by sample size. An I^2 statistic greater than 50% may be considered as substantial heterogeneity and I^2 statistic greater than 75% as considerable heterogeneity (Deeks 2011). High P value for the test of heterogeneity (P value > 0.1) and low I^2 values do not necessarily indicate low heterogeneity (Guyatt 2011). Thus, we also manually examined the variability in point estimates across studies and the overlap of CIs.

Assessment of reporting biases

To be meaningful and appropriate, funnel-plot asymmetry tests must be performed when four criteria are met: no significant heterogeneity (P value for the Chi^2 test of heterogeneity > 0.10), low I^2 statistic (< 50%), 10 or more studies with at least one with significant results, and a ratio of the maximal to minimal variance across studies greater than four (Ioannidis 2007). We could not assess publication bias because these conditions were not met.

Data synthesis

We grouped the results from the included studies by drug used and the effect aimed at for aminoglycoside antibiotics, amitriptyline, anaesthetics, insulin, anticoagulants, ovarian stimulation, anti-rejection drugs and theophylline. We further grouped studies by type of outcome when appropriate (i.e. no evidence of heterogeneity). We constructed Forest plots for the main outcomes without potential unit of analysis error for which data were available for more than one comparison.

The doses of drugs administered to participants and the number of dose changes per participant were described but not compared.

Subgroup analysis and investigation of heterogeneity

We considered the following potential sources of heterogeneity to explain variation in the results of the included studies:

- time of delivery of advice (real time/delayed feedback);
- location of advice (integrated in CPOE systems/other);
- initiation of the computer advice (system-initiated/user-initiated);
- advice given directly to the provider (direct intervention) versus the intermediate of a third party actor (indirect intervention);
- type of hospital (outpatient/inpatient);
- type of advice (recommendation/calculated dose proposed without possibility of change).

Sensitivity analysis

We had planned to perform a sensitivity analysis, excluding high risk of bias studies, but, since most of the identified studies had high risk of bias, we were unable to perform this analysis.

RESULTS

Description of studies

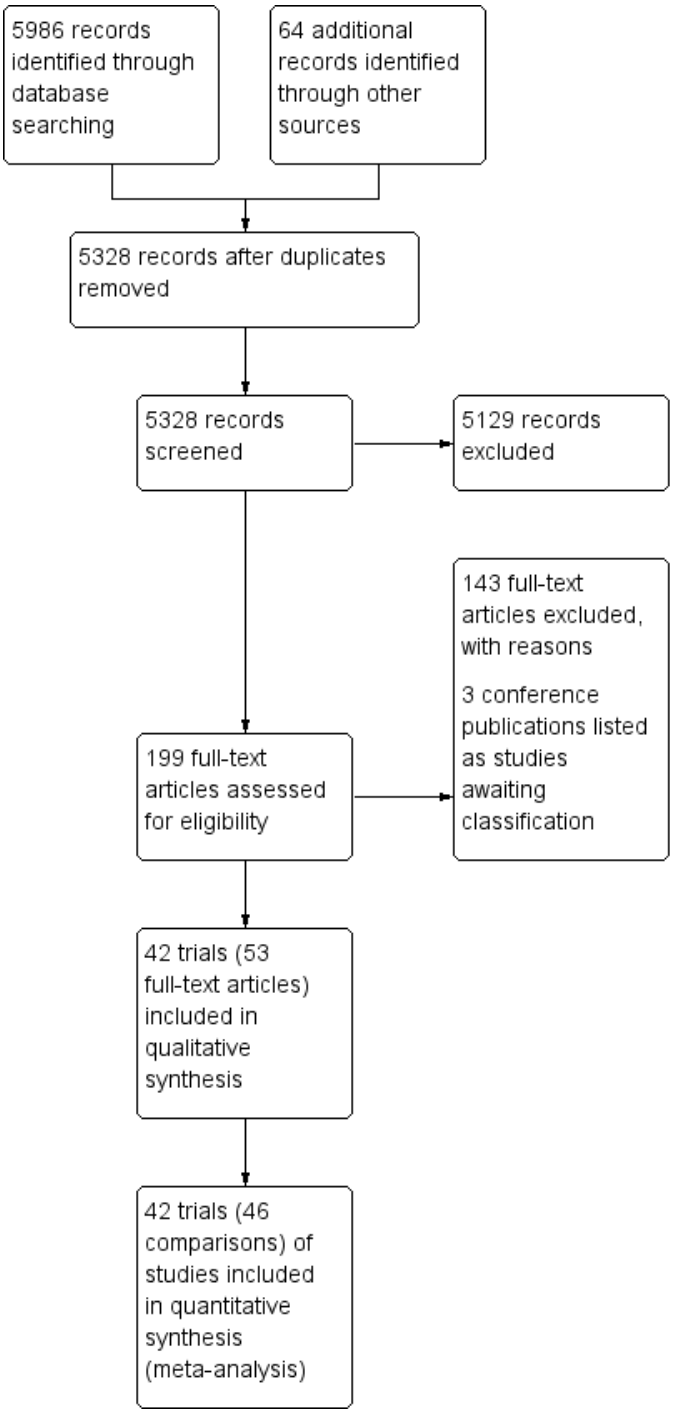
See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.

Results of the search

The initial review identified 15 comparisons (14 articles) (Walton 2001), whereas the previous update of this review identified 26 comparisons (23 articles) that met inclusion criteria (Durieux 2008).

Figure 1 shows the study PRISMA flow chart (Moher 2009). We screened 5328 non-duplicate records, of which 64 were identified through other sources than database searches (references from previous versions of this review and published before 1996, references from bibliography or website of screened articles or systematic reviews). We assessed 199 articles for potential inclusion: 136 articles identified from the new updated search strategy (from January 1996) (including eight from the previous version of the review) and 48 additional relevant articles from handsearches and reference lists of trials and systematic reviews, leading to 176 potential 'new' inclusions as compared with the previous version of the review; and 15 articles from the previous review and published before 1996.

Figure 1. Study flow diagram.



Since the search strategy missed studies we will search pre-1996 for the next update of this review.

Included studies

This update identified 20 new trials with 21 comparisons, for a total of 42 trials and 46 comparisons and are included as follows: 25 comparisons (22 trials) from the previous update of this review (Durieux 2008), and 21 comparisons (20 trials) from this update. These 42 trials were reported in 53 references (many reports for some trials). Three articles were separate cost-effectiveness analyses: Jowett 2009 (main results in Poller 2008 PARMA 5; Poller 2009 DAWN AC), Rousseau 2010 (main results in Le Meur 2007), and Claes 2006 (main results in Claes 2005). One article was a separate safety analysis: Mihajlovic 2010 (main results in Mihajlovic 2003).

In four trials, two different comparisons were analyzed in one article, midazolam and fentanyl continuous infusion anaesthesia for cardiac surgery were independently titrated to maintain haemodynamic stability infusions but analyzed in the same population (Theil 1993 fentanyl; Theil 1993 midazolam). Therefore, these two drugs were reviewed separately. In one article, Vadher 1997 pop1 considered people starting warfarin with a targeted international normalized ratio (INR) between 2 and 3; Vadher 1997 pop2 considered people on long-term treatment with a targeted INR between 3 and 4.5. Poller 1998 pop1 considered inpatients needing anticoagulant therapy (stabilized patients); Poller 1998 pop2 considered outpatients needing anticoagulant therapy (in the stabilization period). The results from two computer-assisted dosage programs (DAWN AC and PARMA 5) were first published in one clinical endpoint report from the European Action on Anticoagulation (EAA), which gave the combined results (Poller 2008) and secondly published in two separate reports (Poller 2008 PARMA 5; Poller 2009 DAWN AC), because the computer-assistance differed considerably between the participant centres in the study using the two alternative programs. We decided to include the two computer-assisted dosage programs as two subgroup analyses.

All studies were RCTs, except two (Chertow 2001; Manotti 2001), which we classified as NRCTs.

In one publication concerning warfarin dosage adjustment (Carter 1987), three groups were studied: we reviewed only the comparison between the group using an analogue-computer method and the group using empiric dosing (control). The third group, using a linear regression model, was excluded because it did not involve any computer assistance.

In one publication (Manotti 2001), two different groups of people were studied: one group starting oral anticoagulants (induction) and one group on long-term treatment (maintenance). The maintenance study was not reviewed because of the absence of relevant data for the primary outcome.

In one publication, two different studies were reported: the first study considered people starting warfarin with a targeted INR between 2 and 3 (Vadher 1997 pop1); the second study considered people on long-term treatment with a targeted INR between 3 and 4.5 (Vadher 1997 pop2).

In one publication (Fitzmaurice 2000), there were two levels of randomization. Practices were randomized to intervention or control. The study used two control populations: people individually randomly allocated to control in the intervention practices (intrapractice controls) and all participants in the control practices (interpractice controls). We did not analyze interpractice controls to avoid a possible unit of analysis error.

In one publication concerning oral anticoagulation therapy at steady state where randomization was at the GP practice level (reported in Claes 2005; Claes 2006), four groups were studied: we reviewed only the comparison between group A (Grol's multifaceted education: summary of the guidelines printed on the cover of a folder containing the anticoagulation files; information booklets on anticoagulation for their patients; website with guidelines, study design, and general information; newsletter sent every two months to inform the GPs on the study progress and requested them to send the anticoagulation files for checking) and group D (Grol's multifaceted education + DAWN AC computer-assisted advice that generated a recommended dosing scheme and the time to next visit). Group A did not correspond to standard practice but it was considered as a control group because GPs in group D also received the multifaceted education. Groups B and C were excluded because the interventions were not computerized advice on drug dosage.

In one publication concerning insulin in cardiac surgery patients (Blaha 2009), three groups were studied: we reviewed only the comparison between the group using the Matias protocol based on the absolute glucose value and the group using computer-based model predictive control algorithm with variable sampling rate (Enhanced software Model Predictive Control (eMPC)). The third group, using the Bath protocol based on the relative glucose change was excluded since most standard protocols in blood glucose management use the absolute glucose value and the Bath protocol had not been used in the hospital before the study.

Four comparisons/three trials included (Poller 1998 pop1; Anderson 2007; Poller 2008 PARMA 5; Poller 2009 DAWN AC) had duplicate publications (Poller 2002; Anderson 2008; Poller 2008), and three comparisons/two trials included (Le Meur 2007; Poller 2008 PARMA 5; Poller 2009 DAWN AC) were mentioned earlier in abstracts (Poller 2003; Le Meur 2007 extract).

Excluded studies

We excluded 143 of the 199 full-text articles assessed for eligi-

bility: 72 because the intervention was not a computerized drug dosage, 38 for an inappropriate design, 12 for absence of relevant data for primary outcome, seven because the patient aid was not under physician control, five because the dose advice was not individualized, three discussions, two conferences publications where contact to author failed (Ghazal-Aswad 1997; Tomek 2011), one abstract published elsewhere (van Leeuwen 2005), one because some participants were already included in another publication (Jankovic 1999) and one comment (Ligtenberg 2006).

One study included in the previous update of the review was excluded because the intervention corresponded to a closed-loop system (automatic optimization of the infusion rate of sodium nitroprusside achieved by an integrated hardware-software closed-loop controller implemented as a small bedside device) (Ruiz 1993).

Ongoing studies

A total of 17 studies are awaiting classification (possibly relevant ongoing studies published between January 2012 and January 2013). Three references corresponding to conference publications not published at the time of the search for this update (Overgaard 2010; Anderson 2011; Nieuwlaat 2011), have been published since then (Anderson 2012; Nieuwlaat 2012; Rasmussen 2012).

Characteristics of the providers

The providers were primarily doctors, although 14 studies (33.3%) targeted several categories of healthcare professionals including pharmacists (Carter 1987; White 1987; Destache 1990; Leehey 1993; Mungall 1994; Anderson 2007), nurses (Vadher 1997; Vadher 1997 pop2; Vadher 1997 pop1; Ageno 1998; Ageno 2000; Fitzmaurice 2000; Blaha 2009), or other healthcare professionals (Claes 2005; Claes 2006; Saager 2008). Three studies addressed only nurses' behaviour (White 1991; Pachler 2008; Cordingley 2009).

Twenty studies (47.6%) were conducted in North America (17 in the US, three in Canada) and 15 (35.7%) in Europe (three studies with numerous countries Poller 1998 pop1; Poller 1998 pop2; Plank 2006; Cordingley 2009). Two studies took place in New Zealand (Begg 1989; Hickling 1989), one in Australia (Hurley 1986), one in Israel (Verner 1992), one in Norway (Asberg 2010), and one in Serbia (Mihajlovic 2003; Mihajlovic 2010). One study was conducted in 13 countries from Europe, Israel and Australia (Poller 2008 PARMA 5; Poller 2009 DAWN AC).

Thirty-one studies (73.8%) were conducted in one centre, and seven studies (16.7%) in two to five centres. One study took place in 11 centres (Le Meur 2007); one study included 12 practices (Fitzmaurice 2000); one study was conducted in 32 centres from Europe (29 centres), Israel (two centres), and Australia (one centre) (Poller 2008 PARMA 5; Poller 2009 DAWN AC); one study included 96 GPs regrouped in 66 GP practices (Claes 2005; Claes 2006).

Twenty-seven comparisons (58.7%) included fewer than 100 participants in the analyses (median: 80 participants, mean: 779 participants).

Target behaviour

The target behaviour of the healthcare provider was the prescription and the dosing of drugs.

Characteristics of the interventions

Most of the studies provided advice about appropriate drug dosages to healthcare professionals who then decided whether to follow this or not. Fifteen studies (35.7%) (18 comparisons) evaluated anticoagulants, 10 studies (23.8%) evaluated the administration of insulin, five studies (11.9%) evaluated the administration of aminoglycoside antibiotics, four studies (9.5%) evaluated theophylline, four studies (9.5%) evaluated anti-rejection drugs requiring adjustments for renal impairment, two studies (4.8%) (three comparisons) evaluated computer-controlled infusions of anaesthetic agents, one study (2.4%) evaluated amitriptyline in the treatment of major depressive episodes and one study (2.4%) evaluated ovarian stimulation by gonadotropins.

Most of the computer support systems used a mathematical model of the pharmacokinetics of the drug to predict the required dose. These models represent the compartments in the body in which the drug is distributed, with rate constants determining the movement of the drug between different compartments. These systems allowed the operator to specify a target serum drug level, which the computer attempted to achieve using Bayesian forecasting methods. Where the effect of the drug was more important than the serum level, pharmacodynamic parameters based on population data could be added to the model (White 1987).

Anticoagulants (fifteen studies, eighteen comparisons)

Fourteen studies evaluated oral anticoagulant and one study evaluated heparin (Mungall 1994). Five studies analyzed initiation of warfarin (Carter 1987; White 1987; Ageno 2000; Manotti 2001; Anderson 2007), with varying target INR ranges (see Characteristics of included studies). Four studies (five comparisons) analyzed long-term warfarin therapy (White 1991; Vadher 1997 pop1; Ageno 2000; Fitzmaurice 2000; Claes 2005; Claes 2006), with varying target INR ranges (see Characteristics of included studies). One study analyzed heparin therapy (Mungall 1994). Six studies (five comparisons) analyzed both initiation and long-term warfarin therapy with at least three months of follow-up (Vadher 1997; Vadher 1997 pop2; Poller 1998 pop1; Poller 1998 pop2; Mitra 2005; Poller 2008 PARMA 5; Poller 2009 DAWN AC).

The setting was outpatient care for six studies (White 1991; Vadher 1997 pop1; Vadher 1997 pop2; Ageno 1998; Poller 1998 pop1; Poller 1998 pop2; Manotti 2001; Poller 2008), community-based

care in two studies (Fitzmaurice 2000; Claes 2005; Claes 2006), and inpatient care for six studies (Carter 1987: White 1987; Mungall 1994; Ageno 2000; Mitra 2005; Anderson 2007); it was mixed in one study (Vadher 1997).

The computer support systems were programs that were not integrated into a CPOE. The computer-generated program DAWN AC (4S Information Systems Ltd.) was used in five studies (Poller 1998 pop1; Poller 1998 pop2; Ageno 2000; Claes 2005; Mitra 2005; Claes 2006; Poller 2009 DAWN AC). Two modules existed in the DAWN AC program (induction and maintenance). Four studies used a (Bayesian) computer pharmacokinetic or a pharmacodynamic model (Carter 1987; White 1987; White 1991; Mungall 1994), or both, whereas one used a pharmacogenetics model (Anderson 2007). One study used the PARMA (Program for Archive, Refertation, and Monitoring of Anticoagulated patients) software program developed in Italy (Manotti 2001), and one comparison used PARMA 5, a new version of the program (Poller 2008 PARMA 5). Other studies used dosage algorithms or prediction rules.

The advice was given in real time to the healthcare professional in all studies except three, where it was unclear (Vadher 1997; Poller 1998 pop1; Poller 1998 pop2; Claes 2005; Claes 2006). The computerized advice was user-initiated in seven studies (White 1987; White 1991; Vadher 1997 pop1; Vadher 1997 pop2; Ageno 1998; Fitzmaurice 2000; Claes 2005; Claes 2006; Anderson 2007), system-initiated in two studies (Manotti 2001; Poller 2008 PARMA 5; Poller 2009 DAWN AC), and it was unclear in six studies (Carter 1987; Mungall 1994; Vadher 1997; Poller 1998 pop1; Poller 1998 pop2; Ageno 1998; Mitra 2005). The intervention was direct in seven studies (White 1991; Vadher 1997 pop1; Vadher 1997 pop2; Ageno 1998; Fitzmaurice 2000; Ageno 2000; Manotti 2001; Anderson 2007), indirect in three studies (dosage determined by pharmacy in Carter 1987 and Mungall 1994, and the pathologist reviewed the computer-generated advice in Claes 2005) and it was unclear in five studies (White 1987; Vadher 1997; Poller 1998 pop1; Poller 1998 pop2; Mitra 2005; Poller 2008).

Three comparisons provided the warfarin maintenance doses per participant (Carter 1987; Vadher 1997 pop1; Vadher 1997 pop2), and there was no significant difference between groups (MD -0.33 mg/day, 95% CI -1.18 to 0.53). One study reported significantly larger amounts of drug prescribed for people with high INR target both of warfarin (computer group = 33.3 mg/week versus manual = 31.3 mg/week; P value < 0.001), and acenocoumarol (computer group = 19.2 mg/week versus manual = 17.8 mg/week; P value < 0.01), whereas there was no significant difference between the doses prescribed for people with low INR target (Manotti 2001). One study analyzed the number of dose adjustments (Anderson 2007): pharmacogenetic guidance significantly decreased the number of required dose adjustments (by 0.62 dose adjustments per participant; 95% CI 0.04 to 1.19; P value = 0.035).

There were two eligible comparisons with potential unit of analysis error that analyzed the proportion of dose adjustments. In one comparison (Ageno 1998), the percentage of dose adjustments performed by the healthcare professionals was 47.4%, whereas the computer needed 31.3% dose adjustments, a statistically significant 34.0% relative reduction (95% CI -41.9% to -24.7%). In the other comparison (Ageno 2000), the proportion of dose adjustments was 48% in the computer group and 45% in the manual group, a non-significant relative increase of 7% (95% CI -10% to 27%).

In Claes 2005, there was no significant difference among the groups in number of tests per participant per month and per cent of participants with treatment changes.

For heparin (Mungall 1994), the mean dose was not significantly different between the computer and the standard groups (MD 100 units/hour, 95% CI -96 to 296).

Insulin (ten studies)

Eight studies (80%) evaluated insulin in people admitted into the intensive care unit with hyperglycaemia: six studies in cardiac surgery patients (Plank 2006; Hovorka 2007; Kremen 2007; Saager 2008; Blaha 2009; Sato 2011) and two studies in critically ill patients (Pachler 2008; Cordingley 2009). One study was conducted in general medical inpatients with type 2 diabetes (Wexler 2010) and one study in diabetic outpatients (Augstein 2007).

The computer support system was integrated into a CPOE in one study (Wexler 2010), whereas other systems were software developed by companies. The software Model Predictive Control (MPC) was used in two studies (Plank 2006; Kremen 2007). The laptop-based algorithm MPC is a model representing the glucoregulatory system. Glucose concentration, insulin dosage and carbohydrate intake are the input variables for the MPC. The insulin infusion rate is the output parameter based on hourly glucose sampling. eMPC was used in four studies (Hovorka 2007; Pachler 2008; Blaha 2009; Cordingley 2009). The eMPC is an enhanced version of the model predictive control algorithm (MPC), which additionally generates the time of the next glucose measurement with an interval between samples varying from 0.5 to 4 hours. All six studies were part of the CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community working towards the development of a closed-loop system to achieve safe tight glucose control in intensive care patients. Three studies used other software that take account of the characteristics of glucose dynamics (KArlsburg Diabetes Management System (KADIS): Augstein 2007, EndoTool Glucose Management System (MD Scientic): Saager 2008, GIN Computer Software (GINCS): Sato 2011), and one study used a weight-based insulin dose calculator (Wexler 2010).

The advice was given in real time to the healthcare professional in all studies except one, where it was unclear (Augstein 2007). The computerized advice was user-initiated in six studies (Plank 2006;

Hovorka 2007; Kremen 2007; Augstein 2007; Pachler 2008; Blaha 2009), system-initiated in two studies (Saager 2008; Wexler 2010), and it was unclear in two studies (Cordingley 2009; Sato 2011). The intervention was direct in seven studies (Hovorka 2007; Pachler 2008; Saager 2008; Cordingley 2009; Blaha 2009; Wexler 2010; Sato 2011), indirect in one study (eMPC algorithm was run by study personnel (input glucose and change of Insulin infusion rate) under the supervision of the healthcare professional in Plank 2006) and it was unclear in two studies (Kremen 2007; Augstein 2007).

Seven comparisons provided the insulin doses. The statistical heterogeneity was moderate. In one study (Hovorka 2007), the mean insulin infusion rate was significantly higher in the computerized glucose management group than standard management protocol group (MD +2.10 insulin units/hour, 95% CI 0.77 to 3.43), whereas there were no significant differences in the others (four comparisons with higher doses in the computer group, two comparisons with higher doses in the standard group). Overall, the insulin doses were higher in the computer groups, but this was not significantly different (pooled SMD 0.23, 95% CI -0.04 to 0.50).

One study reported no differences in the amount of glucose administered between the computer group (79.4 ± 24 g) and the manual group (81.6 ± 28 g) during the study period (before, during and after cardiopulmonary bypass) (MD -2.2 g, 95% CI -19.2 to 14.8) (Sato 2011).

One study analyzed the number of times the insulin rate was changed in 72 hours: the insulin infusion rate was altered a mean of 23.5 times more (95% CI 19.0 to 28.0) in the computer group than in the control group (35.5, 95% CI 31.1 to 39.9 versus 12.0, 95% CI 10.3 to 13.7) (Pachler 2008).

Aminoglycoside antibiotics (five studies)

Five studies (Begg 1989; Hickling 1989; Destache 1990; Burton 1991; Leehey 1993) evaluated the administration of aminoglycoside in inpatient care. All computer support systems used a (Bayesian) pharmacokinetic model with the advice given in real time to the healthcare professional, not integrated into a CPOE, and it was not clear if the computerized advice was user-initiated. The intervention was indirect in two studies (Destache 1990: a clinical pharmacokinetic service reviewed the initial aminoglycoside dose and dosing interval and made an oral recommendation to the attending physician or resident; Leehey 1993: the orders for aminoglycoside dosing were written by a pharmacist with countersignature by a physician and the duration of antibiotic therapy as well as other aspects of clinical care were determined by the primary physicians).

One comparison provided outcomes for the analysis on initial and maintenance doses (Burton 1991). There was no statistical difference between groups for initial doses (MD +8 mg/day, 95% CI -11 to 27) or for maintenance doses (MD +11 mg/day, 95% CI -16 to 38).

Two studies reported data on total administered dose with different magnitude of effects. In one study (Begg 1989), the aminoglycoside dose per day was significantly higher in the pharmacokinetic group than in the standard group (+109 g, 95% CI 67 to 151). In the other study (Leehey 1993), the milligrams per dose were higher and number of doses per day was lower in the pharmacist-directed dosing group compared with the standard group (milligrams/dose: 107 ± 21 versus 91 ± 26; doses/day: 2.0 ± 0.6 versus 2.3 ± 0.5) but the mean total doses of aminoglycoside were not significantly different between groups (pooled MD 141 mg, 95% CI -342 to 624).

One study analyzed the number of dosage changes and indicated higher dosage changes in the group with pharmacokinetic service recommendation than in the control group (MD +0.50 dosage change, 95% CI 0.21 to 0.79) (Destache 1990).

Theophylline (four studies)

Four studies evaluated theophylline (Hurley 1986; Gonzalez 1989; Verner 1992; Casner 1993), a drug that is not considered as the first choice of treatment of asthma at present. However, monitoring serum concentrations of theophylline is essential to ensure that non-toxic doses are achieved (National Asthma 2002). There were no studies on recently introduced drugs where it is considered important to monitor drug levels such as for glycopeptides, antifungal (fluconazole) and antiretroviral drugs.

The setting was inpatient care for all four studies.

All computer support systems used a Bayesian compartmental pharmacokinetic model. The advice was given in real time to the healthcare professional in three studies, whereas it was unclear in one study (Verner 1992). The computer support system was integrated into a CPOE with a direct intervention in one study (Casner 1993), whereas it was unclear for the others. The computerized advice was user-initiated in two studies and it was unclear in two studies.

Three comparisons provided data on initial dose with substantial heterogeneity (Hurley 1986; Gonzalez 1989; Verner 1992). The theophylline initial dose was significantly higher in the computer group (SMD 1.7, 95% CI 0.7 to 2.6), whereas the difference did not reach significance in the two other studies (SMD 0.2, 95% CI -0.1 to 0.6). Two comparisons provided data on maintenance dose and indicated higher doses in the computer group (SMD 0.8, 95% CI 0.5 to 1.1) (Hurley 1986; Gonzalez 1989).

Anti-rejection drugs (four studies)

Four studies evaluated anti-rejection drugs requiring adjustments for renal impairment (Chertow 2001; Le Meur 2007; Asberg 2010; Terrell 2010). Two studies evaluated high-use medications that required adjustments for renal impairment (Chertow 2001; Terrell 2010), one study evaluated cyclosporine A (CsA) in the early post-transplant phase (Asberg 2010), and one study evaluated

mycophenolate mofetil (MMF) dosing in renal transplant patients (Le Meur 2007).

The studies evaluating medications that required adjustments for renal impairment took place in inpatient care, with the computer support system integrated into a CPOE, and the advice system initiated and given in real time. In the study evaluating CsA in early post-transplant phase (Asberg 2010), the individual computer dosing of CsA doses were calculated by a population pharmacokinetic model and suggested to the physician (patients were admitted in nephrology and had a standard clinical follow-up). In the study evaluating MMF dosing in renal transplant patients (Le Meur 2007), the MMF dose adjustments in the concentration-controlled regimen were calculated by a computer program to reach a mycophenolic acid (MPA) area under the curve (AUC) target of 40 mg.h/L and were proposed to the physician.

No study reported data on drug dosages. One eligible study with potential unit of analysis error showed that a computerized decision support system for prescribing drugs in people with renal insufficiency improved the proportion of appropriate orders (RR 1.71, 95% CI 1.64 to 1.78) (Chertow 2001).

Anaesthetic agents (two studies, three comparisons)

Two studies (three comparisons) evaluated computer-controlled infusions of anaesthetic agents (Rodman 1984; Theil 1993 fentanyl; Theil 1993 midazolam). One study evaluated the lidocaine therapy (Rodman 1984), whereas one study evaluated fentanyl and midazolam infusions (Theil 1993 fentanyl; Theil 1993 midazolam).

The setting was inpatient care for the two studies. The computer support system for initial therapy of lidocaine was an individualized linear two-compartment pharmacokinetic model not integrated into a CPOE, and the advice was user-initiated and given at real time. The computer-controlled pump for fentanyl and midazolam infusions used a pharmacokinetic model integrated into a CPOE, and the advice was system-initiated.

Rodman 1984 provided outcomes for the initial, maintenance and total doses. Computerized advice had no significant effect on lidocaine dosage (SMD 2.5, 95% CI 1.3 to 3.8 for initial dose; -0.2, 95% CI -1.0 to 0.7 for maintenance dose; 0.2, 95% CI -0.7 to 1.1 for total dose).

Theil 1993 fentanyl and Theil 1993 midazolam provided outcomes for the initial, maintenance and total doses for both fentanyl and midazolam infusions. Computerized advice had no significant effect on fentanyl drug dosage (SMD 0.5, 95% CI -0.3 to 1.3 for initial dose; 0.0, 95% CI -0.8 to 0.8 for maintenance dose; 0.5, 95% CI -0.3 to 1.3 for total dose), but reduced significantly midazolam initial, maintenance and total drug doses (SMD -1.9, 95% CI -2.9 to -0.9 for initial dose; -1.2, 95% CI -2.1 to -0.3 for maintenance dose; -1.1, 95% CI -1.9 to -0.2 for total dose). There was no significant difference in the number of infusion changes during the cardio-pulmonary bypass (MD -0.2, 95% CI -1.0 to 0.6 for fentanyl; 0.5, 95% CI -0.3 to 1.3 for midazolam).

Antidepressants (one study)

One study evaluated amitriptyline in the treatment of major depressive episodes (Mihajlovic 2003; Mihajlovic 2010). The study took place in one psychiatric clinic of a clinical hospital centre. The computer-aided dose of amitriptyline was calculated using the modified Bayesian method. It was not clear if the computer support system was integrated into a CPOE, if the intervention was direct or if the advice was user-initiated and given at real time. The drug daily doses of amitriptyline plus nortriptyline at day 14 were significantly lower when they were individualized compared with empiric doses (133.3 mg, 95% CI 126.7 to 140.0 versus 148.3 mg, 95% CI 140.2 to 156.4).

Gonadotropins (one study)

One study evaluated ovarian stimulation by gonadotropins (Lesourd 2002). The study included women from three centres who were undergoing ovarian stimulation to treat infertility. The software (GonaSoft) was created by the author to help clinicians to monitor ovarian stimulation and to provide a tool for evaluation of efficiency and complications. The software was not integrated into a CPOE. The intervention was direct with the advice given at real time.

There was no significant difference between groups in the number of follicle-stimulating hormone units administered (860 units, 95% CI 776 to 944 in the intervention group versus 938 units, 95% CI 825 to 1051 in the control group).

Risk of bias in included studies

See Figure 2; Figure 3.

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

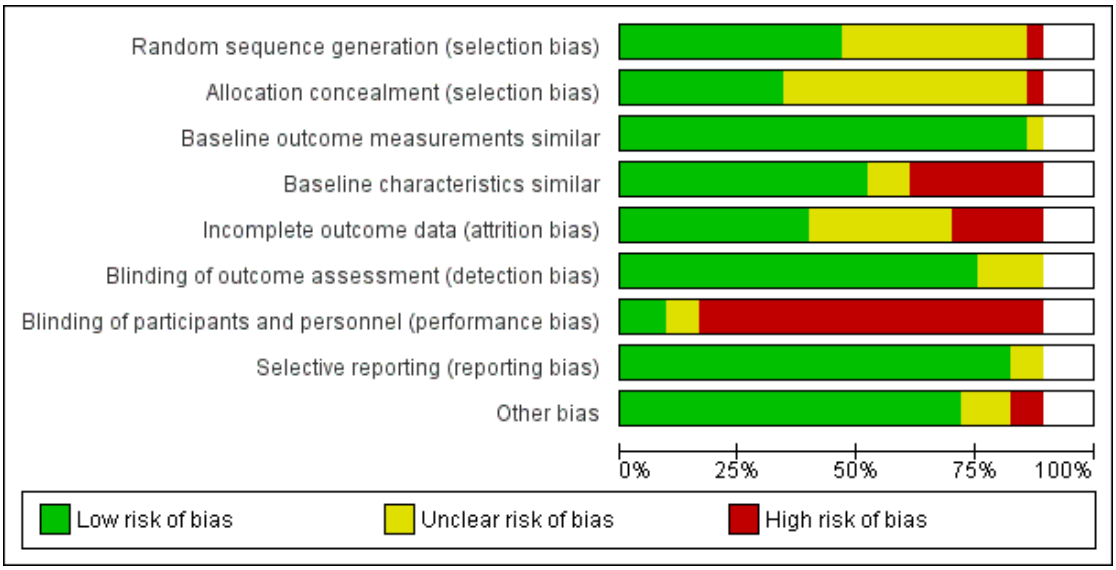
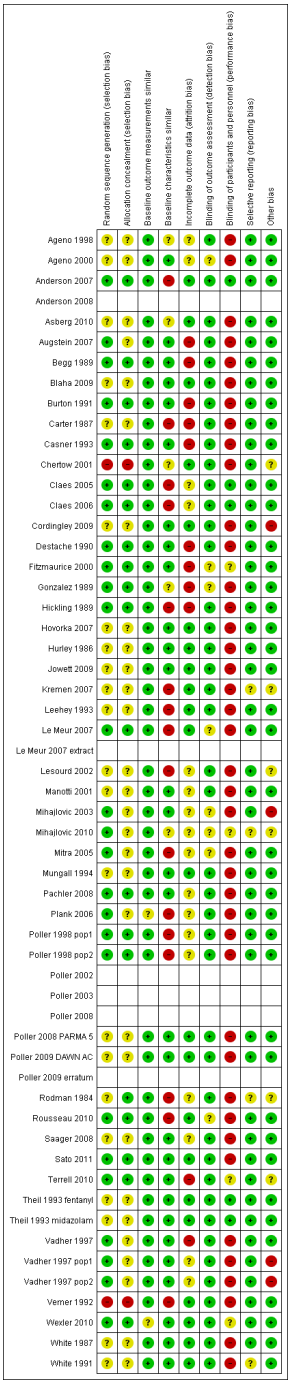


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



Four studies were not assessed for the risk of bias, since they were cost-effectiveness or safety analyses conducted as a part of previous included studies (same trial): Claes 2006 (see Claes 2005); Jowett 2009 (see Poller 2008 PARMA 5; Poller 2009 DAWN AC); Mihajlovic 2010 (see Mihajlovic 2003); and Rousseau 2010 (see Le Meur 2007).

Random sequence generation (selection bias)

The sequence generation process used a random component in 21 studies (50%). A non-random method was used in two studies (5%): in one study the study periods were four alternating eight-week blocks of intervention and control subperiods (Chertow 2001); and in one study, the randomization was based on the final digit in the patient's identification card number (odds versus even) (Verner 1992). The sequence generation process was not specified in 19 studies (45%).

Allocation concealment (selection bias)

The allocation was adequately concealed in 16 studies (38%). The unit of allocation was institution, team or provider in five studies (Burton 1991; Fitzmaurice 2000; Claes 2005; Terrell 2010; Wexler 2010), but cluster effect was not taken into account in statistical analysis for Burton 1991 and Wexler 2010. The unit of allocation was by participant or episode of care and there was some form of centralized randomization scheme in 11 studies (on-site computer system: eight studies, sealed opaque envelopes: three studies). The allocation was not considered adequately concealed in the two studies (5%) where a non-random method was used (Verner 1992; Chertow 2001). The allocation concealment was not specified in 24 studies (57%).

Baseline outcome measurements similar

The mean blood glucose was measured prior to the intervention and no important differences were present across study groups in eight (80%) of the 10 studies on insulin drug administration. One study reported the blood glucose at entry for each centre but not across study group (Plank 2006), and in one study there were many data reported on blood glucose but it was unclear if results given were baseline measurements (Wexler 2010).
Other studies were considered at 'low risk' because baseline outcome measurements were not relevant (baseline data realized before medication intake).

Baseline characteristics similar

Of the five studies where the unit of allocation was by institution, team or professional, only one reported the characteristics of providers (Terrell 2010). Baseline characteristics of participants were reported and similar in 26 studies (62%). Seven studies (17%) reported differences between participants in control and intervention groups, one study reported the participants' characteristics only in a subgroup of participants (Carter 1987), one study reported the participants' characteristics by centres (Plank 2006), and three studies did not report participants' characteristics (Hickling 1989; Poller 1998 pop1; Poller 1998 pop2; Claes 2005). Four studies mentioned participants' characteristics in text but no data were presented (Gonzalez 1989; Ageno 2000; Chertow 2001; Asberg 2010).

Incomplete outcome data (attrition bias)

In 18 studies (43%), the missing outcome measures were unlikely to bias the results (e.g. the proportions of missing data were similar in the intervention and control groups or the proportions of missing data were unlikely to overturn the study result). In 13 studies (31%), missing outcome measures were not specified in the paper or it was unclear if missing data could overturn the study result. In 11 studies, the missing outcome data were likely to bias the results (Carter 1987; Begg 1989; Gonzalez 1989; Hickling 1989; Destache 1990; Burton 1991; Casner 1993; Vadher 1997; Fitzmaurice 2000; Augstein 2007; Terrell 2010).

Blinding of outcome assessment (detection bias)

In 36 studies (86%), the assessment of primary outcome was objective or blinded. In six studies (14%), there was a risk of detection bias: five studies used clinical events as main outcomes and they were not clearly defined (Gonzalez 1989; Ageno 2000; Fitzmaurice 2000; Mitra 2005; Le Meur 2007); and one study used a hetero-questionnaire as main outcome (Mihajlovic 2003).

Blinding of participants and personnel (performance bias)

When studies were randomized by participant, the same healthcare professional may have given treatment both to intervention and control groups: it is possible that computerized advice influenced the treatment of the control groups. Protection against contamination was considered to be done only in three studies (Theil 1993 fentanyl; Theil 1993 midazolam; Claes 2005; Claes 2006; Anderson 2007), and it was unclear for three studies were it was possible that communication between intervention and control professionals could have occurred (Fitzmaurice 2000; Terrell 2010; Wexler 2010).
Thirty-seven studies (88%) randomized the participants, but in two of them the participants were blinded (Theil 1993 fentanyl; Theil 1993 midazolam; Anderson 2007). Two studies randomized the GP practices (Fitzmaurice 2000; Claes 2005; Claes 2006), one

study randomized 42 emergency medicine faculty and resident physicians from one urban public hospital (Terrell 2010), and one study randomized seven teams of providers (42 internal medicine residents) in general medical acute care units of one medical centre (Wexler 2010). There was a risk of performance bias in one study where the house staff teams were randomized (17 house staff teams in one Veterans Administration medical centre) and at the end of each four months during the study, intervention groups were changed to control and vice versa (Burton 1991).

Selective reporting (reporting bias)

The relevant outcomes were reported in the results section in 39 studies (93%). In three studies, the outcomes were not presented in the methods section (Rodman 1984; White 1991; Kremen 2007).

Other bias

There was no evidence of other risk of biases in 34 studies (81%), an evidence of other risk of bias in three studies (7%) and it was unclear in five studies (12%).

In one study, an erratum had been published because there were some inconsistencies in the text and tables; we found other inconsistencies in tables, full text, and abstract; the author was contacted but had not replied (Cordingley 2009, by January 2012). There is a risk of selection bias for one study (Mihajlovic 2003; Mihajlovic 2010): there was a first publication in 1999 including 15 participants during 1997 (Jankovic 1999, study excluded because the author confirmed that the participants were included in the Mihajlovic study), a second publication in 2003 on main outcomes including 60 participants during 1997 (Mihajlovic 2003), and a third publication in 2010 on clinical adverse events (Mihajlovic 2010). In one study, there was a risk of contamination due to logistical problems ("it was difficult to shield the clinicians from the CDSS suggestions") and the nurse practitioners used the computer-decision support system and were compared with the clinician group of three junior doctors undergoing general professional training in general medicine (Vadher 1997 pop1; Vadher 1997 pop2).

There was potential other risk of bias in five studies: in one study, the Cockcroft-Gault formula might overestimate renal function when the serum creatinine was increasing, and underestimate renal function when the serum creatinine was decreasing (Chertow 2001); one study was described as a pilot study (10 participants in each group), the article was in Czech language so it was difficult to understand all details (authors were contacted in February 2012 but queries remained unanswered) (Kremen 2007); in one study, few results were reported (one sentence in the results) so there was not enough information to evaluate the bias of the study (Lesourd 2002); in one study, only 20 participants were included (Rodman 1984); and in one study, 46% participant visits were excluded (only prescription that required dosage adjustment were analyzed), there was no adjustment for within-patient correlation, and providers in the intervention group initially prescribed targeted medications more often than control physicians did and consequently had substantially more opportunities to adjust dosing (Terrell 2010).

Protection against bias

No study met the nine previous criteria for protection against bias. Two studies met eight criteria (Anderson 2007; Sato 2011), nine studies met seven criteria (Begg 1989; Destache 1990; Burton 1991; Casner 1993; Theil 1993 fentanyl; Theil 1993 midazolam; Claes 2005; Claes 2006; Pachler 2008; Wexler 2010), 16 studies met six criteria (Hurley 1986; White 1987; Hickling 1989; White 1991; Mungall 1994; Vadher 1997; Poller 1998 pop1; Poller 1998 pop2; Fitzmaurice 2000; Augstein 2007; Hovorka 2007; Le Meur 2007; Poller 2008 PARMA 5; Blaha 2009; Poller 2009 DAWN AC; Terrell 2010), nine studies met five criteria (Gonzalez 1989; Verner 1992; Leehey 1993; Vadher 1997 pop1; Vadher 1997 pop2; Manotti 2001; Saager 2008; Cordingley 2009; Asberg 2010), seven studies met four criteria (Carter 1987; Ageno 1998; Ageno 2000; Chertow 2001; Mihajlovic 2003; Mitra 2005; Plank 2006; Mihajlovic 2010), and three studies met three criteria (Rodman 1984; Lesourd 2002; Kremen 2007).

Power calculation

Fifteen studies (36%) reported a sample size calculation, among them, one study was presented as a non-inferiority trial but no margin was addressed (Pachler 2008). The power calculation was not reported in 22 studies (53%) and in five studies (12%) the authors specifically reported that the study might be underpowered (White 1987; Gonzalez 1989; Casner 1993; Mitra 2005; Asberg 2010).

Effects of interventions

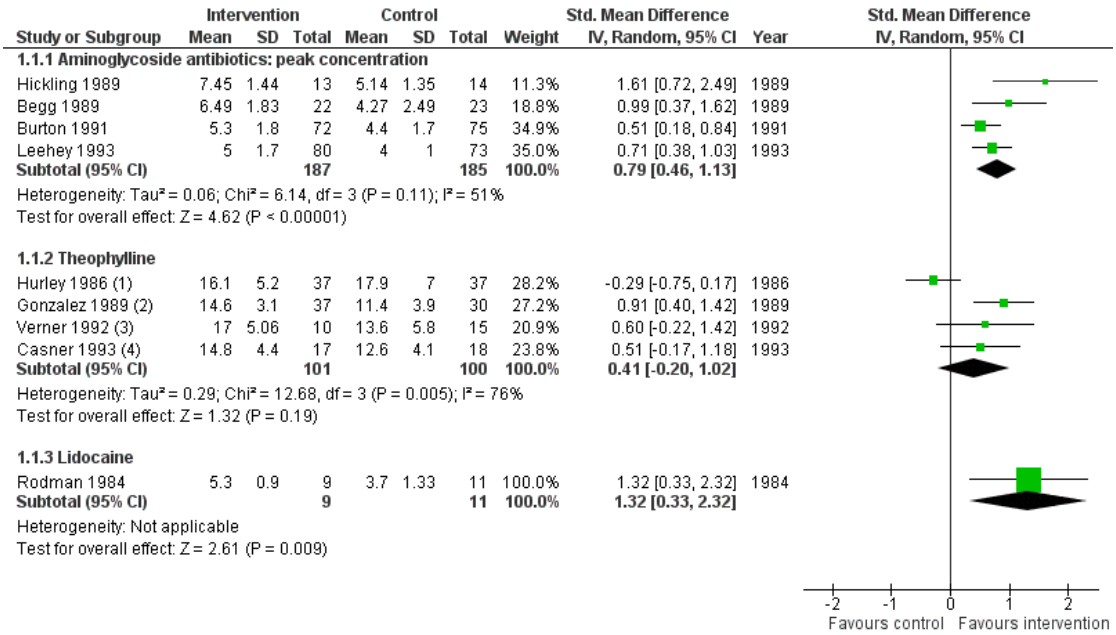
See: **Summary of findings for the main comparison** Computerized advice on drug dosage for leading serum concentrations within therapeutic range; **Summary of findings 2** Computerized advice on drug dosage for leading physiological parameters within therapeutic range; **Summary of findings 3** Computerized advice on drug dosage for reducing time to achieve therapeutic control; **Summary of findings 4** Computerized advice on drug dosage for leading to fewer clinical adverse events; **Summary of findings 5** Saving healthcare resources for saving healthcare resources

See: Summary of findings for the main comparison; Summary of findings 2, Summary of findings 3; Summary of findings 4; Summary of findings 5.

Hypothesis 1. Decisions on drug dosage based on computer advice lead more often to drug levels within the therapeutic range

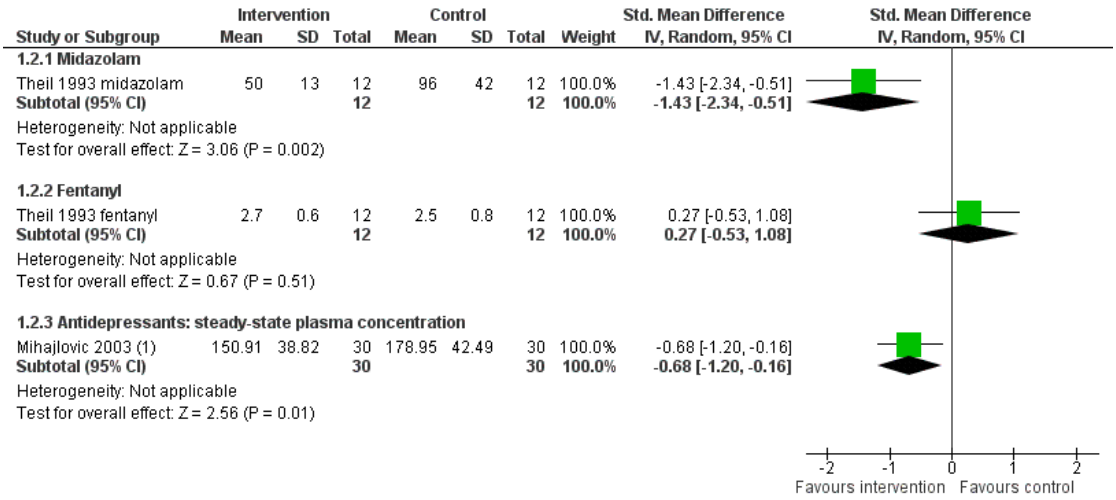
For this comparison, the outcomes analyzed were: the serum concentrations (Analysis 1.1; Analysis 1.2; Figure 4; Figure 5), the proportion of time for which the plasma drug concentrations was within the therapeutic range (Analysis 1.3; Figure 6), the proportion of participants with plasma drug concentrations within the therapeutic range (at fixed time) and the proportion of participants with toxic drug levels (Analysis 1.4; Figure 7).

Figure 4. Forest plot of comparison: 1 Serum concentrations and therapeutic range, outcome: 1.1 Serum concentrations (mg/L) - part A (SMD > 0 in favour of the intervention).



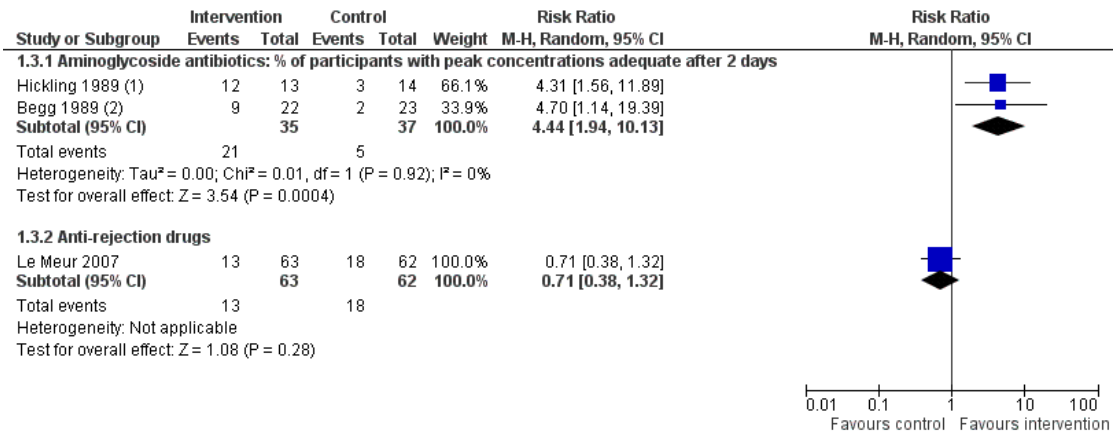
(1) Mean serum concentration at day 2.
(2) Theophylline concentration (4 h post load).
(3) Serum theophylline concentration 20 minutes after completion of loading dose infusion.
(4) Serum theophylline level at C3 (just before discontinuation of the infusion). Theophylline maintenance for asthma.

Figure 5. Forest plot of comparison: 1 Serum concentrations and therapeutic range, outcome: 1.2 Serum concentrations (ng/L) - part B (SMD < 0 in favour of the intervention).



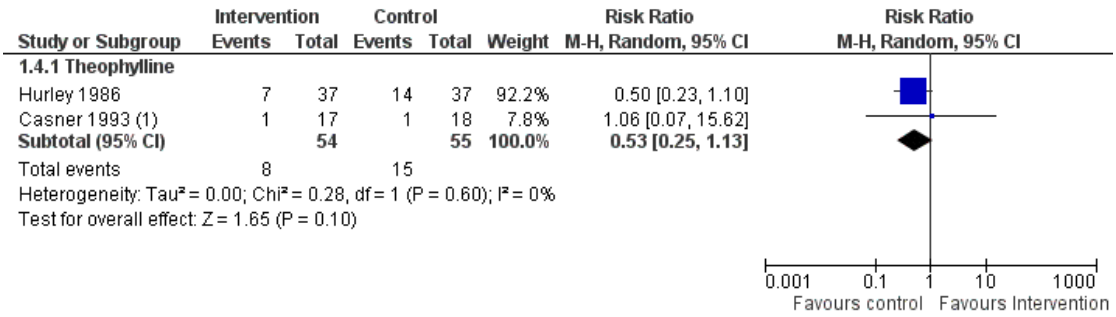
(1) Amitriptyline+nortriptyline concentration.

Figure 6. Forest plot of comparison: 1 Serum concentrations and therapeutic range, outcome: 1.3 Proportion of participants within therapeutic range.



(1) Peak plasma concentrations 6-10 mg/L after 2 days
(2) Peak plasma concentrations 6-10 mg/L after 2 days

Figure 7. Forest plot of comparison: 1 Serum concentrations and therapeutic range, outcome: 1.4 Proportion of participants with toxic drug levels.



(1) Theophylline toxicity (nausea, vomiting, tremor, tachycardia and seizures)

Serum concentrations

There was a high clinical and statistical heterogeneity between drugs so we did not pool the results. Since the interpretation of the direction of change in serum concentration varied according to the drug, we grouped the drugs in two Forest plots (part A and part B). Part A (Analysis 1.1; Figure 4) includes the drugs for which an SMD greater than 0 corresponds to a difference in favour of the intervention; Part B (Analysis 1.2; Figure 5) includes the drugs for which an SMD less than 0 corresponds to a difference in favour of the intervention.

Anticoagulants (fifteen studies, eighteen comparisons)

No data available.

Insulin (ten studies)

No data available.

Aminoglycoside antibiotics (five studies)

Four comparisons (Begg 1989; Hickling 1989; Burton 1991; Leehey 1993) analyzed the aminoglycoside target peak concentration and the objective was to obtain a higher target peak concentration since target peak concentrations are often not met. Heterogeneity was moderate (inconsistency I^2 = 51%, P value from the Chi^2 = 0.11) but the CIs for the results of individual studies overlapped and all studies resulted in a significant higher aminoglycoside peak concentration in the computer group (pooled SMD 0.79, 95% CI 0.46 to 1.13), which was in favour of the intervention.

In Burton 1991, the proportion of participants with maximum peak serum aminoglycoside concentrations greater than 4 mg/L was greater in the Bayesian pharmacokinetic dosing group (RR 1.37, 95% CI 1.11 to 1.70; odds ratio (OR) 3.19, 95% CI 1.46 to 6.94).

One study analyzed the aminoglycoside trough concentration (residual) and the objective was to obtain a lower trough concentration (Leehey 1993): the mean serum trough drug concentration was lower in the pharmacist-directed dosing group compared with the control group (SMD -0.42, 95% CI -0.74 to -0.09).

Theophylline (four studies)

Four comparisons analyzed the theophylline concentration: Hurley 1986 compared the mean serum concentration at day two, Gonzalez 1989 compared the concentration four hours post load, Verner 1992 compared the serum concentration 20 minutes after completion of loading dose infusion and Casner 1993 compared the serum level just before discontinuation of the infusion. The Forest plot and heterogeneity statistics showed high statistical heterogeneity (inconsistency I^2 = 76%, P value from the Chi^2 = 0.005). The theophylline concentration was significantly higher in the computer group in one comparison (Gonzalez 1989), which was in favour of the intervention; tended to be higher in the computer group (although it did not reach statistical significance) in two comparisons (Verner 1992; Casner 1993); and tended to be lower in one comparison (Hurley 1986). The pooled difference was not significant (SMD 0.41, 95% CI -0.20 to 1.02).

Anti-rejection drugs (four studies)

No data available.

Anaesthetic agents (two studies, three comparisons)

Rodman 1984 showed that computer-assisted initial lidocaine therapy significantly increased the lidocaine concentration (SMD

1.32, 95% CI 0.33 to 2.32), which is in favour of the intervention (Analysis part A).
In two comparisons dealing with anaesthesiology (Theil 1993 fentanyl; Theil 1993 midazolam), the objective was to obtain a lower administered drug dose in order to provide a reduction in time for extubation. Computerized advice had no effect on fentanyl serum concentrations but significantly reduced midazolam serum concentrations (SMD -1.43, 95% CI -2.34 to -0.51), which was in favour of the intervention (Analysis part B).

Antidepressants (one study)

The steady-state plasma concentrations of amitriptyline plus nortriptyline during the treatment course (day 14) was significantly lower in the individualized regimen compared with the empiric dose regimen (SMD -0.68, 95% CI -41.20 to -0.16), which was in favour of the intervention.

Gonadotropins (one study)

No data available.

Proportion of time for which the plasma drug concentrations were within the therapeutic range/proportion of participants with plasma drug concentrations within the therapeutic range (at a fixed time) (Analysis 1.3)

Anticoagulants (fifteen studies, eighteen comparisons)

No data available.

Insulin (ten studies)

No data available.

Aminoglycoside antibiotics (five studies)

Several studies have suggested that the mortality in people with severe infections treated with aminoglycosides may be substantially reduced if adequate peak plasma concentrations are achieved early in the course of treatment (Moore 1984a, Moore 1984b, Moore 1987). Thus, accurate dose prescription is important, not only to avoid toxicity associated with overdosage, but more important to avoid the higher mortality associated with underdosage during the first one or two days of treatment.
Three studies analyzed the proportion of participants with aminoglycoside peak concentration adequate: one study (Destache 1990) considered the first peak aminoglycoside serum 'adequate' 30 minutes after infusion whereas two studies (Hickling 1989; Begg 1989) considered the peak plasma concentrations within 6 to 10 mg/L after two days, so we pooled only the results of these two last studies. There was no evidence of difference in Destache 1990 (RR 1.02, 95% CI 0.63 to 1.64), whereas there were significantly more participants within the therapeutic range after two days in the computer group for the two other studies (pooled RR 4.44, 95% CI 1.94 to 10.13).
Hickling 1989 and Begg 1989 also analyzed the proportion of participants with aminoglycoside peak and trough concentrations adequate: Hickling 1989 considered the peak trough concentrations lower than 2 mg/L after two days whereas Begg 1989 considered the peak trough concentrations within 1 to 2 mg/L after two days. Both comparisons tended to have more participants with aminoglycoside peak and trough concentrations adequate in the computer group and the pooled effect showed a significant difference between groups (pooled RR 3.88, 95% CI 1.04 to 14.44).

Theophylline (four studies)

Hurley 1986 reported that during oral therapy more monitored than control participants had trough concentrations in the therapeutic range (RR 1.60, 95% CI 1.00 to 2.55).
One study reported that serum theophylline concentrations during maintenance therapy in the computer group were maintained within the therapeutic range (10 to 20 µg/mL) longer than in the control group (77% versus 51%, P versus < 0.05), but the study included a small number of participants (n = 25) (Verner 1992).

Anti-rejection drugs (four studies)

In Le Meur 2007, there was no significant difference between concentration-controlled doses and xed-dose MMF on the proportion of participants within therapeutic range at day 14 (MPA AUC > 30 mg.h/L). The AUC is a model for determining MPA exposure. MPA is the active metabolite of the inactive prodrug MMF. However, by day 14, median MPA exposure was significantly higher in the concentration-controlled group than in the fixed-dose group (with a majority of participants in the concentration-controlled group, but not in the fixed-dose group, having met targeted levels), and at one month, the concentration-controlled group again had significantly higher median MPA AUC, with more than 90% of participants achieving target levels.
In Asberg 2010, the overall percentage of whole-blood concentrations of cyclosporine within the therapeutic window was not different between groups (SMD 0.23, 95% CI -0.39 to 0.85; MD 3.80%, 95% CI -6.25% to 13.85%).

Anaesthetic agents (two studies, three comparisons)

No data available.

Antidepressants (one study)

No data available.

Gonadotropins (one study)

No data available.

Proportion of participants with toxic drug levels (Analysis 1.4)

Anticoagulants (fifteen studies, eighteen comparisons)

No data available.

Insulin (ten studies)

No data available.

Aminoglycosides (five studies)

No data available.

Theophylline (four studies)

Two studies analyzed the proportion of participants with toxic drug levels. In Hurley 1986, fewer monitored participants in whom infusion rates were based on pharmacokinetic analysis had serum concentrations in the toxic range but the difference was not significant (RR 0.50, 95% CI 0.23 to 1.10; OR 0.38, 95% CI 0.13 to 1.09). Casner 1993 found no statistical difference between the empiric and kinetic groups in the number of toxic (> 20 mg/L) levels (one in each group).

Anti-rejection drugs (four studies)

In Terrell 2010, where the physicians were randomized to decision support intervention group or control group, usual care physicians were more likely to dose medications excessively than intervention physicians were (OR 3.9, 95% CI 1.7 to 9.0, according to a mixed-effects logistic regression to adjust for within-physician correlation). After adjusting for participant age, sex, race and physician status, this difference remains significant in favour of intervention (OR usual care versus intervention 4.3, 95% CI 1.4 to 12.8).

Anaesthetic agents (two studies, three comparisons)

No data available.

Antidepressants (one study)

No data available.

Gonadotropins (one study)

No data available.

Summary

The results differed according to drugs. In summary, in spite of high heterogeneity and small number of studies, comparisons on serum concentrations were in favour of the computer group for aminoglycoside antibiotics (higher target peak and lower trough concentrations) and antidepressants (one study). Results were contrasted for theophylline and anaesthetic agents.

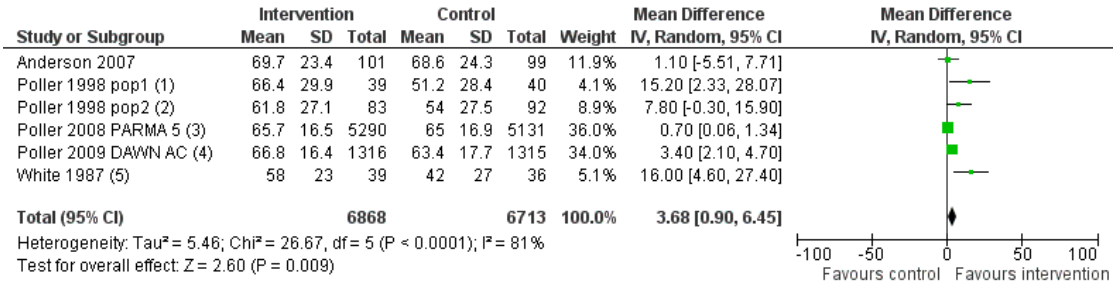
Computerized advice improved the proportion of participants for aminoglycoside antibiotics and theophylline (one study), and the proportion of time for theophylline (one study) for which the plasma drug concentrations were within the therapeutic range, but not for anti-rejection drugs before day 14.

There were three comparisons on toxic drug levels: there was no evidence of difference for theophylline (two studies) whereas the CPOE with decision support significantly reduced excessive dosing of targeted medications in one study on people with renal impairment where physicians were randomized.

Hypothesis 2. Decisions on drug dosage based on computer advice lead more often to a physiological parameter being maintained within the desired range (e.g. blood pressure or prothrombin time)

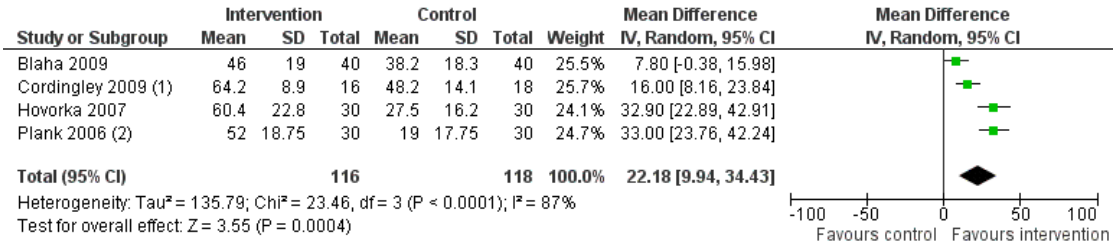
For this comparison, the outcomes analyzed was the proportion of time for which the studied physiological parameter was maintained within the target range (Analysis 2.1; Analysis 2.2; Analysis 2.3; Figure 8; Figure 9; Figure 10).

Figure 8. Forest plot of comparison: 2 Physiological parameters, outcome: 2.1 Oral anticoagulants: % time in target INR range.



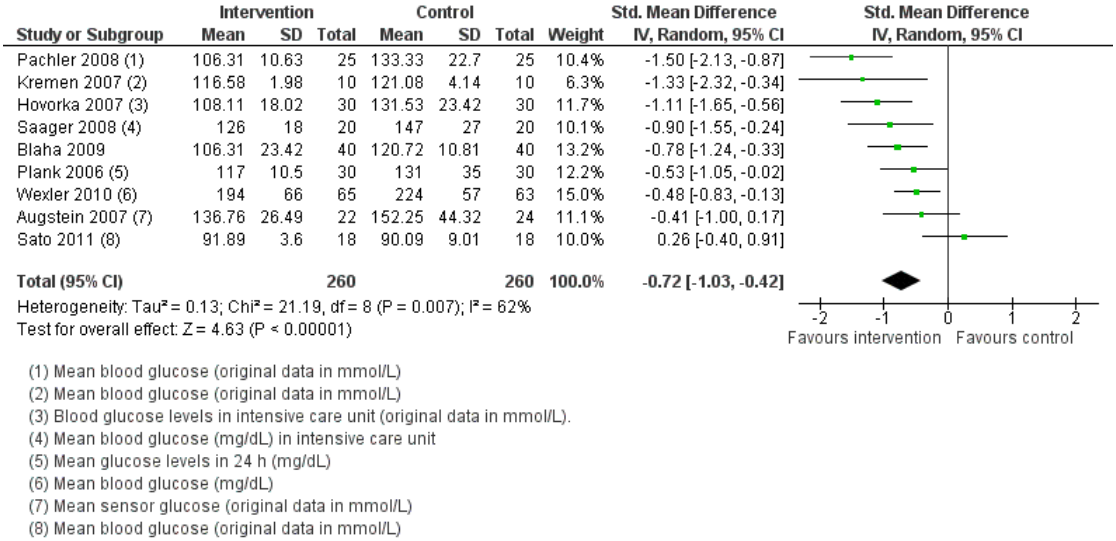
(1) The INR target ranges were decided by the individual centre, based on one of: the guidelines on oral anticoagulation of the British Society
(2) The INR target ranges were decided by the individual centre, based on one of: the guidelines on oral anticoagulation of the British Society
(3) The INR target ranges were locally decided.
(4) The INR target ranges were locally decided.
(5) The therapeutic range was defined as PR=1.8 ± 0.4, or, using a generalized formula, PR±(0.22)*PR.

Figure 9. Forest plot of comparison: 2 Physiological parameters, outcome: 2.2 Insulin: % time in target glucose range.



(1) Means and standard deviation were estimated from medians and ranges.
(2) % of time within the target range for blood glucose in the first 24 h (80-110 mg/dL ou 4.4-6.1 mmol/L). Means were estimated from med

Figure 10. Forest plot of comparison: 2 Physiological parameters, outcome: 2.3 Insulin: mean blood glucose (mg/dL).



(1) Mean blood glucose (original data in mmol/L)
(2) Mean blood glucose (original data in mmol/L)
(3) Blood glucose levels in intensive care unit (original data in mmol/L).
(4) Mean blood glucose (mg/dL) in intensive care unit
(5) Mean glucose levels in 24 h (mg/dL)
(6) Mean blood glucose (mg/dL)
(7) Mean sensor glucose (original data in mmol/L)
(8) Mean blood glucose (original data in mmol/L)

Oral anticoagulants (fifteen studies, eighteen comparisons): proportion of time in target international normalized ratio range

The main outcome reported was the percentage of time spent in target INR range calculated for each participant as a mean time in range using interpolation methods between INR values. Six comparisons analyzed the mean % of TIR using various INR ranges (see Description of the intervention) (White 1987; Poller 1998 pop1; Poller 1998 pop2; Anderson 2007; Poller 2008 PARMA 5; Poller 2009 DAWN AC). The magnitude of effects differed between studies and the statistical heterogeneity was high (I^2 = 79%) but all studies were in favour of the computer groups: the difference was significant in four studies (White 1987; Poller 1998 pop1; Poller 2008 PARMA 5; Poller 2009 DAWN AC), and did not reach significance in two studies (Poller 1998 pop2 considering outpatients in the stabilization period; and Anderson 2007 considering people starting oral anticoagulation). The pooled SMD favoured the computer group (SMD 0.19, 95% CI 0.06 to 0.33; MD 3.68%, 95% CI 0.90% to 6.45%) (Analysis 2.1; Figure 8).

In one study where GP practices were randomized, there was a significant increase in percentage of time within 0.5 INR from target, from 49.5% at baseline to 60% after implementing the different interventions, but there was no evidence that the increases from baseline were different between the four intervention groups (P value = 0.8) (Claes 2005). The increase was +8% (95% CI 2.0% to 13.5%) in the group with multifaceted education and +11% (95% CI 5.5% to 16.5%) in the group with multifaceted education plus DAWN AC computer-assisted advice.

Another comparison on people within target final PT time showed no evidence of difference in anticoagulant control in people whose dose was determined by computer, compared with those who were treated by a nurse specialist (RR 0.87, 95% CI 0.47 to 1.61) (White 1991). Finally, one comparison analyzed the proportion of participants reaching a stable state of anticoagulation (three INR measurements within therapeutic range) and was in favour of the computer group compared with the control group (RR 1.46, 95% CI 1.07 to 2.00) (Manotti 2001).

Five comparisons reported the number of days per 100 patient-days of treatment spent in the INR therapeutic range but the inconsistency across studies was very high (combined incidence rate ratio 1.10, 95% CI 1.00 to 1.20, inconsistency I^2 = 91%) (Vadher 1997; Vadher 1997 pop1; Vadher 1997 pop2; Ageno 1998; Mitra 2005): in two studies, participants in the intervention group spent significantly more time in the therapeutic range (Vadher 1997 pop1; Mitra 2005), whereas there was no evidence of difference in three studies.

Two comparisons analyzed the proportion of INRs measurements within therapeutic range and were in favour of computerized advice of drug dosage (RR 1.10, 95% CI 1.02 to 1.19) (Ageno 1998; Fitzmaurice 2000). Ageno 1998 and Ageno 2000 compared the proportions of INRs above 5: there was no evidence of difference between the computer and standard groups. In Claes 2005, during the intervention period there was a significant difference in per cent of participants with a least one INR above 5 between the four intervention groups (P value = 0.009), but there was no

evidence that the decreases from baseline were different between the four intervention groups (P = 0.28) and group A (multifaceted education) and group D (multifaceted education plus DAWN AC computer-assisted advice) had the closest results. In Ageno 1998, the INRs below 2 (underanticoagulated patients) were more in the computer-controlled group than in the manual group (RR 1.55, 95% CI 1.11 to 2.16) whereas in Claes 2005 there was no statistically significant difference from baseline in the decrease of per cent of participants with at least one INR less than 2 (P = 0.67).

Insulin (ten studies): percentage of time in target glucose range (four studies), hyperglycaemia index (nine studies)

Four studies of the CLINICIP project analyzed the percentage of time in target glucose range (Plank 2006; Hovorka 2007; Blaha 2009; Cordingley 2009). The magnitude of effects differed between studies and the statistical heterogeneity was high (I^2 = 83%) but all studies were in favour of the computer groups: the difference was significant in three studies (Plank 2006; Hovorka 2007; Cordingley 2009), and did not reach significance in one study (Blaha 2009). The pooled SMD was in favour of the computer group (SMD 1.27, 95% CI 0.56 to 1.98; MD 22.18%, 95% CI 9.94% to 34.43%) (Analysis 2.2; Figure 9).

In one study with a potential unit of analysis error, the percentage of time in target range was significantly higher with the computer software program (SMD 1.91, 95% CI 1.70 to 2.11; MD 21.70%, 95% CI 20.02% to 23.38%) (Sato 2011). In the same study, participants in the computer group were significantly more likely to have all measurements within the target glycaemic range than participants in the manual group (RR 9.00, 95% CI 1.27 to 63.89).

In a CBA study, the change in A1C (primary outcome) was -0.34% ± 0.49% in the group with the diabetes management system-based decision support compared with +0.27% ± 0.67% in the group without the system (MD -0.60%, 95% CI -0.96% to -0.25%) (Augstein 2007).

Two studies analyzed the hyperglycaemic index (HGI) for the assessment of glucose control (Pachler 2008; Cordingley 2009). In Pachler 2008, the HGI was defined as the AUC above the upper limit of normal (glucose level 6.1 mmol/L, modified from the original 6.0 mmol/L) divided by the total length of stay (time in study). The advantage of this measure of glucose control is the independence of the number of measurements, and it is not falsely lowered by hypoglycaemic values. In theory, the best HGI of 0.0 mM indicates that all glucose values were below the upper target limit. An HGI around 2.0 mM shows that the person was exposed on average to glucose values of 8.1 mM (exceeding the upper target limit of 6.1 mM) during the observed period. In general, a low HGI and a low number of hypoglycaemic events indicate tight and safe blood glucose control. In Cordingley 2009, there were some inconsistencies in the text and tables so conclusions should be made with caution: in one centre (n = 20) the HGI was not significantly different between groups whereas in the other (n = 14) the HGI was significantly greater in the standard care group. In Pachler 2008, the HGI was significantly lower in the computer group (MD -1.20 mmol/L, 95% CI -1.63 to -0.77).

The time in blood glucose range was higher in the computer-guided glucose management during surgery (Saager 2008: MD 57.00 minutes, 95% CI 9.57 to 104.43), and after surgery in the intensive care unit (Kremen 2007; Saager 2008: pooled MD 257.92 minutes, 95% CI 60.96 to 454.87).

Nine studies reported the mean blood glucose with high heterogeneity (I^2 = 86%, one study with opposite direction): the mean blood glucose was significantly lower with the computer advice (pooled SMD -0.72, 95% CI -1.03 to -0.42; pooled MD -14.81 mg/dL, 95% CI -22.06 to -7.56) (Analysis 2.3) (Plank 2006; Augstein 2007; Hovorka 2007; Kremen 2007; Pachler 2008; Saager 2008; Blaha 2009; Wexler 2010; Sato 2011). Excluding two studies with potential unit of analysis error did not change the conclusions (pooled SMD -0.55, 95% CI -0.83 to -0.27; pooled MD -10.48 mg/dL, 95% CI -17.10 to -3.86) (Hovorka 2007; Pachler 2008).

Aminoglycoside antibiotics (five studies)

No data available.

Theophylline (four studies)

No data available.

Anti-rejection drugs (four studies)

No data available.

Anaesthetic agents (two studies, three comparisons)

No data available.

Antidepressants (one study)

No data available.

Gonadotropins (one study)

No data available.

Summary

In summary, in spite of difference in magnitude effects, computerized advice led more often to a physiological parameter within the desired range for oral anticoagulants (significantly higher percentages of time in target INR range) and for insulin (significantly higher percentages of time in target glucose, lower levels of mean blood glucose).

This result may be explained by the fact that computer advice improved the sampling time and intervals for warfarin or insulin. These two drugs have a narrow therapeutic window. They have variable effects depending on the plasma concentration: a lower dose is ineffective and a higher dose is hazardous. For these drugs, sampling time is critical, since the drug concentration varies over the entire dosing interval and with the duration of dosing in relation to achieving a steady state. Sampling interval, the number of sampling, is also important. For insulin, in three studies, this interval was significantly lower in the computer groups (Hovorka 2007; Pachler 2008; Cordingley 2009), in one study, there was no significant difference between groups (Blaha 2009), whereas in one study, mean sampling intervals were significantly longer in the computer-assisted group compared with the manual group (Sato 2011).

Hypothesis 3. Decisions on drug dosage based on computer advice led to more rapid therapeutic control, assessed by a physiological parameter

For this comparison, the outcomes analyzed were the time to achieve therapeutic range and the time to stabilization (Analysis 3.1; Analysis 3.2; Figure 11; Figure 12).

Figure 11. Forest plot of comparison: 3 Time to achieve therapeutic control, outcome: 3.1 Time to achieve therapeutic range.

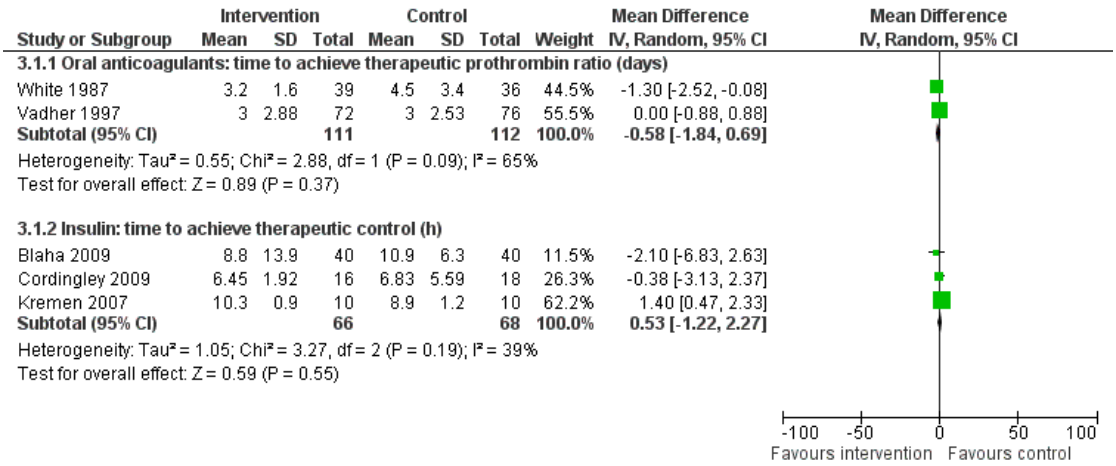
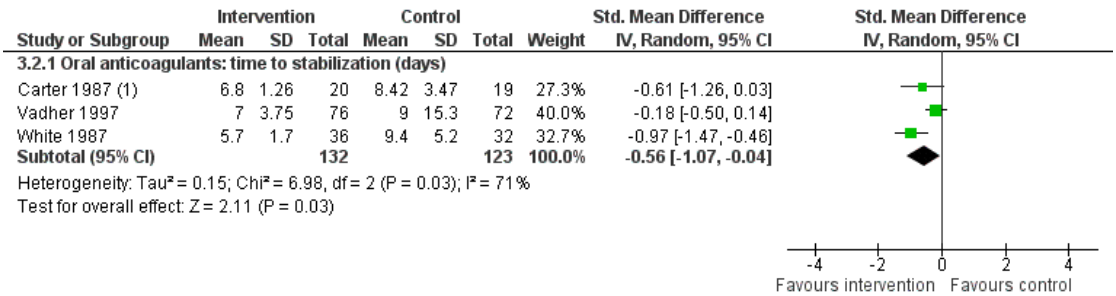


Figure 12. Forest plot of comparison: 3 Time to achieve therapeutic control, outcome: 3.2 Time to stabilization.



(1) For the 39 patients who achieved stable prothrombin ratios before discharge

Oral anticoagulants (fifteen studies, eighteen comparisons)

Two comparisons analyzed the "time to achieve" therapeutic PT ratio (White 1987; Vadher 1997). There was no evidence of difference between groups (SMD -0.22, 95% CI -0.69 to 0.26; MD -0.58 days, 95% CI -1.84 to 0.6).

Three comparisons analyzed the "time to stabilization" (Carter 1987; White 1987; Vadher 1997). In Carter 1987, the outcome was reported for participants who achieved stable PT ratios before discharge. The pooled effect showed a significant reduction in time to achieve stabilization (SMD -0.56, 95% CI -1.07 to -0.04; MD -2.49 days, 95% CI -3.93 to -1.05) even if there was an high inconsistency (I^2 = 71%).

Insulin (ten studies)

The "time to target" (time to establish blood glucose control) for insulin was reported in three studies. In one study, the computer advice led to less rapid control of glycaemia (Kremen 2007), whereas there was no significant difference in Blaha 2009 and Cordingley 2009. There was no evidence of difference between groups (SMD 0.22, 95% CI -0.52 to 0.95; MD 0.53 hour, 95% CI -1.22 to 2.27).

Aminoglycoside antibiotics (five studies)

No data available.

Theophylline (four studies)

No data available.

Anti-rejection drugs (four studies)

No data available.

Anaesthetic agents (two studies, three comparisons)

No data available.

Antidepressants (one study)

No data available.

Gonadotropins (one study)

No data available.

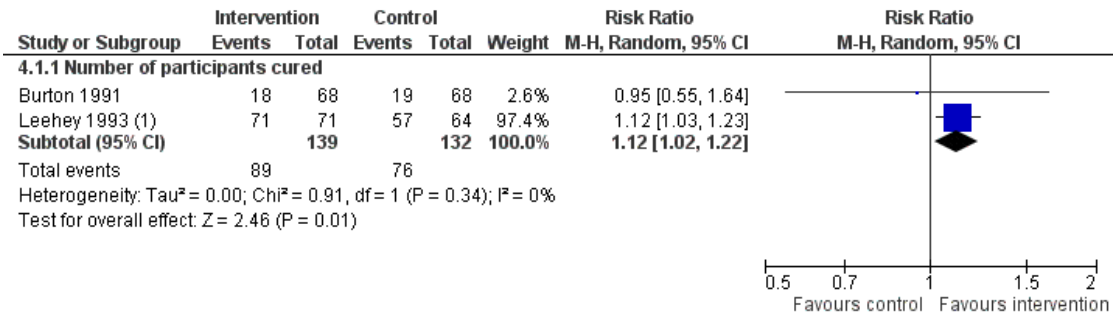
Summary

The pooled effect showed a significant reduction in time to achieve stabilization for oral anticoagulants (three comparisons) whereas there was no evidence of difference for insulin.

Hypothesis 4. Decisions on drug dosage based on computer advice lead to more effectiveness, assessed by clinical improvement

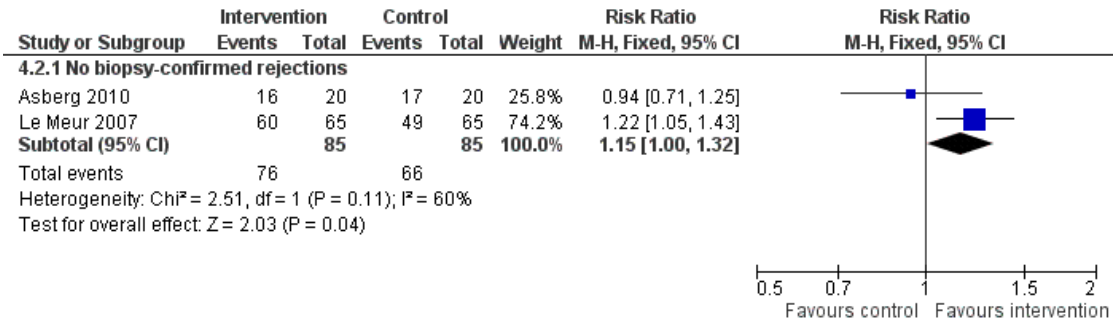
For this comparison, the outcomes analyzed was the proportion of participants with clinical improvement (Analysis 4.1; Analysis 4.2; Figure 13; Figure 14). Forest plots are only presented for aminoglycoside antibiotics and anti-rejection drugs (no study or only one for other drugs).

Figure 13. Forest plot of comparison: 4 Clinical improvement, outcome: 4.1 Aminoglycoside antibiotics.



(1) Clinical cure of infection or improvement

Figure 14. Forest plot of comparison: 4 Clinical improvement, outcome: 4.2 Anti-rejection drugs.



Anticoagulants (fifteen studies, eighteen comparisons)

No data available.

Insulin (ten studies)

No data available.

Aminoglycoside antibiotics (five studies)

Two studies reported efficacy outcomes. In Burton 1991, there were no statistical differences in the number of participants cured (RR 0.95, 95% CI 0.55 to 1.64), whereas in Leehey 1993, there was more success to respond to treatment in the pharmacist-direct dosing based on a Bayesian pharmacokinetic dosing program (RR 1.12, 95% CI to 1.03 to 1.23).

Theophylline (four studies)

No data available.

Anti-rejection drugs (four studies)

Two studies reported efficacy outcomes on biopsy-confirmed acute rejections. In Asberg 2010, there were no statistical differences in the number of participants without acute rejections (RR 0.94, 95% CI 0.71 to 1.25), whereas in Le Meur 2007, there were more participants with clinical improvement (no acute rejections) in the individualized MMF dosing group (RR 1.22, 95% CI 1.05 to 1.43).

Anaesthetic agents (two studies, three comparisons)

No data available.

Antidepressants (one study)

In Mihajlovic 2003, the participants from individualized or empiric doses of amitriptyline were evaluated clinically using the Hamilton Depression Rating Scale (HAM-D; 21 items) and Clinical Global Impression Scale (CGI). Total HAM-D scores were significantly lower in the experimental group after day 28 (MD -2.80, 95% CI -4.93 to -0.67). CGI scores had a statistically significant difference between the groups after day 28 for the three items (in favour of the intervention for Severity of illness and Therapeutic effect, and in favour of the control for Global improvement).

Gonadotropins (one study)

In the study on the effectiveness of a computerized decision support system for ovarian stimulation with gonadotropins (Lesourd 2002), there were no statistical differences in the number of participants with clinical pregnancies (RR 1.15, 95% CI 0.59 to 2.27).

Summary

For each drug, there were, at most, two comparisons. Some comparisons showed significant improvement with computer advice whereas there was no evidence of differences in others.

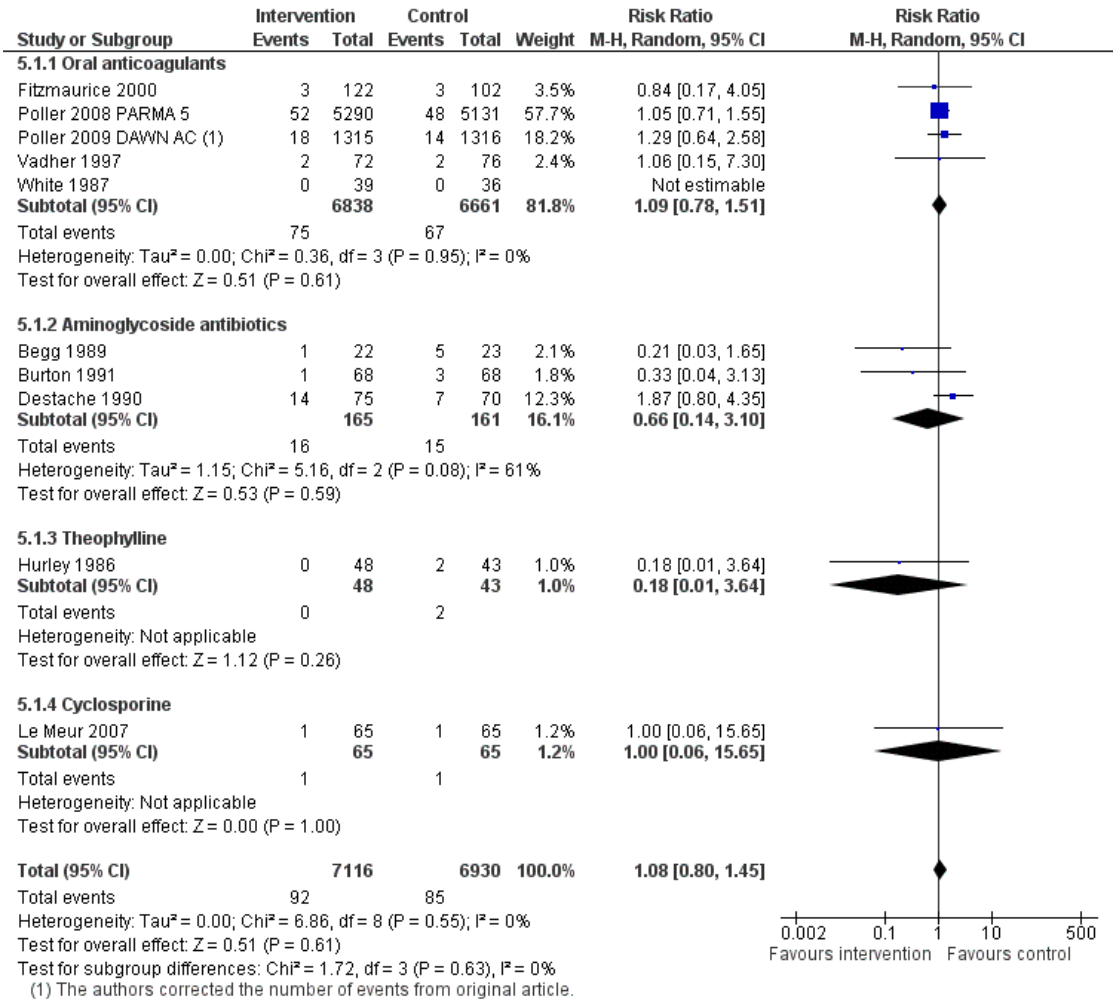
Hypothesis 5. Decisions on drug dosage based on computer advice lead to fewer unwanted effects

For this comparison, we considered two outcomes: death and adverse reactions.

Death

Ten comparisons analyzed death rates (Analysis 5.1; Figure 15). Globally, there was no significant difference observed between the computer and control groups (RR 1.08, 95% CI 0.80 to 1.45).

Figure 15. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.1 Death.



Clinical adverse events

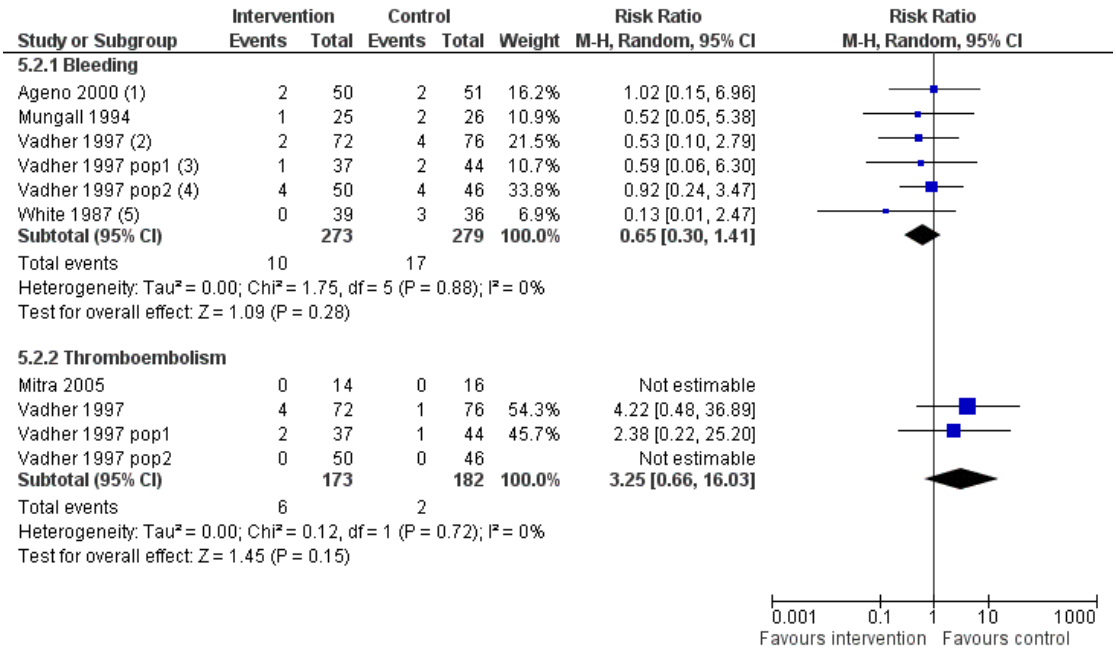
Nineteen comparisons assessed the proportion of participants with clinical adverse events. Since there was a great diversity of drugs and of type of clinical adverse events, we did not pool the results that were presented by drug.

Anticoagulants (fifteen studies, eighteen comparisons)

Bleeding events

The proportion of participants with bleeding events was available in five comparisons (nine events in computer group, 15 events in control group). In Ageno 2000, the minor bleeding events were observed until discharge or until the seventh day of treatment, in Vadher 1997; Vadher 1997 pop1; Vadher 1997 pop2, haemorrhagic events were collected during the follow-up (maximum length of follow-up: 3 to 13 months) and in White 1987, the bleeding complications were collected during hospitalization. There was a trend towards fewer people with bleeding events although it did not reach statistical significance (pooled RR 0.65, 95% CI 0.30 to 1.41) (Analysis 5.2; Figure 16).

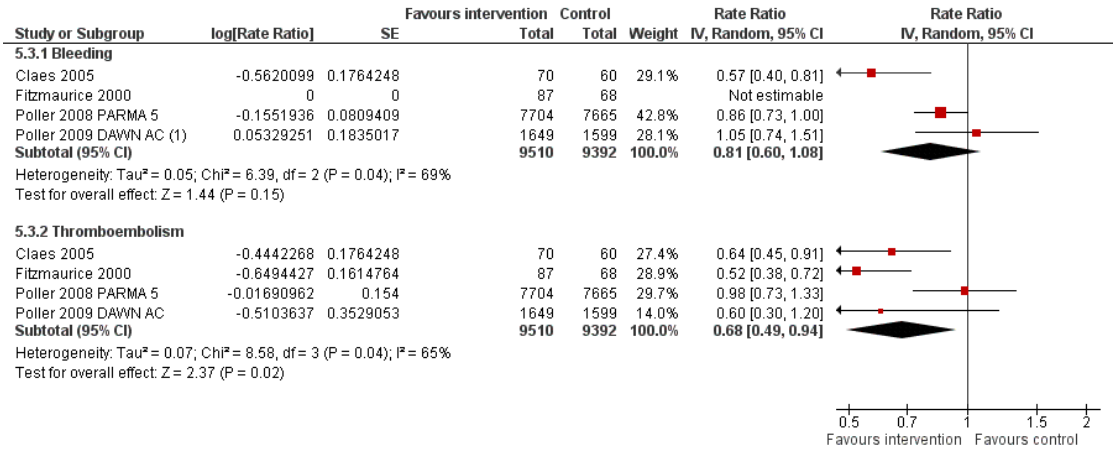
Figure 16. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.2 Anticoagulants: events.



(1) Minor bleedings (until discharge or until the 7th day of treatment)
(2) Haemorrhagic events (maximum length of follow-up: 13 months).
(3) Haemorrhagic events (maximum length of follow-up: 3 months).
(4) Haemorrhagic events (maximum length of follow-up: 6 months).
(5) Bleeding complications (length of follow-up: In-hospital).

The participant exposure time was reported in four comparisons but the bleeding incidence rate could be calculated only in three comparisons (in Fitzmaurice 2000, there was no serious bleeding in the control group). In two studies, there was significantly less bleeding events in the computer group (Claes 2005; Poller 2008 PARMA 5), whereas the difference was not statistically significant in one study (Poller 2009 DAWN AC). The pooled effect showed a non-significant reduction in bleeding events with an estimated rate ratio of 0.81 (95% CI 0.60 to 1.08) (Analysis 5.3; Figure 17).

Figure 17. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.3 Anticoagulants: event rates.



(1) The authors corrected the number of events from original article.

For heparin, there was no statistical difference in bleeding events between the computer-assisted and the nomogram-directed therapy (Mungall 1994).

Thromboembolism

In two studies, there was no thromboembolism due to undertreatment in both computer and standard dosing groups (Vadher 1997 pop2; Mitra 2005). In two studies, the number of participants with thromboembolism tended to be higher in the computer group but the pooled effect showed no statistical difference between groups (pooled RR 3.25, 95% CI 0.66 to 16.03) (Vadher 1997; Vadher 1997 pop1) (Analysis 5.2; Figure 16).

For the incidence rate, in two studies, there was significantly less thromboembolism events in the computer group (Fitzmaurice 2000; Claes 2005), whereas the difference was not significant in two studies (Poller 2008 PARMA 5; Poller 2009 DAWN AC). The pooled effect showed a significant reduction in thromboembolism events with an estimated rate ratio of 0.68 (95% CI 0.49 to 0.94) but the inconsistency was high (I^2 = 65%) (Analysis 5.3; Figure 17).

Total clinical adverse events

In Anderson 2007, total clinical adverse events (clinical events plus INR 4 or greater) were numerically fewer in the pharmacogenetic than standard arm (34 versus 42), although the difference was not significant (P value = 0.26) and the serious clinical events were infrequent (pharmacogenetic 4, standard 5) and were unrelated to out-of-range INRs.

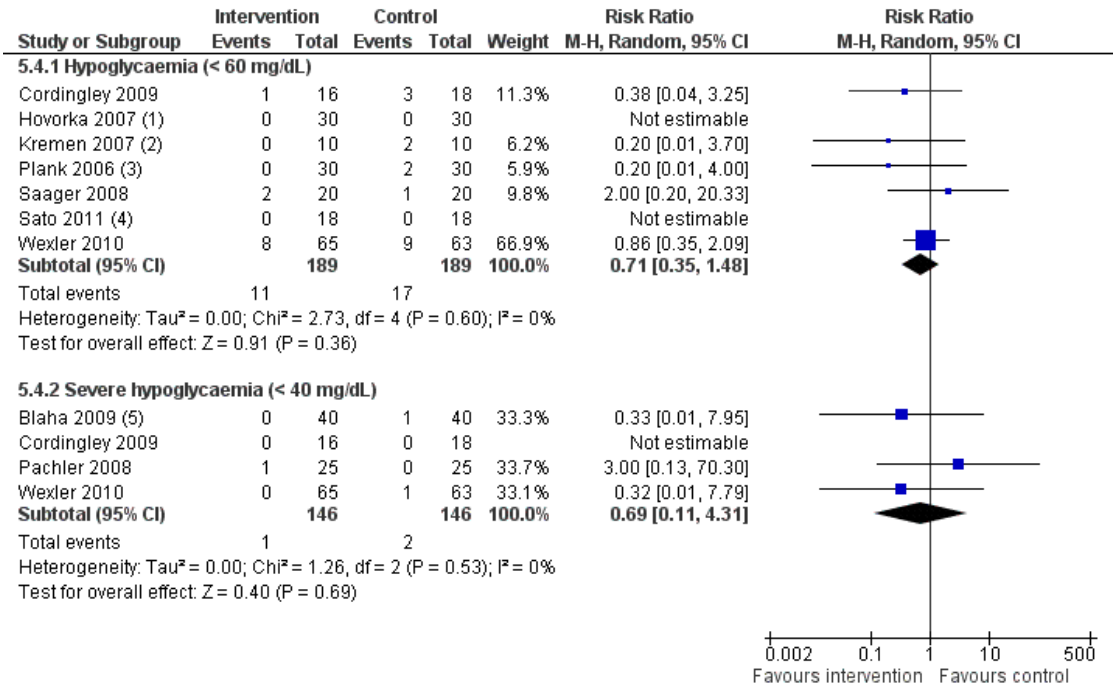
In Mungall 1994 (heparin), there was a trend towards less clinical adverse events in the computer-assisted heparin therapy compared with nomogram-directed therapy (RR 0.08, 95% CI 0.00 to 1.35).

Insulin (ten studies)

Hypoglycaemia

The proportion of participants with hypoglycaemia was available in seven comparisons (11 events in computer group, 17 events in control group). Hypoglycaemia was defined as blood glucose less than 60 mg/dL (< 3.3 mmol/L) in three studies (Saager 2008; Cordingley 2009; Wexler 2010), less than less 54 mg/dL (< 3.0 mmol/L) in one study (Plank 2006), and less than 52 mg/dL (< 2.9 mmol/L) in three studies (Hovorka 2007; Kremen 2007; Sato 2011). No significant difference was observed between the computer and control groups (pooled RR 0.71, 95% CI 0.35 to 1.48) (Analysis 5.4; Figure 18).

Figure 18. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.4 Insulin.



(1) Blood glucose < 2.9 mmol/L (< 52 mg/dL).
(2) Blood glucose < 2.9 mmol/L (< 52 mg/dL).
(3) Blood glucose level < 54 mg/dL.
(4) Blood glucose < 2.9 mmol/L (< 52 mg/dL).
(5) Blood glucose level < 2.3 mmol/L (< 41 mg/dL).

Severe hypoglycaemia

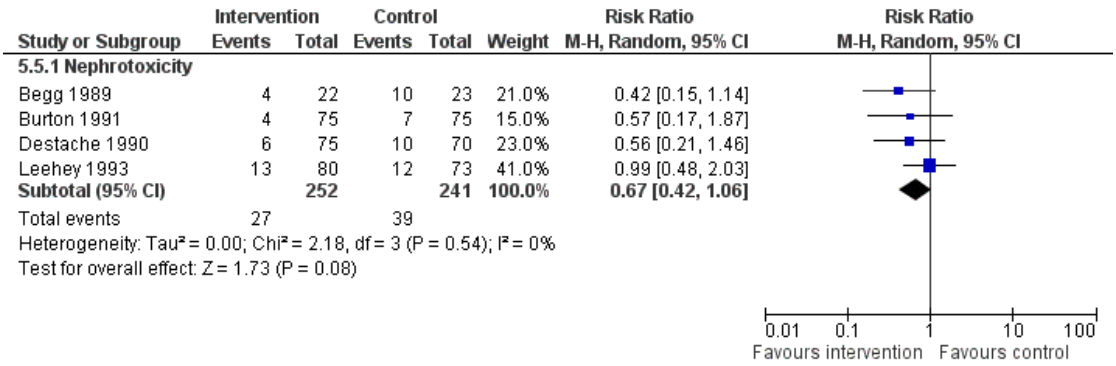
The proportion of participants with severe hypoglycaemia was available in four comparisons (one event in computer group, two events in control group). Severe hypoglycaemia was defined as blood glucose less than 40 mg/dL (< 2.2 mmol/L) in three studies (Pachler 2008; Cordingley 2009; Wexler 2010), and less than less 41 mg/dL (< 2.3 mmol/L) in one study (Blaha 2009), and less than 42 mg/dL (<2.9 mmol/L) in three studies (Hovorka 2007; Kremen 2007; Sato 2011). No significant difference was observed between the computer and control groups (pooled RR 0.69, 95% CI 0.11 to 4.31).

Aminoglycoside antibiotics (five studies)

Nephrotoxicity

Four studies reported outcomes on nephrotoxicity (Begg 1989; Destache 1990; Burton 1991; Leehey 1993). There was a trend towards lower nephrotoxicity in computer group although the difference was not significant (pooled RR 0.67, 95% CI 0.42 to 1.06) (Analysis 5.5; Figure 19).

Figure 19. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.5 Aminoglycoside antibiotics.



Need for dialysis

Leehey 1993 compared people who needed dialysis. No difference was observed between the pharmacist-directed dosing using a Bayesian pharmacokinetic dosing program and the control group (RR 0.30, 95% CI 0.03 to 2.86).

Total clinical adverse events

In Gonzalez 1989, adverse reactions occurred in 7% of participants with population-based emergency department guidelines dosing, and 10% of participants with Bayesian-derived pharmacokinetic dosing (RR 1.62, 95% CI 0.32 to 8.26).

Theophylline (four studies)

Anti-rejection drugs (four studies)

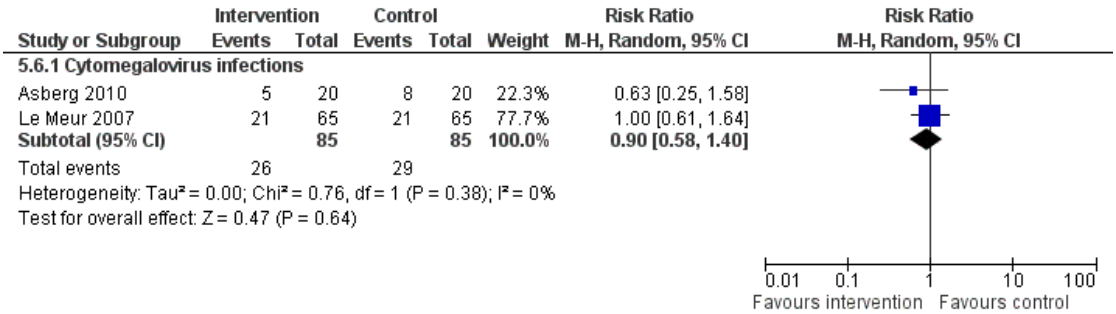
Tachycardia

Casner 1993 analyzed the theophylline toxicity (including nausea, vomiting, tremor, tachycardia and seizures): one participant had a tachycardia in the kinetic group whereas there was no episode of toxicity in the empiric group (RR 3.17, 95% CI 0.14 to 72.80).

Cytomegalovirus infections

Two comparisons reported outcomes on cytomegalovirus infections (Le Meur 2007; Asberg 2010). No significant difference was observed between the computer and control groups (pooled RR 0.90, 95% CI 0.58 to 1.40) (Analysis 5.6; Figure 20).

Figure 20. Forest plot of comparison: 5 Clinical adverse events, outcome: 5.6 Anti-rejection drugs.



Total clinical adverse events

Le Meur 2007 analyzed clinical adverse events including anaemia, leukopenia, gastrointestinal adverse events and infections. There was no statistical difference between individualized doses based on therapeutic monitoring of MPA and fixed-dose MMF (RR 1.07, 95% CI 0.98 to 1.17).

Anaesthetic agents (two studies, three comparisons)

Total clinical adverse events

In Rodman 1984, there was no clinical adverse event in the people monitored clinically (monitoring of rhythm, intermittent hard-copy rhythm strips, serial ECGs, daily measurements of electrolyte and cardiac enzyme levels, liver function tests).

Antidepressants (one study)

Total clinical adverse events

The comparison of safety between individualized and empiric dose regimen of amitriptyline in the treatment of major depressive episode (Mihajlovic 2003) was studied in Mihajlovic 2010. The CGI scale and originally designed questionnaire were used for clinical adverse events assessment. In the experimental group, 69 complaints on nine different types of adverse effects were recorded during the eight-week treatment period and in control group, 111 complaints on 12 different types of adverse effects were recorded. Mihajlovic 2010 indicated that "significantly higher number of patients complaining on adverse effects were in the control group". Nevertheless, none of the comparisons during the eight-week treatment period was significant (RR: day 14 0.63, 95% CI 0.34 to 1.15; day 28 0.71, 95% CI 0.41 to 1.21; day 42 0.75, 95% CI 0.30 to 1.90; day 56 0.75, 95% CI 0.30 to 1.90).

Gonadotropins (one study)

No data available.

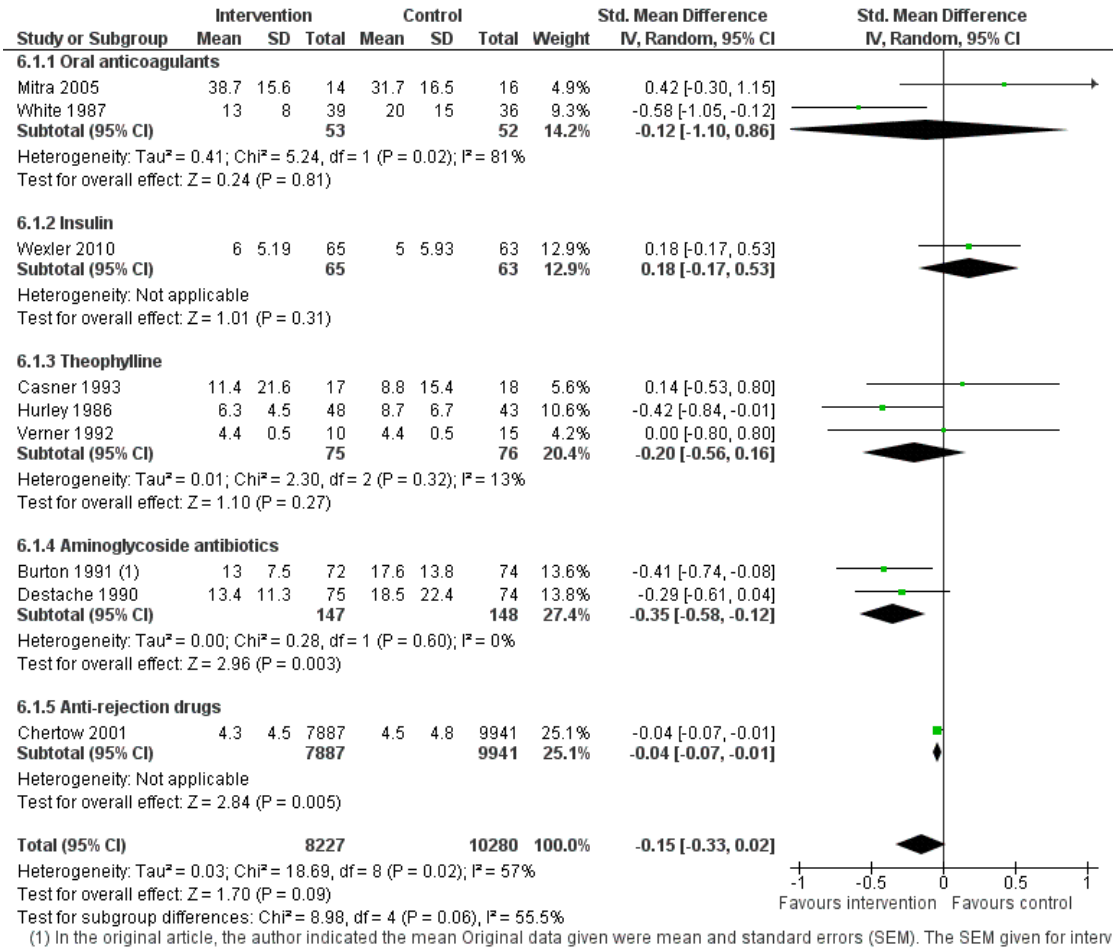
Summary

No significant difference on death was observed between the computer and control groups. For clinical adverse events, we did not pool the results because of the diversity of outcomes. There was a trend for less nephrotoxicity for aminoglycoside antibiotics, for less bleeding and thromboembolism events for anticoagulants with the computer group. When considering the incidence rates for anticoagulants, which is a more precise outcome measure taking into account the exposure time, this difference was significant in favour of the computer group for thromboembolism despite a high heterogeneity. There was no evidence of difference for insulin, theophylline, anaesthetic agents, anti-rejection drugs and antidepressants.

Hypothesis 6. Computer advice reduces the cost of health care or the use of resources (length of stay)

For this comparison, the outcomes analyzed were the length of stay (Analysis 6.1; Figure 21) and the cost per participant.

Figure 21. Forest plot of comparison: 6 Healthcare resources, outcome: 6.1 Length of stay (days).



Length of stay

Nine comparisons analyzed the length of stay (oral anticoagulants: White 1987; Mitra 2005; insulin: Wexler 2010; aminoglycoside: Destache 1990; Burton 1991; theophylline: Hurley 1986; Verner 1992; Casner 1993; cyclosporine: Chertow 2001). There was a significant reduction of the length of stay in the computer group in four comparisons (Hurley 1986; White 1987; Burton 1991; Chertow 2001), whereas the difference was not significant in five comparisons. The pooled effect tended to be in favour of the computer group (SMD -0.15, 95% CI -0.33 to 0.02).

Costs per participant and incremental cost-effectiveness ratio

Five studies analyzed the costs of interventions using computer advice on drug dosage.

In Destache 1990, clinical pharmacokinetic service direct costs were significantly lower than usual care (without clinical pharmacokinetic service monitoring) for aminoglycoside antibiotics: USD7102.56 ± 8898.18 compared with USD13,758.64 ± 22,874.31 (P value < 0.02).

In Chertow 2001, there were no significant differences between intervention and control periods in estimated hospital and pharmacy costs for cyclosporine.

In Claes 2006 (main results in Claes 2005), the total cost per participant per month was EUR53.79 for usual care, EUR50.62 for intervention A (multifaceted intervention) and EUR53.20 for intervention D (multifaceted intervention plus DAWN AC computer advice) for anticoagulants.

Jowett 2009 reported the cost-effectiveness for anticoagulants of the randomized multicentre study of two computer-assisted dosage programs (DAWN AC or PARMA 5) versus manual dosing conducted by Poller et al. (Poller 2008 PARMA 5; Poller 2009 DAWN AC). Dosing time and costs were available in 28 of the 32 clinics participating. Total overall costs per participant were significantly lower in the computer-dosing arm (EUR -50.5, bootstrapped 95% CI -76.8 to -24.1), mainly driven by the difference in dosing costs. The authors concluded that computer-assisted dosage with the two programs (DAWN AC and PARMA 5) was not less effective clinically but was lower in cost than manual dosage.

In Rousseau 2010 (main results in Le Meur 2007), the mean total yearly cost per participant was EUR47,477 (95% CI 43,933 to 51,020) in the concentration-controlled group and EUR46,783 (95% CI 44,152 to 49,414) in the fixed-dose group (P value = 0.7) for mycophenolate.

In three studies (Claes 2006; Jowett 2009; Rousseau 2010), the incremental cost-effectiveness ratio (ICER) was reported. The ICER represents the additional cost required to provide one unit of additional effect. In Jowett 2009, as the costs were lower and the intervention more favourable, calculation of an ICER in this case was not appropriate. In Rousseau 2010, the incremental 12-month cost was EUR3757 per treatment failure (Purchasing Power Parities United States/France: USD4129). In Claes 2006, the ICER for intervention A (multifaceted intervention) was EUR5.2 per day within range (DWR) and for intervention D (multifaceted intervention plus DAWN AC computer advice) EUR4.9 per DWR. Intervention A was less effective but also slightly less costly compared with D resulting in comparable cost-effectiveness ratios.

Summary

There was a trend to a reduction of the length of stay in the computer groups. In most of trials, the computer-assisted dosage was not less effective but was lower in cost than manual dosage resulting in a comparable or better cost-effectiveness ratio than usual care.

Subgroup analyses

No study compared the effect of decision support logistics or organizations of care. We found no studies where the computerized advice was delivered by delayed feedback.

Since fewer than 10 studies were available for each characteristic to model, we did not investigate heterogeneity.

ADDITIONAL SUMMARY OF FINDINGS *[Explanation]*

Computerized advice on drug dosage for leading physiological parameters within therapeutic range

Patient or population: patients with leading physiological parameters within therapeutic range
Settings: outpatient/inpatient
Intervention: computerized advice on drug dosage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Computerized advice on drug dosage				
Oral anticoagulants: time in target INR range (%)	-	The mean oral anticoagulants: time in target INR range (%) in the intervention groups was **0.19 standard deviations higher** (0.06 to 0.33 higher)	-	13,581 (6 studies)	⊕○○○ **very low**[1,2,3]	SMD 0.19 (95% CI 0.06 to 0.33)
Insulin: time in target glucose range (%)	-	The mean insulin: time in target glucose range (%) in the intervention groups was **1.27 standard deviations higher** (0.56 to 1.98 higher)	-	234 (4 studies)	⊕⊕○○ **low**[3,4,5]	SMD 1.27 (95% CI 0.56 to 1.98)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **INR:** international normalized ratio; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No information given on random sequence generation and allocation concealment in half of the studies.
[2] I^2 = 79%.
[3] No funnel plot was performed since the validity conditions were not met.
[4] No blinding of participants and personnel in all studies.
[5] I^2 = 83%.

Computerized advice on drug dosage for reducing time to achieve therapeutic control

Patient or population: patients with reducing time to achieve therapeutic control
Settings: outpatient/inpatient
Intervention: computerized advice on drug dosage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Computerized advice on drug dosage				
Time to achieve therapeutic range - oral anticoagulants: time to achieve therapeutic prothrombin ratio (days)	-	The mean time to achieve therapeutic range - oral anticoagulants: time to achieve therapeutic prothrombin ratio (days) in the intervention groups was **0.22 standard deviations lower** (0.69 lower to 0.26 higher)	-	223 (2 studies)	⊕⊕◯◯ **low**[1,2,3]	SMD -0.22 (95% CI -0.69 to 0.26)
Time to achieve therapeutic range - insulin: time to achieve therapeutic control (hours)	-	The mean time to achieve therapeutic range - insulin: time to achieve therapeutic control (hours) in the intervention groups was **0.14 standard deviations lower** (0.98 lower to 0.7	-	194 (4 studies)	⊕◯◯◯ **very low**[3,4,5]	SMD -0.14 (95% CI -0.98 to 0.7)

		higher)				
Time to stabilization - oral anticoagulants: time to stabilization (days)	-	The mean time to stabilization - oral anticoagulants: time to stabilization (days) in the intervention groups was **0.56 standard deviations lower** (1.07 to 0.04 lower)	-	255 (3 studies)	⊕◯◯◯ **very low**[3,6,7]	SMD -0.56 (95% CI -1.07 to -0.04)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Allocation concealment was unclear, and there was no blinding of participants and personnel in both studies.
[2] I^2 = 66%.
[3] No funnel plot performed but very small studies in favour of the intervention.
[4] In all studies: the random sequence generation and the allocation concealment were unclear, and there was no blinding of participants and personnel.
[5] I^2 = 86%. Meta-analysis should be interpreted with caution.
[6] Sequence generation and/or allocation concealment were unclear in all studies. There was no blinding of participants and personnel in all studies. Data were incomplete in two studies.
[7] I^2 = 71%.

Computerized advice on drug dosage for leading to fewer clinical adverse events

Patient or population: patients with leading to fewer clinical adverse events
Settings: outpatient/inpatient
Intervention: computerized advice on drug dosage

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Computerized advice on drug dosage				
Death	**Study population**		**RR 1.08** (0.8 to 1.45)	14,046 (10 studies)	⊕⊕◯◯ **low**[1,2]	-
	12 per 1000	**13 per 1000** (10 to 18)				
	Moderate					
	28 per 1000	**30 per 1000** (22 to 41)				
Anticoagulants: events - bleeding	**Study population**		**RR 0.65** (0.3 to 1.41)	552 (6 studies)	⊕⊕◯◯ **low**[2,3]	-
	61 per 1000	**40 per 1000** (18 to 86)				
	Moderate					
	65 per 1000	**42 per 1000** (20 to 92)				
Anticoagulants: events - thromboembolism	**Study population**		**RR 3.25** (0.66 to 16.03)	355 (4 studies)	⊕◯◯◯ **very low**[2,4,5]	-

	11 per 1000	**36 per 1000** (7 to 176)				
	Moderate					
	7 per 1000	**23 per 1000** (5 to 112)				
Insulin - hypoglycaemia (< 60 mg/dL)	**Study population**		**RR 0.71** (0.35 to 1.48)	378 (7 studies)	⊕⊕◯◯ **low**[2,6]	-
	90 per 1000	**64 per 1000** (31 to 133)				
	Moderate					
	67 per 1000	**48 per 1000** (23 to 99)				
Insulin - severe hypoglycaemia (< 40 mg/dL)	**Study population**		**RR 0.69** (0.11 to 4.31)	292 (4 studies)	⊕◯◯◯ **very low**[2,7,8]	-
	14 per 1000	**9 per 1000** (2 to 59)				
	Moderate					
	8 per 1000	**6 per 1000** (1 to 34)				
Aminoglycoside antibiotics - nephrotoxicity	**Study population**		**RR 0.67** (0.42 to 1.06)	493 (4 studies)	⊕⊕◯◯ **low**[2,9]	-
	162 per 1000	**108 per 1000** (68 to 172)				
	Moderate					
	154 per 1000	**103 per 1000** (65 to 163)				

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] No (or unclear) blinding of participants and personnel in all studies. In half of the studies: sequence generation and/or allocation concealment were unclear, and the data were incomplete.
[2] No funnel plot was performed since the validity criteria were not met.
[3] In all studies: sequence generation or allocation concealment, or both were unclear, and there was no blinding of participants or personnel. Data were incomplete or unclear in four studies.
[4] Allocation concealment was unclear in all studies. There was no blinding of participants and personnel in all studies and the blinding of outcome assessment was unclear in one study. Data were incomplete or unclear in all studies.
[5] Large confidence interval due to very small studies (n = 335 for four studies) and a few events (n = 8).
[6] No (or unclear) sequence generation or allocation concealment, or both in all studies. No (or unclear) blinding of participants or personnel in all studies. Selective reporting in one study.
[7] Random sequence generation and allocation concealment were unclear in half of the studies. No (or unclear) blinding of participants or personnel in all studies.
[8] Large confidence interval due to only three events for 292 participants.
[9] No blinding of participants and personnel in all studies. Incomplete outcome data in three studies. Baseline characteristics not comparable in one study.

Saving healthcare resources for saving healthcare resources

Patient or population: saving healthcare resources
Settings:
Intervention: saving healthcare resources

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Saving healthcare resources				
Length of stay (days)	-	The mean length of stay (days) in the intervention groups was **0.15 standard deviations lower** (0.33 lower to 0.02 higher)	-	18,507 (9 studies)	⊕◯◯◯ **very low**[1,2]	SMD -0.15 (95% CI -0.33 to 0.02)
Length of stay (days) - oral anticoagulants	-	The mean length of stay (days) - oral anticoagulants in the intervention groups was **0.12 standard deviations lower** (1.1 lower to 0.86 higher)	-	105 (2 studies)	⊕◯◯◯ **very low**[2,3,4,5]	SMD -0.12 (95% CI -1.1 to 0.86)
Length of stay (days) - insulin	-	The mean length of stay (days) - insulin in the intervention groups was **0.18 standard deviations higher** (0.17 lower to 0.53	-	128 (1 study)	⊕⊕⊕⊕ **high**[6]	SMD 0.18 (95% CI -0.17 to 0.53)

		higher)				
Length of stay (days) - theophylline	-	The mean length of stay (days) - theophylline in the intervention groups was **0.2 standard deviations lower** (0.56 lower to 0.16 higher)	-	151 (3 studies)	⊕⊕◯◯ **low**[2,7,8]	SMD -0.2 (95% CI -0.56 to 0.16)
Length of stay (days) - aminoglycoside antibiotics	-	The mean length of stay (days) - aminoglycoside antibiotics in the intervention groups was **0.35 standard deviations lower** (0.58 to 0.12 lower)	-	295 (2 studies)	⊕⊕⊕◯ **moderate**[2,9]	SMD -0.35 (95% CI -0.58 to -0.12)
Length of stay (days) - anti-rejection drugs	-	The mean length of stay (days) - anti-rejection drugs in the intervention groups was **0.04 standard deviations lower** (0.07 to 0.01 lower)	-	17,828 (1 study)	⊕⊕⊕◯ **moderate**[2,10]	SMD -0.04 (95% CI -0.07 to -0.01)

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval; **SMD:** standardized mean difference.

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] I^2 = 57%.

[2] No funnel plot was performed since the validity criteria were not met.

[3] No blinding of participants and personnel in all studies, and blinding of outcome assessment unclear in half of the studies. Random sequence generation or allocation concealment, or both unclear in all studies.

[4] I^2 = 81%. Meta-analysis should be interpreted with caution.

[5] Although small studies (n = 105 for all the studies).

[6] To be interpreted with caution since based on only one monocentric study of 128 participants.

[7] No blinding of participants and personnel in the three studies. No or unclear random sequence generation and allocation concealment in two studies.

[8] Although small studies (n = 151 for all studies).

[9] No blinding of participants and personnel in all studies.

[10] Alternating time series design with four consecutive two-month period.

DISCUSSION

Summary of main results

This update found similar results to the previous review (Durieux 2008), and, in addition, specific therapeutic areas where the intervention is beneficial (the level of evidence was based upon the 'Summary of findings' tables):

1. For oral anticoagulants, CDSS led more often to an INR within the desired range and reduced the time to achieve stabilization of PT and the incidence rates of thromboembolism, in a statistical significant manner.

2. For insulin, it significantly improved the percentage of time in target glucose and reduced the mean blood glucose. For clinical outcomes, there was no efficacy outcome assessed and the difference for safety outcomes was not statistically significant.

3. For aminoglycoside antibiotics, it was significantly more efficient for reaching appropriate drug serum concentrations. For clinical outcomes, positive treatment response was inconsistent in the two studies.

For all these drugs, the quality of evidence was very low due to the high heterogeneity, the low quality and small sample size in most of studies.

4. For the other drugs (theophylline, anti-rejection drugs, anaesthetic agents, antidepressants and gonadotropins), the level of evidence was too low (small number and sample size of studies) to conclude.

5. Overall, CDSS tended to reduce the length of stay but the difference did not reach statistical significance. Quality of evidence by drugs was low or moderate since there were generally only one or two trials studying this outcome. In most trials, the computer-assisted dosage had lower or equivalent costs than manual dosage.

Overall completeness and applicability of evidence

This review included 46 comparisons, of which 18 (39%) concerned anticoagulants and 10 (22%) insulin dosage, providing more consistent results for these drugs than for others (fewer than five comparisons). Five comparisons (10%) concerned aminoglycoside antibiotics but all studies were published before 1993. Three comparisons concerned theophylline, a drug that is not considered as the first-choice treatment of asthma at present. However, monitoring serum concentrations of theophylline is essential to ensure that non-toxic doses are achieved (National Asthma 2002). Compared with the last version of this review, our update included new drugs such as insulin and anti-rejection drugs. We found no studies concerning some new drugs for which it is considered important to monitor drug levels such as glycopeptides, antifungal (fluconazole) and antiretroviral drugs. CDSS may be more efficient in sampling time and intervals for drugs with a narrow therapeutic window such as insulin or oral anticoagulants. However, we found no studies for other drugs with narrow therapeutic indexes (such as lithium, vancomycin, levothyroxine, digoxin, carbamazepine and phenytoin).

Quality of the evidence

However, the findings need to be read with caution.

First, the quality of studies was generally low (see 'Summary of findings' tables). There was no blinding of participants and personnel in all studies. The random sequence generation or the allocation concealment, or both were unclear in half of the studies. In most comparisons, sample size was small.

Second, even when grouping the studies by drug, heterogeneity remained high because of the widely different outcome definitions, clinical contexts or organizations of care. This issue limits the comparability between studies and the interpretation of the clinical significance of the results presented with the SMDs. Besides, the intervention type varied between studies. For example, Anderson 2007 used a pharmacogenetic guidance program for warfarin initiation. This differs totally with all the other studies on oral anticoagulants.

Third, for some indicators (length of stay, mortality), crude results can be affected by unknown confounding factors.

Last, the results are significant for relevant physiological outcomes (assessed for oral anticoagulants and insulin). However, efficacy clinical outcomes were assessed only for four drugs (aminoglycoside antibiotics, anti-rejection drugs, antidepressants and gonadotropins) and there were at most two comparisons for each drug. For aminoglycoside antibiotics and anti-rejection drugs (two comparisons), the studies showed contradictory results.

For safety clinical events, no significant difference on death was observed between the computer and control groups. For clinical adverse events, there was a trend for less nephrotoxicity for aminoglycoside antibiotics, for fewer bleeding and thromboembolism events for anticoagulants with the computer group. When considering the incidence rates for thromboembolism, this difference was significantly in favour of the computer group for anticoagulants despite a high heterogeneity. There was no significant difference in clinical adverse events for the other drugs.

Potential biases in the review process

We identified no potential biases. We considered congress reports and other sources of unpublished studies.

Agreements and disagreements with other studies or reviews

Nine reviews assessed the effect of computer advice on drug dosage. All found a low methodological quality and a high heterogeneity

of studies included. Most presented a publication bias or no evaluation of the methodological quality of the studies included. We could not compare our results with seven reviews that reported their quantitative results as the percentage of studies that showed a significant improvement with computer advice (Garg 2005 updated by Nieuwlaat 2011a; Yourman 2008; Eslami 2009; Mollon 2009; Pearson 2009; Robertson 2010).

Two old reviews (Chatellier 1998; Fitzmaurice 1998a) suggested that computer advice may improve therapeutic INR control for oral anticoagulants, but no meta-analysis was performed and the evaluation of the quality of studies included was not clear or adequate.

Eslami 2009 performed a systematic review on tight glycaemic control with insulin in intensive care units, but performed no meta-analysis because of the high heterogeneity. The results were expressed as the percentage of studies that showed a significant improvement with computer advice on the blood glucose regulatory process. Although most studies reported a positive effect, the evidence was very low: the review only searched for published studies in MEDLINE, there was no evaluation of the methodological quality of studies, which were mostly before-after designs. Causality was difficult to determine because of the simultaneous implementation of a new tight glycaemic control protocol with computer advice.

Three other reviews assessed the effect of computer advice more generally on all drugs, focusing on drug dosage, but their results were expressed as the percentage of studies that showed a significant improvement with computer advice (Mollon 2009; Pearson 2009; Robertson 2010). Mollon 2009 excluded all RCTs that focused only on dose adjustment.

Two reviews assessed the general benefits of computer advice: Yourman 2008 for improving medication prescribing in older adults and Garg 2005, updated by Nieuwlaat 2011a, for drug monitoring and dosing. Unlike us, their results were the percentage of studies that showed a significant improvement with computer advice. A study was considered to have a positive effect (i.e. CDSS showed improvement) if at least 50% of the relevant study outcomes were statistically significantly positive. This approach does not give insight in the magnitude of effects and may have underestimated the overall efficacy. In contrast, there is a risk for publication bias of positive RCTs, which could cause overestimation of CDSS efficacy. Yourman 2008 found that computer advice was effective in improving medication prescribing in older adults, and Nieuwlaat 2011a in improving the process of care. In Yourman 2008, there was no evaluation of the methodological quality of included studies, a likely publication bias and a high heterogeneity. In Nieuwlaat 2011a, the studies were small and of low quality when using a 10-point-scale extended from the Jadad scale.

AUTHORS' CONCLUSIONS

Implications for practice

1. Analysis of trials suggests that computerized advice for drug dosage has some benefits over routine care. It increases the serum concentrations for aminoglycoside antibiotics. It improves the proportion of time for which the plasma drug is within the therapeutic range for aminoglycoside antibiotics and theophylline. It leads to a physiological parameter more often within the desired range for oral anticoagulants and insulin. It decreases the time to achieve stabilization for oral anticoagulants. It also reduces the length of hospital stay, and tends to decrease unwanted effects of anti-rejection drugs and aminoglycoside antibiotics. It significantly decreases unwanted effects for anticoagulants.

2. The results are based on studies mainly of low quality, concerning a small number of drugs. Even when analyzing by drugs, the heterogeneity was important for half of the outcomes.

3. No conclusion could be drawn concerning the logistics of the computerized support and organization of care aspects. It is not certain that these benefits could be achieved with different computer systems in different clinical situations.

Implications for research

1. More studies are needed to demonstrate that the use of computers improves the quality of care. Well-designed trials randomized by clusters are mandatory for assessment of the effect of computerized support systems on drug dosage.

2. These studies should address the identification of the factors that predict a successful and acceptable system: the decision support logistics, the organizations of care and the healthcare professionals' characteristics.

3. Studies evaluating other drugs with a narrow therapeutic window or complicated pharmacokinetics (e.g. antibiotics) are needed. These studies should address the identification of the factors that predict a successful and acceptable system: the decision support logistics, the organizations of care and the healthcare professionals' characteristics.

4. Since the last update in 2008, we have found 22 additional trials, which indicate that this field is in rapid extension, especially with the advent of computer physician order entry (CPOE) systems. Future research should look at other directions than only drug dosage.

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REFERENCES

References to studies included in this review

Ageno 1998 *{published data only}*
Ageno W, Turpie AG. A randomized comparison of a computer-based dosing program with a manual system to monitor oral anticoagulant therapy. *Thrombosis Research* 1998;**91**(5):237–40.

Ageno 2000 *{published data only}*
Ageno W, Johnson J, Nowacki B, Turpie AG. A computer generated induction system for hospitalized patients starting on oral anticoagulant therapy. *Thrombosis & Haemostasis* 2000;**83**(6):849–52. [0340–6245]

Anderson 2007 *{published data only}*
Anderson JL, Horne BD, Stevens SM, Grove AS, Barton S, et al. Randomized trial of genotype-guided versus standard warfarin dosing in patients initiating oral anticoagulation. *Circulation* 2007;**116**(22):2563–70.

Anderson 2008 *{published data only}*
Anderson JL. A double blind randomised trial of genotype guided versus standard warfarin dosing in patients initiated on oral anticoagulation: the COUMAGEN study. *Clinical Research in Cardiology* 2008;**97**:8.

Asberg 2010 *{published data only}*
Asberg A, Falck P, Undset LH, Dorje C, Holdaas H, Hartmann A, et al. Computer-assisted cyclosporine dosing performs better than traditional dosing in renal transplant recipients: results of a pilot study. *Therapeutic Drug Monitoring* 2010;**32**(2):152–8.

Augstein 2007 *{published data only}*
Augstein P, Vogt L, Kohnert KD, Freyse EJ, Heinke P, Salzsieder E. Outpatient assessment of Karlsburg Diabetes Management System-based decision support. *Diabetes Care* 2007;**30**(7):1704–8.

Begg 1989 *{published data only}*
Begg EJ, Atkinson HC, Jeffery GM, Taylor NW. Individualised aminoglycoside dosage based on pharmacokinetic analysis is superior to dosage based on physician intuition at achieving target plasma drug concentrations. *British Journal of Clinical Pharmacology* 1989;**28**(2):137–41.

Blaha 2009 *{published data only}*
Blaha J, Kopecky P, Matias M, Hovorka R, Kunstyr J, Kotulak T, et al. Comparison of three protocols for tight glycemic control in cardiac surgery patients. *Diabetes Care* 2009;**32**:757–61.

Burton 1991 *{published data only}*
Burton ME, Ash CL, Hill DPJ, Handy T, Shepherd MD, Vasko MR. A controlled trial of the cost benefit of computerized Bayesian aminoglycoside administration. *Clinical Pharmacology and Therapeutics* 1991;**49**(6):685–94.

Carter 1987 *{published data only}*
Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clinical Pharmacy* 1987;**6**(1):37–45.

Casner 1993 *{published data only}*
Casner PR, Reilly R, Ho H. A randomized controlled trial of computerized pharmacokinetic theophylline dosing versus empiric physician dosing. *Clinical Pharmacology and Therapeutics* 1993;**53**(6):684–90.

Chertow 2001 *{published data only}*
Chertow GM, Lee J, Kuperman GJ, Burdick E, Horsky J, Seger DL, et al. Guided medication dosing for inpatients with renal insufficiency. *JAMA* 2001;**286**(22):2839–44.

Claes 2005 *{published data only}*
Claes N, Buntinx F, Vijgen J, Arnout J, Vermylen J, Fieuws S, et al. The Belgian Improvement Study on Oral Anticoagulation Therapy: a randomized clinical trial. *European Heart Journal* 2005;**26**:2159–65.

Claes 2006 *{published data only}*
Claes N, Moeremans K, Frank B, Jef A, Jos V, Herman VL, et al. Estimating the cost-effectiveness of quality-improving interventions in oral anticoagulation management within general practice. *Value in Health* 2006;**9**:369–76.

Cordingley 2009 *{published data only}*
Cordingley JJ, Vlasselaers D, Dormand NC, Wouters PJ, Squire SD, Chassin LJ, et al. Intensive insulin therapy: enhanced Model Predictive Control algorithm versus standard care. *Intensive Care Medicine* 2009;**35**(1):123–8.

Destache 1990 *{published data only}*
Destache CJ, Meyer SK, Bittner MJ, Hermann KG. Impact of a clinical pharmacokinetic service on patients treated with aminoglycosides: a cost-benefit analysis. *Therapeutic Drug Monitoring* 1990;**12**(5):419–26.

Fitzmaurice 2000 *{published data only}*
Fitzmaurice DA, Hobbs FD, Murray ET, Holder RL, Allan TF, Rose PE. Oral anticoagulation management in primary care with the use of computerized decision support and near-patient testing: a randomized, controlled trial. *Archives of Internal Medicine* 2000;**160**(15):2343–8.

Gonzalez 1989 *{published data only}*
Gonzalez ER, Vanderheyden BA, Ornato JP, Comstock TG. Computer-assisted optimization of aminophylline therapy in the emergency department. *American Journal of Emergency Medicine* 1989;**7**(4):395–401.

Hickling 1989 *{published data only}*
Hickling K, Begg E, Moore ML. A prospective randomised trial comparing individualised pharmacokinetic dosage prediction for aminoglycosides with prediction based on estimated creatinine clearance in critically ill patients. *Intensive Care Medicine* 1989;**15**(4):233–7.

Hovorka 2007 *{published data only}*
Hovorka R, Kremen J, Blaha J, Matias M, Anderlova K, Bosanska L, et al. Blood glucose control by a model predictive control algorithm with variable sampling rate versus a routine glucose management protocol in cardiac surgery patients: a randomized controlled trial. *Journal of Clinical Endocrinology & Metabolism* 2007;**92**:2960–4.

Hurley 1986 *{published data only}*
Hurley SF, Dziukas LJ, McNeil JJ, Brignell MJ. A randomized controlled clinical trial of pharmacokinetic theophylline dosing. *American Review of Respiratory Disease* 1986;**134**(6):1219–24.

Jowett 2009 *{published data only}*
Jowett S, Bryan S, Poller L, Van Den Besselaar AMHP, Van Der Meer FJM, Palareti G, et al. The cost-effectiveness of computer-assisted anticoagulant dosage: results from the European Action on Anticoagulation (EAA) multicentre study. Journal of Thrombosis & Haemostasis 2009; Vol. 7, issue 9:1482–90.

Kremen 2007 *{published data only}*
Kremen J, Blaha J, Kopecky P, Bosansk L, Kotrlikova E, Roubicek T, et al. The treatment of hyperglycaemia in critically ill patients: comparison of standard protocol and computer algorithm [In Czech]. *Vnitrni Lekarstvi* 2007;**53**(12):1269–73.

Leehey 1993 *{published data only}*
Leehey DJ, Braun BI, Tholl DA, Chung LS, Gross CA, Roback JA, et al. Can pharmacokinetic dosing decrease nephrotoxicity associated with aminoglycoside therapy. *Journal of the American Society of Nephrology* 1993;**4**:81–90.

Le Meur 2007 *{published data only}*
Le Meur Y, Buchler M, Thierry A, Caillard S, Villemain F, Lavaud S, et al. Individualized mycophenolate mofetil dosing based on drug exposure significantly improves patient outcomes after renal transplantation. *American Journal of Transplantation* 2007;**7**(11):2496–503. [1600–6135]

Le Meur 2007 extract *{published data only}*
Individualized dosing of MMF is superior to fixed dosing in renal transplant patients. Nature Clinical Practice Nephrology 2008; Vol. 4, issue 1:9. [1745–8323]

Lesourd 2002 *{published data only}*
Lesourd F, Avril C, Boujennah A, Parinaud J. A computerized decision support system for ovarian stimulation by gonadotropins. *Fertility and Sterility* 2002; **77**(3):456–60.

Manotti 2001 *{published data only}*
Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated Program for Oral Anticoagulant Treatment). *Haematologica* 2001;**86**(10):1060–70.

Mihajlovic 2003 *{published data only}*
Mihajlovic GS, Milovanovic DR, Jankovic SM. Comparison of efficacy and safety between individualized and empiric dose regimen of amitriptyline in the treatment of major depressive episode. *Psychiatry & Clinical Neurosciences* 2003; **57**(6):580–5. [1323–1316]

Mihajlovic 2010 *{published data only}*
Mihajlovic G, Djukic-Dejanovic S, Jovanovic-Mihajlovic N, Jankovic S, Janjic V, Jovanovic M, et al. Comparison of safety between individualized and empiric dose regimen of amitriptyline in the treatment of major depressive episode. Psychiatria Danubina 2010; Vol. 22, issue 2:354–7. [0353–5053]

Mitra 2005 *{published data only}*
Mitra R, Marciello MA, Brain C, Ahangar B, Burke DT. Efficacy of computer-aided dosing of warfarin among patients in a rehabilitation hospital. *American Journal of Physical Medicine & Rehabilitation* 2005;**84**(6):423–7. [0894–9115]

Mungall 1994 *{published data only}*
Mungall DR, Anbe D, Forrester PL, Luoma T, Genovese R, Mahan J, et al. A prospective randomized comparison of the accuracy of computer-assisted versus GUSTO nomogram--directed heparin therapy. *Clinical Pharmacology and Therapeutics* 1994;**55**(5):591–6.

Pachler 2008 *{published data only}*
Pachler C, Plank J, Weinhandl H, Chassin LJ, Wilinska ME, Kulnik R, et al. Tight glycaemic control by an automated algorithm with time-variant sampling in medical ICU patients. *Intensive Care Medicine* 2008;**34**(7):1224–30. [0342–4642]

Plank 2006 *{published data only}*
Plank J, Blaha J, Cordingley J, Wilinska ME, Chassin LJ, Morgan C, et al. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients. *Diabetes Care* 2006;**29**(2):271–6. [0149–5992]

Poller 1998 pop1 *{published data only}*
Poller L, Shiach CR, MacCallum PK, Johansen AM, Munster AM, Magalhaes A, et al. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. *Lancet* 1998;**352** (9139):1505–9.

Poller 1998 pop2 *{published data only}*
Poller L, Shiach CR, MacCallum PK, Johansen AM, Munster AM, Magalhaes A, et al. Multicentre randomised study of computerised anticoagulant dosage. European Concerted Action on Anticoagulation. *Lancet* 1998;**352** (9139):1505–9.

Poller 2002 *{published data only}*
Poller L. European Concerted Action on Anticoagulation (ECAA): studies on computer-assisted anticoagulant dosage. *Turkish Journal of Haematology* 2002;**19**(2):179–84. [1300–7777]

Poller 2003 *{published data only}*
Poller L, Jespersen J, Tripodi A, Van Den Besselaar AMHP, Van der Mer FJM, Shiac C, et al. European Action on Anticoagulation - cost effectiveness of computer assisted anticoagulant dosage. *Journal of Thrombosis & Haemostasis* 2003;**1**(Suppl 1):Abstract.

Poller 2008 *{published data only}*
Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. An international multicenter randomized study of computer-assisted oral anticoagulant dosage vs. medical staff dosage. Journal of Thrombosis & Haemostasis 2008; Vol. 6, issue 6:935–43.

Poller 2008 PARMA 5 *{published data only}*
Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. A multicentre randomised clinical endpoint study of PARMA 5 computer-assisted oral anticoagulant dosage. British Journal of Haematology 2008; Vol. 143, issue 2: 274–83.

Poller 2009 DAWN AC *{published data only}*
Poller L, Keown M, Ibrahim S, Lowe G, Moia M, Turpie AG, et al. A multicentre randomised assessment of the DAWN AC computer-assisted oral anticoagulant dosage program. *Thrombosis & Haemostasis* 2009;**101**(3):487–94. [0340–6245]

Poller 2009 erratum *{published data only}*
Poller. Erratum: A multicentre randomised assessment of the DAWN AC computer-assisted oral anticoagulant dosage program (Thrombosis and Haemostasis (2009) 101 (487-494)). *Thrombosis and Haemostasis* 2009;**101**(4):794. [0340–6245]

Rodman 1984 *{published data only}*
Rodman JH, Jelliffe RW, Kolb E, Tuey DB, de Guzman MF, Wagers PW, et al. Clinical studies with computer-assisted initial lidocaine therapy. *Archives of Internal Medicine* 1984; **144**(4):703–9.

Rousseau 2010 *{published data only}*
Rousseau A, Laroche M-L, Venisse N, Loichot-Roselmac C, Turcant A, Hoizey G, et al. Cost-effectiveness analysis of individualized mycophenolate mofetil dosing in kidney transplant patients in the APOMYGRE trial. Transplantation 2010; Vol. 89, issue 10:1255–62.

Saager 2008 *{published data only}*
Saager L, Collins GL, Burnside B, Tymkew H, Zhang L, Jacobsohn E, et al. A randomized study in diabetic patients undergoing cardiac surgery comparing computer-guided glucose management with a standard sliding scale protocol. Journal of Cardiothoracic & Vascular Anesthesia 2008; Vol. 22, issue 3:377–82.

Sato 2011 *{published data only}*
Sato T, Carvalho G, Sato H, Lattermann R, Schricker T. Glucose and insulin administration while maintaining normoglycemia during cardiac surgery using a computer-assisted algorithm. *Diabetes Technology & Therapeutics* 2011;**13**:79–84.

Terrell 2010 *{published data only}*
Terrell KM, Perkins AJ, Hui SL, Callahan CM, Dexter PR, Miller DK. Computerized decision support for medication dosing in renal insufficiency: a randomized, controlled trial. Annals of Emergency Medicine 2010; Vol. 56, issue 6: 623–9.

Theil 1993 fentanyl *{published data only}*
Theil DR, Stanley TE 3rd, White WD, Goodman DK, Glass PS, Bai SA, et al. Midazolam and fentanyl continuous infusion anesthesia for cardiac surgery: a comparison of computer-assisted versus manual infusion systems. *Journal of Cardiothoracic and Vascular Anesthesia* 1993;**7**(3):300–6.

Theil 1993 midazolam *{published data only}*
Theil DR, Stanley TE 3rd, White WD, Goodman DK, Glass PS, Bai SA, et al. Midazolam and fentanyl continuous infusion anesthesia for cardiac surgery: a comparison of computer-assisted versus manual infusion systems. *Journal of Cardiothoracic and Vascular Anesthesia* 1993;**7**(3):300–6.

Vadher 1997 *{published data only}*
Vadher B, Patterson DL, Leaning M. Evaluation of a decision support system for initiation and control of oral anticoagulation in a randomised trial. *BMJ* 1997;**314** (7089):1252–6.

Vadher 1997 pop1 *{published data only}*
Vadher BD, Patterson DL, Leaning M. Comparison of oral anticoagulant control by a nurse-practitioner using a computer decision-support system with that by clinicians. *Clinical and Laboratory Haematology* 1997;**19**(3):203–7.

Vadher 1997 pop2 *{published data only}*
Vadher BD, Patterson DL, Leaning M. Comparison of oral anticoagulant control by a nurse-practitioner using a computer decision-support system with that by clinicians. *Clinical and Laboratory Haematology* 1997;**19**(3):203–7.

Verner 1992 *{published data only}*
Verner D, Seligmann H, Platt S, Dany S, Almog S, Zulty L, et al. Computer assisted design of a theophylline dosing regimen in acute bronchospasm: serum concentrations and clinical outcome. *European Journal of Clinical Pharmacology* 1992;**43**(1):29–33.

Wexler 2010 *{published data only}*
Wexler DJ, Shrader P, Burns SM, Cagliero E. Effectiveness of a computerized insulin order template in general medical inpatients with type 2 diabetes: a cluster randomized trial. Diabetes Care 2010; Vol. 33, issue 10:2181–3.

White 1987 *{published data only}*
White RH, Hong R, Venook AP, Daschbach MM, Murray W, Mungall DR, et al. Initiation of warfarin therapy: comparison of physician dosing with computer-assisted dosing. *Journal of General Internal Medicine* 1987;**2**(3): 141–8.

White 1991 *{published data only}*
White RH, Mungall D. Outpatient management of warfarin therapy: comparison of computer-predicted dosage adjustment to skilled professional care. *Therapeutic Drug Monitoring* 1991;**13**(1):46–50.

References to studies excluded from this review

Abbrecht 1982 *{published data only}*
Abbrecht PH, O'Leary TJ, Behrendt DM. Evaluation of a computer-assisted method for individualized anticoagulation: retrospective and prospective studies with a pharmacodynamic model. *Clinical Pharmacology and Therapeutics* 1982;**32**(1):129–36.

Absalom 2003 *{published data only}*
Absalom AR, Kenny GNC. Closed-loop control of propofol anaesthesia using bispectral index: performance assessment in patients receiving computer-controlled propofol and manually controlled remifentanil infusions for minor surgery. *British Journal of Anaesthesia* 2003;**90**(6):737–41. [0007–0912]

Albisser 2007 *{published data only}*
Albisser AM, Wright CE, Sakkal S. Averting iatrogenic hypoglycemia through glucose prediction in clinical practice: progress towards a new procedure in diabetes. *Diabetes Research and Clinical Practice* 2007;**76**:207–14.

Alvis 1985 *{published data only}*
Alvis JM, Reves JG, Govier AV, Menkhaus PG, Henling CE, Spain JA, et al. Computer-assisted continuous infusions of fentanyl during cardiac anesthesia: comparison with a manual method. *Anesthesiology* 1985;**63**(1):41-9.

Barletta 2009 *{published data only}*
Barletta J, McAllen K, Eriksson E, Thayer S, Deines G, Blau S, et al. The effect of a computer-assisted insulin infusion protocol on glucose control and variability in a surgical intensive care unit. Critical Care Medicine 2009: A25. [0090–3493]

Barras 2008 *{published data only}*
Barras MA, Duffull SB, Atherton JJ, Green B. Individualized compared with conventional dosing of enoxaparin. *Clinical Pharmacology & Therapeutics* 2008;**83**(6):882–8.

Barras 2010 *{published data only}*
Barras MA, Duffull SB, Atherton JJ, Green B. Individualized dosing of enoxaparin for subjects with renal impairment is superior to conventional dosing at achieving therapeutic concentrations. *Therapeutic Drug Monitoring* 2010;**32**(4): 482–8.

Bartal 2003 *{published data only}*
Bartal C, Danon A, Schlaeffer F, Reisenberg K, Alkan M, Smoliakov R, et al. Pharmacokinetic dosing of aminoglycosides: a controlled trial. *American Journal of Medicine* 2003;**114**:194–8.

Berg 2009 *{published data only}*
Berg T, Weich V, Teuber G, Klinker H, Moller B, Rasenack J, et al. Individualized treatment strategy according to early viral kinetics in hepatitis C virus type 1-infected patients. *Hepatology* 2009;**50**(2):369–77.

Burger 2003 *{published data only}*
Burger D, Hugen P, Reiss P, Gyssens I, Schneider M, Kroon F, et al. Therapeutic drug monitoring of nelfinavir and indinavir in treatment-naive HIV-1-infected individuals. *AIDS* 2003;**17**(8):1157–65. [0269–9370]

Bury 2005 *{published data only}*
Bury J, Hurt C, Roy A, Cheesman L, Bradburn M, Cross S, et al. LISA: a web-based decision-support system for trial management of childhood acute lymphoblastic leukaemia. *British Journal of Haematology* 2005;**129**(6):746–54.

Caraballo 2008 *{published data only}*
Caraballo PJ, North F, Peters S, Puffer M, Nyman M, Epps S, et al. Use of decision support to prevent errors when documenting height and weight in the hospital electronic medical record. AMIA 2008; Vol. Annual Symposium Proceedings/AMIA Symposium:890.

Carter 1987a *{published data only}*
Carter BL, Taylor JW, Becker A. Evaluation of three dosage-prediction methods for initial in-hospital stabilization of warfarin therapy. *Clinical Pharmacy* 1987;**6**(1):37–45.

Cavalcanti 2009 *{published data only}*
Cavalcanti AB, Silva E, Pereira AJ, Caldeira-Filho M, Almeida FP, Westphal GA, et al. A randomized controlled trial comparing a computer-assisted insulin infusion protocol with a strict and a conventional protocol for glucose control in critically ill patients. *Journal of Critical Care* 2009;**24**:371–8.

Chan 2006 *{published data only}*
Chan ALF, Wang H-Y, Leung HWC. Incorporation of a gentamicin dosage calculator into a computerized prescriber-order-entry system. *American Journal of Health-System Pharmacy* 2006;**63**(14):1344–5. [1079–2082]

Chiarelli 1990 *{published data only}*
Chiarelli F, Tumini S, Morgese G, Albisser AM. Controlled study in diabetic children comparing insulin-dosage adjustment by manual and computer algorithms. *Diabetes Care* 1990;**13**(10):1080–4.

Cohen 2007 *{published data only}*
Cohen P, Rogol AD, Howard CP, Bright GM, Kappelgaard A-M, Rosenfeld RG, et al. Insulin growth factor-based dosing of growth hormone therapy in children: a randomized, controlled study. *Journal of Clinical*

Endocrinology & Metabolism 2007;**92**(7):2480–6. [0021–972X]

Collins 2004 ***{published data only}***
Collins CD, Pedersen CA, Schneider PJ, Miller AS, Sierawski SJ, Roux RK. Effect on amphotericin B lipid complex use of a clinical decision support system for computerized prescriber order entry. *American Journal of Health-System Pharmacy* 2004;**61**(13):1395–9. [1079–2082]

Cupissol 1996 ***{published data only}***
Cupissol D, BrŠS J, Gestin-Boyer C, Nouguier-Soul J, Vian L, Tep A, et al. Validation of a new interactive software monitoring a controlled-flow infusion pump for cisplatin dosage regimen adjustment. *Bulletin du Cancer* 1996;**83**(8): 664–76.

Demakis 2000 ***{published data only}***
Demakis JG, Beauchamp C, Cull WL, Denwood R, Eisen SA, Lofgren R, et al. Improving residents' compliance with standards of ambulatory care. Results from the VA Cooperative Study on Computerized Reminders. *JAMA* 2000;**284**:1411–6.

Dillon 1989 ***{published data only}***
Dillon KR, Dougherty SH, Casner P, Polly S. Individualized pharmacokinetic versus standard dosing of amikacin: a comparison of therapeutic outcomes. *Journal of Antimicrobial Chemotherapy* 1989;**24**:581–9.

Donovan 2010 ***{published data only}***
Donovan JL, Kanaan AO, Thomson MS, Rochon P, Lee M, Gavendo L, et al. Effect of clinical decision support on psychotropic medication prescribing in the long-term care setting. *Journal of the American Geriatrics Society* 2010;**58** (5):1005–7. [0002–8614]

Doran 2004 ***{published data only}***
Doran CV, Hudson NH, Moorhead KT, Chase JG, Shaw GM, Hann CE. Derivative weighted active insulin control modelling and clinical trials for ICU patients. Medical Engineering & Physics 2004; Vol. 26, issue 10:855–66. [1350–4533]

Dortch 2008 ***{published data only}***
Dortch MJ, Mowery NT, Ozdas A, Dossett L, Cao H, Collier B, et al. A computerized insulin infusion titration protocol improves glucose control with less hypoglycemia compared to a manual titration protocol in a trauma intensive care unit. *Journal of Parenteral and Enteral Nutrition* 2008;**32**(1):18–27. [0148–6071]

Evans 1998 ***{published data only}***
Evans RS, Pestotnik SL, Classen DC, Clemmer TP, Weaver LK, Orme JF, et al. A computer-assisted management program for antibiotics and other antiinfective agents. *New England Journal of Medicine* 1998;**338**(4):232–8. [0028–4793]

Evans 1998a ***{published data only}***
Evans WE, Relling MV, Rodman JH, Crom WR, Boyett JM, Pui CH. Conventional compared with individualized chemotherapy for childhood acute lymphoblastic leukemia. *New England Journal of Medicine* 1998;**338**(8):499–505. [0028–4793]

Evans 1999 ***{published data only}***
Evans RS, Pestotnik SL, Classen DC, Burke JP. Evaluation of a computer-assisted antibiotic-dose monitor. *Annals of Pharmacotherapy* 1999;**33**(10):1026–31. [1060–0280]

Faber 2006 ***{published data only}***
Faber E, Pytlik R, Slaby J, Zapletalova J, Kozak T, Raida L, et al. Individually determined dosing of filgrastim after autologous peripheral stem cell transplantation in patients with malignant lymphoma - results of a prospective multicentre controlled trial. *European Journal of Haematology* 2006;**77**(6):493–500. [0902–4441]

Feldstein 2006 ***{published data only}***
Feldstein AC, Smith DH, Perrin N, Yang X, Rix M, Raebel MA, et al. Improved therapeutic monitoring with several interventions. A randomized trial. *Archives of Internal Medicine* 2006;**166**:1848–54.

Fety 1998 ***{published data only}***
Fety R, Rolland F, Barberi-Heyob M, Hardouin A, Campion L, Conroy T, et al. Clinical impact of pharmacokinetically-guided dose adaptation of 5-fluorouracil: results from a multicentric randomized trial in patients with locally advanced head and neck carcinomas. *Clinical Cancer Research* 1998;**4**(9):2039–45. [1078–0432]

Field 2009 ***{published data only}***
Field TS, Rochon P, Lee M, Baril JL, Gurwitz JH. Computerized clinical decision support during medication ordering for long-term care residents with renal insufciency. Pharmacoepidemiology and Drug Safety (PDS) 2009: S121–2. [1053–8569]

Field 2009a ***{published data only}***
Field TS, Rochon P, Lee M, Gavendo L, Baril JL, Gurwitz JH. Computerized clinical decision support during medication ordering for long-term care residents with renal insufficiency. *Journal of the American Medical Informatics Association* 2009;**16**(4):480–5. [1067–5027]

Fihn 1994 ***{published data only}***
Fihn SD, McDonell MB, Vermes D, Henikoff JG, Martin DC, Callahan CM, et al. A computerized intervention to improve timing of outpatient follow-up: a multicenter randomized trial in patients treated with warfarin. *Journal of General Internal Medicine* 1994;**9**(3):131–9.

Fitzmaurice 1996 ***{published data only}***
Fitzmaurice DA, Hobbs FD, Murray ET, Bradley CP, Holder R. Evaluation of computerized decision support for oral anticoagulation management based in primary care. *British Journal of General Practice* 1996;**46**(410):533–5. [0960–1643]

Fitzmaurice 1998 ***{published data only}***
Fitzmaurice DA, Hobbs FD, Murray ET. Primary care anticoagulant clinic management using computerized decision support and near patient international normalized ratio (INR) testing: routine data from a practice nurse-led clinic. *Family Practice* 1998;**15**(2):144–6.

Flanders 2009 *{published data only}*
Flanders SJ, Juneja R, Roudebush CP, Carroll J, Golas A, Elias BL. Glycemic control and insulin safety: the impact of computerized intravenous insulin dosing. American Journal of Medical Quality 2009; Vol. 24, issue 6:489–97.

Fritsch 2009 *{published data only}*
Fritsch N, Nouette-Gaulain K, Bordes M, Semjen F, Meymat Y, Cros A-M. Target-controlled inhalation induction with sevoflurane in children: a prospective pilot study. *Paediatric Anaesthesia* 2009;**19**(2):126–32.

Fukudo 2009 *{published data only}*
Fukudo M, Yano I, Shinsako K, Katsura T, Takada Y, Uemoto S, et al. Prospective evaluation of the Bayesian method for individualizing tacrolimus dose early after living-donor liver transplantation. *Journal of Clinical Pharmacology* 2009;**49**(7):789–97. [0091–2700]

Gamelin 2008 *{published data only}*
Gamelin E, Delva R, Jacob J, Merrouche Y, Raoul JL, Pezet D, et al. Individual fluorouracil dose adjustment based on pharmacokinetic follow-up compared with conventional dosage: results of a multicenter randomized trial of patients with metastatic colorectal cancer. *Journal of Clinical Oncology* 2008;**26**(13):2099–105.

Ghazal-Aswad 1997 *{published data only}*
Ghazal-Aswad S, Highley M, Bailey N, Lind M, Siddiqui N, Sinha DP, et al. A randomised phase III study to compare the toxicity and efficacy of carboplatin given by pharmacokinetically guided formula compared to conventional dosing in epithelial ovarian cancer. *Acta Obstetrica et Gynecologica Scandinavica* 1997;**76**:26.

Gopakumaran 2004 *{published data only}*
Gopakumaran B. "Intelligent dosing system": a useful computer program for diabetes management?. Diabetes Technology and Therapeutics 2004; Vol. 6, issue 3:336–8. [1520–9156]

Griffey 2012 *{published data only}*
Griffey R T, Lo H G, Burdick E, Keohane C, Bates D W. Guided medication dosing for elderly emergency patients using real-time, computerized decision support. *Journal of the American Medical Informatics Association* 2012;**19**: 86–93.

Guarracino 2001 *{published data only}*
Guarracino F, De Cosmo D, Penzo D, Tedesco M, Bossi A, Zussa C, et al. Automated protamine dose assay in heparin reversal management after cardiopulmonary by pass. *Minerva Anestesiologica* 2001;**67**(4):165–9. [0375–9393]

Guarracino 2003 *{published data only}*
Guarracino F, Penzo D, De Cosmo D, Vardanega A, De Stefani R. Pharmacokinetic-based total intravenous anaesthesia using remifentanil and propofol for surgical myocardial revascularization. *European Journal of Anaesthesiology* 2003;**20**(5):385–90. [0265–0215]

Hermayer 2007 *{published data only}*
Hermayer KL, Neal DE, Hushion TV, Irving MG, Arnold PC, Kozlowski L, et al. Outcomes of a cardiothoracic intensive care web-based online intravenous insulin infusion calculator study at a Medical University Hospital. *Diabetes Technology & Therapeutics* 2007;**9**(6):523–34. [1520–9156]

Hobbs 1996 *{published data only}*
Hobbs FD, Delaney BC, Carson A, Kenkre JE. A prospective controlled trial of computerized decision support for lipid management in primary care. *Family Practice* 1996;**13**(2):133–7.

Hoffman 2004 *{published data only}*
Hoffman AR, Strasburger CJ, Zagar A, Blum WF, Kehely A, Hartman ML, et al. Efficacy and tolerability of an individualized dosing regimen for adult growth hormone replacement therapy in comparison with fixed body weight-based dosing. *Journal of Clinical Endocrinology & Metabolism* 2004;**89**(7):3224–33. [0021–972X]

Horn 2002 *{published data only}*
Horn W, Popow C, Miksch S, Kirchner L, Seyfang A. Development and evaluation of VIE-PNN, a knowledge-based system for calculating the parenteral nutrition of newborn infants. *Artificial Intelligence in Medicine* 2002;**24** (3):217–28.

Hwang 2004 *{published data only}*
Hwang HG, Chang IC, Hung WF, Sung ML, Yen D. The design and evaluation of clinical decision support systems in the area of pharmacokinetics. *Medical Informatics and the Internet in Medicine* 2004;**29**(3-4):239–51.

Jankovic 1999 *{published data only}*
Jankovic SM, Timotijevic I, Mihajlovic GS, Dukic-Dejanovic S. Comparison of two approaches to amitriptyline dose individualisation. *European Journal of Drug Metabolism & Pharmacokinetics* 1999;**24**(2):163–8. [0398–7639]

Jannuzzi 2000 *{published data only}*
Jannuzzi G, Cian P, Fattore C, Gatti G, Bartoli A, Monaco F, et al. A multicenter randomized controlled trial on the clinical impact of therapeutic drug monitoring in patients with newly diagnosed epilepsy. The Italian TDM Study Group in Epilepsy. *Epilepsia* 2000;**41**(2):222–30. [0013–9580]

Jellinek 2005 *{published data only}*
Jellinek SP, Cohen V, Likourezos A, Goldman WM, Lashley EL. Analyzing a health-system's use of unfractionated heparin to ensure optimal anticoagulation. *Journal of Pharmacy Technology* 2005;**21**(2):69–78. [8755–1225]

Judge 2006 *{published data only}*
Judge J, Field T S, DeFlorio M, Laprino J, Auger J, Rochon P, et al. Prescribers' responses to alerts during medication ordering in the long term care setting. *Journal of the American Medical Informatics Association* 2006;**13**:385–90.

Jung 2009 *{published data only}*
Jung H, Land C, Nicolay C, De Schepper J, Blum WF, Schonau E. Growth response to an individualized versus fixed dose GH treatment in short children born small for gestational age: the OPTIMA study. European Journal of Endocrinology 2009; Vol. 160, issue 2:149–56.

Kazemi 2011 *{published data only}*
Kazemi A, Ellenius J, Pourasghar F, Tofighi S, Salehi A, Amanati A, et al. The effect of computerized physician order entry and decision support system on medication errors in the neonatal ward: experiences from an Iranian teaching hospital. *Journal of Medical Systems* 2011;**35**(1): 25–37. [0148–5598]

Kirk 2005 *{published data only}*
Kirk RC, Li-Meng Goh D, Packia J, Min Kam H, Ong BKC. Computer calculated dose in paediatric prescribing. *Drug Safety* 2005;**28**(9):817–24. [0114–5916]

Koide 2000 *{published data only}*
Koide D, Ohe K, Ross-Degnan D, Kaihara S. Computerized reminders to monitor liver function to improve the use of etretinate. *International Journal of Medical Informatics* 2000; **57**:11–9.

Kristrom 2009 *{published data only}*
Kristrom B, Aronson AS, Dahlgren J, Gustafsson J, Halldin M, Ivarsson SA, et al. Growth hormone (GH) dosing during catch-up growth guided by individual responsiveness decreases growth response variability in prepubertal children with GH deficiency or idiopathic short stature. *Journal of Clinical Endocrinology & Metabolism* 2009;**94**(2):483–90. [0021–972X]

Kroese 2005 *{published data only}*
Kroese WLG, Avery AJ, Savelyich BSP, Brown NS, Schers H, Howard R, et al. Assessing the accuracy of a computerized decision support system for digoxin dosing in primary care: an observational study. *Journal of Clinical Pharmacy & Therapeutics* 2005;**30**(3):279–83. [0269–4727]

la Cour Freiesleben 2009 *{published data only}*
la Cour Freiesleben N, Lossl K, Bogstad J, Bredkjaer HE, Toft B, Rosendahl M, et al. Individual versus standard dose of rFSH in a mild stimulation protocol for intrauterine insemination: a randomized study. *Human Reproduction* 2009;**24**(10):2523–30.

Lester 2006 *{published data only}*
Lester WT, Grant RW, Barnett GO, Chueh HC. Randomized controlled trial of an informatics-based intervention to increase statin prescription for secondary prevention of coronary disease. *Journal of General Internal Medicine* 2006;**21**:22–9.

Ligtenberg 2006 *{published data only}*
Ligtenberg JJ, Meertens JH, Monteban-Kooistra WE, Tulleken JE, Zijlstra JG. Multicentric, randomized, controlled trial to evaluate blood glucose control by the model predictive control algorithm versus routine glucose management protocols in intensive care unit patients: response to Plank et al. Diabetes Care 2006; Vol. 29, issue 8:1987–8.

Lillis 2003 *{published data only}*
Lillis K. Automated dosing. Computerized physician order entry reduces risk of medication and dosing errors in neonatal ICU. *Health Management Technology* 2003;**24**(11): 36–7. [1074–4770]

Liu 2006 *{published data only}*
Liu N, Chazot T, Genty A, Landais A, Restoux A, McGee K, et al. Titration of propofol for anesthetic induction and maintenance guided by the bispectral index: closed-loop versus manual control. A prospective, randomized, multicenter study. *Anesthesiology* 2006;**104**(4):686–95. [0003–3022]

Manotti 2001 maintenance *{published data only}*
Manotti C, Moia M, Palareti G, Pengo V, Ria L, Dettori AG. Effect of computer-aided management on the quality of treatment in anticoagulated patients: a prospective, randomized, multicenter trial of APROAT (Automated PRogram for Oral Anticoagulant Treatment). *Haematologica* 2001;**86**(10):1060–70.

Mar Fernandez 1996 *{published data only}*
Fernandez de Gatta MD, Calvo MV, Hernandez JM, Caballero D, San Miguel JF, Dominguez-Gil A. Cost-effectiveness analysis of serum vancomycin concentration monitoring in patients with hematologic malignancies. *Clinical Pharmacology & Therapeutics* 1996;**60**(3):332–40. [0009–9236]

Mar Fernandez 2009 *{published data only}*
Mar Fernandez de Gatta MD, Victoria Calvo M, Ardanuy R, Dominguez-Gil A, Lanao JM, Moreno SR. Evaluation of population pharmacokinetic models for amikacin dosage individualization in critically ill patients. *Journal of Pharmacy & Pharmacology* 2009;**61**(6):759–66. [0022–3573]

Matheny 2008 *{published data only}*
Matheny ME, Sequist TD, Seger AC, Fiskio JM, Sperling M, Bugbee D, et al. A randomized trial of electronic clinical reminders to improve medication laboratory monitoring. *Journal of the American Medical Informatics Association* 2008; **15**:424–9.

Maurizi 2011 *{published data only}*
Maurizi AR, Lauria A, Maggi D, Palermo A, Fioriti E, Manfrini S, et al. A novel insulin unit calculator for the management of type 1 diabetes. *Diabetes Technology & Therapeutics* 2011;**13**:425–8.

McCluggage 2010 *{published data only}*
McCluggage L, Lee K, Potter T, Dugger R, Pakyz A. Implementation and evaluation of vancomycin nomogram guidelines in a computerized prescriber-order-entry system. *American Journal of Health-System Pharmacy* 2010;**67**(1): 70–5.

McCowan 2001 *{published data only}*
McCowan C, Neville RG, Ricketts IW, Warner FC, Hoskins G, Thomas GE. Lessons from a randomized controlled trial designed to evaluate computer decision support software to improve the management of asthma. *Medical Informatics and the Internet in Medicine* 2001;**26**:191–201.

McCoy 2008 *{published data only}*
McCoy AB, Peterson JF, Gadd CS, Danciu I, Waitman LR. A system to improve medication safety in the setting of acute kidney injury: initial provider response. Annual Symposium Proceedings/AMIA Symposium 2008:1051.

McCoy 2010 *{published data only}*
McCoy AB, Waitman LR, Gadd CS, Danciu I, Smith JP, Lewis JB, et al. A computerized provider order entry intervention for medication safety during acute kidney injury: a quality improvement report. *American Journal of Kidney Diseases* 2010;**56**(5):832–41.

McDonald 1976 *{published data only}*
McDonald CJ. Use of a computer to detect and respond to clinical events: its effect on clinician behavior. *Annals of Internal Medicine* 1976;**84**(2):162–7.

McDonald 1980 *{published data only}*
McDonald CJ, Wilson GA, McCabe GP, Jr. Physician response to computer reminders. *JAMA* 1980;**244**(14): 1579–81.

McMichael 1993 *{published data only}*
McMichael J, Lieberman R, Doyle H, McCauley J, Fung J, Starzl TE. An intelligent and cost-effective computer dosing system for individualizing FK506 therapy in transplantation and autoimmune disorders. *Journal of Clinical Pharmacology* 1993;**33**(7):599–605.

McMullin 1997 *{published data only}*
McMullin ST, Reichley RM, Kahn MG, Dunagan WC, Bailey TC. Automated system for identifying potential dosage problems at a large university hospital. *American Journal of Health-System Pharmacy* 1997;**54**(5):545–9. [1079–2082]

McMullin 2004 *{published data only}*
McMullin ST, Lonergan TP, Rynearson CS, Doerr TD, Veregge PA, Scanlan ES. Impact of an evidence-based computerized decision support system on primary care prescription costs. Annals of Family Medicine 2004; Vol. 2, issue 5:494–8. [1544–1709]

McMullin 2005 *{published data only}*
McMullin ST, Lonergan TP, Rynearson CS. Twelve-month drug cost savings related to use of an electronic prescribing system with integrated decision support in primary care. *Journal of Managed Care Pharmacy* 2005;**11**(4):322–32. [1083–4087]

Motykie 1999 *{published data only}*
Motykie GD, Mokhtee D, Zebala LP, Caprini JA, Kudrna JC, Mungall DR. The use of a Bayesian forecasting model in the management of warfarin therapy after total hip arthroplasty. *Journal of Arthroplasty* 1999;**14**(8):988–93. [0883–5403]

Mullett 2001 *{published data only}*
Mullett CJ, Evans RS, Christenson JC, Dean JM. Development and impact of a computerized pediatric antiinfective decision support program. *Pediatrics* 2001;**108** (4):E75.

Murchie 1989 *{published data only}*
Murchie CJ, Kenny GN. Comparison among manual, computer-assisted, and closed-loop control of blood pressure after cardiac surgery. *Journal of Cardiothoracic Anesthesia* 1989;**3**(1):16–19.

Nash 2005 *{published data only}*
Nash IS, Rojas M, Hebert P, Marrone SR, Colgan C, Fisher LA, et al. Reducing excessive medication administration in hospitalized adults with renal dysfunction. *American Journal of Medical Quality* 2005;**20**(2):64–9. [1062–8606]

Newby 2002 *{published data only}*
Newby LK, Harrington RA, Bhapkar MV, Van de Werf F, Hochman JS, Granger CB, et al. An automated strategy for bedside aPTT determination and unfractionated heparin infusion adjustment in acute coronary syndromes: insights from PARAGON A. *Journal of Thrombosis & Thrombolysis* 2002;**14**(1):33–42. [0929–5305]

Nieuwenhuyze 1995 *{published data only}*
Van den Nieuwenhuyzen MC, Engbers FH, Burm AG, Vletter AA, van Kleef JW, Bovill JG. Computer-controlled infusion of alfentanil versus patient-controlled administration of morphine for postoperative analgesia: a double-blind randomized trial. *Anesthesia and Analgesia* 1995;**81**(4):671–9.

Nightingale 2000 *{published data only}*
Nightingale PG, Adu D, Richards NT, Peters M. Implementation of rules based computerised bedside prescribing and administration: intervention study. *BMJ* 2000;**320**(7237):750–3.

Oppenheim 2002 *{published data only}*
Oppenheim MI, Vidal C, Velasco FT, Boyer AG, Cooper MR, Hayes JG, et al. Impact of a computerized alert during physician order entry on medication dosing in patients with renal impairment. *Proceedings/AMIA Annual Symposium* 2002:577–81. [1531–605X]

Overhage 1997 *{published data only}*
Overhage JM, Tierney WM, Zhou XH, McDonald CJ. A randomized trial of "corollary orders" to prevent errors of omission. *Journal of the American Medical Informatics Association* 1997;**4**:364–75.

Palen 2006 *{published data only}*
Palen TE, Raebel M, Lyons E, Magid DM. Evaluation of laboratory monitoring alerts within a computerized physician order entry system for medication orders. *American Journal of Managed Care* 2006;**12**:389–95.

Pea 2002 *{published data only}*
Pea F, Bertolissi M, Di Silvestre A, Poz D, Giordano F, Furlanut M. TDM coupled with Bayesian forecasting should be considered an invaluable tool for optimizing vancomycin daily exposure in unstable critically ill patients. *International Journal of Antimicrobial Agents* 2002;**20**(5): 326–32. [0924–8579]

Peck 1973 *{published data only}*
Peck CC, Sheiner LB, Martin CM, Combs DT, Melmon KL. Computer-assisted digoxin therapy. *New England Journal of Medicine* 1973;**289**(9):441–6.

Peters 1996 *{published data only}*
Peters A, Kerner W. Analytical design and clinical application of an intelligent control system for insulin treatment [Analytisches Design und klinische Anwendung

eineslernfähigen Regelsystems für die Pharmakotherapie mit Insulin]. *Biomedizinische Technik* 1996;**41**(1-2):2–13.

Peterson 1986 *{published data only}*
Peterson CM, Jovanovic L, Chanoch LH. Randomized trial of computer-assisted insulin delivery in patients with type I diabetes beginning pump therapy. *American Journal of Medicine* 1986;**81**(1):69–72.

Peterson 2005 *{published data only}*
Peterson JF, Kuperman GJ, Shek C, Patel M, Avorn J, Bates DW. Guided prescription of psychotropic medications for geriatric inpatients. *Archives of Internal Medicine* 2005;**165**(7):802–7. [0003–9926]

Peterson 2007 *{published data only}*
Peterson JF, Rosenbaum BP, Waitman LR, Habermann R, Powers J, Harrell D, et al. Physicians' response to guided geriatric dosing: initial results from a randomized trial. *Studies in Health Technology & Informatics* 2007;**129**(Pt 2):1037–40. [0926–9630]

Phillips 2008 *{published data only}*
Phillips IE, Nelsen C, Peterson J, Sullivan TM, Waitman LR. Improving aminoglycoside dosing through computerized clinical decision support and pharmacy therapeutic monitoring systems. AMIA 2008; Vol. Annual Symposium Proceedings/AMIA Symposium.:1093.

Piazza 2009 *{published data only}*
Piazza G, Goldhaber SZ. Computerized decision support for the cardiovascular clinician: applications for venous thromboembolism prevention and beyond. Circulation 2009; Vol. 120, issue 12:1133–7. [0009–7322]

Poller 1993 *{published data only}*
Poller L, Wright D, Rowlands M. Prospective comparative study of computer programs used for management of warfarin. *Journal of Clinical Pathology* 1993;**46**(4):299-303.

Popovic-Todorovic 2003 *{published data only}*
Popovic-Todorovic B, Loft A, Bredkjaeer HE, Bangsboll S, Nielsen IK, Andersen AN. A prospective randomized clinical trial comparing an individual dose of recombinant FSH based on predictive factors versus a 'standard' dose of 150 IU/day in 'standard' patients undergoing IVF/ICSI treatment. *Human Reproduction* 2003;**18**(11):2275–82. [0268–1161]

Proost 2003 *{published data only}*
Proost JH, Punt NC. Dose individualization in PharmDIS-e+. *International Journal of Clinical Pharmacology and Therapeutics* 2003;**41**(10):451–8. [0946–1965]

Roberts 2010 *{published data only}*
Roberts GW, Farmer CJ, Cheney PC, Govis SM, Belcher TW, Walsh SA, et al. Clinical decision support implemented with academic detailing improves prescribing of key renally cleared drugs in the hospital setting. Journal of the American Medical Informatics Association 2010; Vol. 17, issue 3:308–12.

Rochon 2006 *{published data only}*
Rochon PA, Field TS, Bates DW, Lee M, Gavendo L, Erramuspe-Mainard J, et al. Clinical application of a computerized system for physician order entry with clinical decision support to prevent adverse drug events in long-term care. *CMAJ* 2006;**174**(1):52–4. [0820–3946]

Rood 2005 *{published data only}*
Rood E, Bosman RJ, van der Spoel JI, Taylor P, Zandstra DF. Use of a computerized guideline for glucose regulation in the intensive care unit improved both guideline adherence and glucose regulation. *Journal of the American Medical Informatics Association* 2005;**12**(2):172–80. [1067–5027]

Rothschild 2002 *{published data only}*
Rothschild JM, Lee TH, Bae T, Bates DW. Clinician use of a palmtop drug reference guide. Journal of the American Medical Informatics Association 2002; Vol. 9, issue 3:223–9. [1067–5027]

Rothschild 2003 *{published data only}*
Rothschild JM, Keohane CA, Thompson S, Bates DW. Intelligent intravenous infusion pumps to improve medication administration safety. Annual Symposium Proceedings/AMIA Symposium 2003:992.

Rothschild 2005 *{published data only}*
Rothschild JM, Keohane CA, Cook EF, Orav EJ, Burdick E, Thompson S, et al. A controlled trial of smart infusion pumps to improve medication safety in critically ill patients. Critical Care Medicine 2005; Vol. 33, issue 3:533–40. [0090–3493]

Rotman 1996 *{published data only}*
Rotman BL, Sullivan AN, McDonald TW, Brown BW, DeSmedt P, Goodnature D, et al. A randomized controlled trial of a computer based physician workstation in an outpatient setting: implementation barriers to outcome evaluation. *Journal of the American Medical Informatics Association* 1996;**3**(5):340–8.

Roumie 2005 *{published data only}*
Roumie CL, Elasy TA, Greevy R, Griffin MR, Liu X, Stone WJ, et al. Improving blood pressure control through provider education, provider alerts, and patient education: a cluster randomized trial. *Annals of Internal Medicine* 2006;**145**:165–75.

Ruiz 1993 *{published data only}*
Ruiz R, Borches D, Gonzalez A, Corral J. A new sodium-nitroprusside-infusion controller for the regulation of arterial blood pressure. *Biomedical Instrumentation & Technology* 1993;**27**(3):244–51.

Ryff-de Leche 1992 *{published data only}*
Ryff-de Leche A, Engler H, Nutzi E, Berger M, Berger W. Clinical application of two computerized diabetes management systems: comparison with the log-book method. *Diabetes Research* 1992;**19**(3):97–105.

Santana 2003 *{published data only}*
Santana VM, Zamboni WC, Kirstein MN, Tan M, Liu T, Gajjar A, et al. A pilot study of protracted topotecan dosing using a pharmacokinetically guided dosing approach in children with solid tumors. *Clinical Cancer Research* 2003;**9**(2):633–40. [1078–0432]

Santana 2005 *{published data only}*
Santana VM, Furman WL, Billups CA, Hoffer F, Davidoff AM, Houghton PJ, et al. Improved response in high-risk neuroblastoma with protracted topotecan administration using a pharmacokinetically guided dosing approach. Journal of Clinical Oncology 2005; Vol. 23, issue 18: 4039–47. [0732–183X]

Schneider 2005 *{published data only}*
Schneider BL, Gulseth MP, Cusick MA, Sisson DC, Tomsche JJ. Computer program to assist pharmacy management of an inpatient warfarin dosing service. *American Journal of Health-System Pharmacy* 2005;**62**(22): 2393–6. [1079–2082]

Schrezenmeir 2002 *{published data only}*
Schrezenmeir J, Dirting K, Papazov P. Controlled multicenter study on the effect of computer assistance in intensive insulin therapy of type 1 diabetics. *Computer Methods & Programs in Biomedicine* 2002;**69**(2):97–114. [0169–2607]

Shiach 2002 *{published data only}*
Shiach CR, Campbell B, Poller L, Keown M, Chauhan N. Randomised cross-over study of near patient testing versus hospital laboratory testing with computer assisted dosing in a community anticoagulant clinic. *British Journal of Haematology* 2002;**117**(Suppl 1):33.

Shieh 2006 *{published data only}*
Shieh J-S, Fu M, Huang S-J, Kao M-C. Comparison of the applicability of rule-based and self-organizing fuzzy logic controllers for sedation control of intracranial pressure pattern in a neurosurgical intensive care unit. *IEEE Transactions on Biomedical Engineering* 2006;**53**(8):1700–5. [0018–9294]

Soper 2006 *{published data only}*
Soper J, Chan GTC, Skinner JR, Spinetto HD, Gentles TL. Management of oral anticoagulation in a population of children with cardiac disease using a computerised system to support decision-making. *Cardiology in the Young* 2006; **16**(3):256–60. [1047–9511]

Sparano 2006 *{published data only}*
Sparano JA. TAILORx: trial assigning individualized options for treatment (Rx). *Clinical Breast Cancer* 2006;**7** (4):347–50. [1526–8209]

Strack 1985 *{published data only}*
Strack T, Bergeler J, Beyer J, Hutten H. Computer assisted conventional insulin therapy. *Life Support Systems* 1985;**3 Suppl 1**:568–72.

Tamblyn 2003 *{published data only}*
Tamblyn R, Huang A, Perreault R, Jacques A, Roy D, Hanley J, et al. The medical office of the 21st century (MOXXI): effectiveness of computerized decision-making support in reducing inappropriate prescribing in primary care. *CMAJ* 2003;**169**(6):549–56.

Tamblyn 2008 *{published data only}*
Tamblyn R, Huang A, Taylor L, Kawasumi Y, Bartlett G, Grad R, et al. A randomized trial of the effectiveness of on-demand versus computer-triggered drug decision support in primary care. *Journal of the American Medical Informatics Association* 2008;**15**(4):430–8. [1067–5027]

Tamblyn 2010 *{published data only}*
Tamblyn R, Reidel K, Huang A, Taylor L, Winslade N, Bartlett G, et al. Increasing the detection and response to adherence problems with cardiovascular medication in primary care through computerized drug management systems: a randomized controlled trial. *Medical Decision Making* 2010;**30**(2):176–88.

Terrell 2009 *{published data only}*
Terrell KM, Perkins AJ, Dexter PR, Hui SL, Callahan CM, Miller DK. Computerized decision support to reduce potentially inappropriate prescribing to older emergency department patients: a randomized, controlled trial. *Journal of the American Geriatrics Society* 2009;**57**(8):1388–94.

Thomson 2011 *{published data only}*
Thomson BKA, MacRae JM, Barnieh L, Zhang J, MacKay E, Manning MA, et al. Evaluation of an electronic warfarin nomogram for anticoagulation of hemodialysis patients. *BMC Nephrology* 2011;**12**:46.

Tierney 2005 *{published data only}*
Tierney WM, Overhage JM, Murray MD, Harris LE, Zhou XH, Eckert GJ, et al. Can computer-generated evidence-based care suggestions enhance evidence-based management of asthma and chronic obstructive pulmonary disease? A randomized, controlled trial. *Health Services Research* 2005; **40**:477–97.

Tomek 2011 *{published data only}*
Tomek A, Mat'oka V, Kumstov T, Rmek M, Arbochov I, T'ovkov K, et al. Warfarin loading dose guided by pharmacogenetics is effective and safe in cardioembolic stroke patients. Proceedings of the 20th European Stroke Conference; 2011 May 24-27; Hamburg, Germany. 2011.

Traugott 2011 *{published data only}*
Traugott KA, Maxwell PR, Green K, Frei C, Lewis JS, 2nd. Effects of therapeutic drug monitoring criteria in a computerized prescriber-order-entry system on the appropriateness of vancomycin level orders. *American Journal of Health-System Pharmacy* 2011;**68**(4):347–52.

Trivedi 2007 *{published data only}*
Trivedi MH, Daly EJ. Measurement-based care for refractory depression: a clinical decision support model for clinical research and practice. *Drug & Alcohol Dependence* 2007;**88 Suppl 2**:S61–71. [0376–8716]

Trivedi 2007a *{published data only}*
Trivedi MH, Rush AJ, Gaynes BN, Stewart JW, Wisniewski SR, Warden D, et al. Maximizing the adequacy of medication treatment in controlled trials and clinical practice: STAR(*)D measurement-based care. *Neuropsychopharmacology* 2007;**32**(12):2479–89. [0893–133X]

van der Bol 2010 *{published data only}*
van der Bol JM, Mathijssen RHJ, Creemers G-JM, Planting AST, Loos WJ, Wiemer EAC, et al. A CYP3A4 phenotype-

based dosing algorithm for individualized treatment of irinotecan. *Clinical Cancer Research* 2010;**16**(2):736–42. [1078–0432]

van Leeuwen 2005 *{published data only}*
van Leeuwen Y, Rombouts EK, Kruithof CJ, Van Der Meer FJM, Rosendaal FR. Comparison between two computer algorithms in oral anticoagulant dosage: a double blind randomised controlled trial. Journal of Thrombosis & Haemostasis 2005; Vol. 3:1.

van Leeuwen 2007 *{published data only}*
van Leeuwen Y, Rombouts EK, Kruithof CJ, van der Meer FJM, Rosendaal FR. Improved control of oral anticoagulant dosing: a randomized controlled trial comparing two computer algorithms. *Journal of Thrombosis & Haemostasis* 2007;**5**(8):1644–9. [1538–7933]

van Lent-Evers 1999 *{published data only}*
van Lent-Evers NA, Mathot RA, Geus WP, van Hout BA, Vinks AA. Impact of goal-oriented and model-based clinical pharmacokinetic dosing of aminoglycosides on clinical outcome: a cost-effectiveness analysis. *Therapeutic Drug Monitoring* 1999;**21**(1):63–73. [0163–4356]

Van Wyk 2008 *{published data only}*
Van Wyk JT, Van Wijk MAM, Sturkenboom MCJM, Mosseveld M, Moorman PW, van der Lei J. Electronic alerts versus on-demand decision support to improve dyslipidemia treatment: a cluster randomized controlled trial. Circulation 2008; Vol. 117, issue 3:371–8. [0009–7322]

Verstappen 2007 *{published data only}*
Verstappen SMM, Jacobs JWG, van der Veen MJ, Heurkens AHM, Schenk Y, ter Borg EJ, et al. Intensive treatment with methotrexate in early rheumatoid arthritis: aiming for remission. Computer Assisted Management in Early Rheumatoid Arthritis (CAMERA, an open-label strategy trial). *Annals of the Rheumatic Diseases* 2007;**66**(11): 1443–9. [0003–4967]

Verstappen 2010 *{published data only}*
Verstappen SMM, Bakker MF, Heurkens AHM, van der Veen MJ, Kruize AA, Geurts MAW, et al. Adverse events and factors associated with toxicity in patients with early rheumatoid arthritis treated with methotrexate tight control therapy: the CAMERA study. Annals of the Rheumatic Diseases 2010; Vol. 69, issue 6:1044–8.

Wasmuth 2007 *{published data only}*
Wasmuth JC, Lambertz I, Voigt E, Vogel M, Hoffmann C, Burger D, et al. Maintenance of indinavir by dose adjustment in HIV-1-infected patients with indinavir-related toxicity. *European Journal of Clinical Pharmacology* 2007;**63**(10):901–8.

Wasmuth 2007a *{published data only}*
Wasmuth JC, Rodermann E, Voigt E, Vogel M, Lauenroth-Mai E, Jessen A, et al. Comparison of indinavir + ritonavir 600 + 100 mg vs. 400 + 100 mg BID combinations in HIV1-infected patients guided by therapeutic drug monitoring. *European Journal of Medical Research* 2007;**12** (7):289–94. [0949–2321]

Whipple 1991 *{published data only}*
Whipple JK, Ausman RK, Franson T, Quebbeman EJ. Effect of individualized pharmacokinetic dosing on patient outcome. *Critical Care Medicine* 1991;**19**:1480–5.

White 1984 *{published data only}*
White KS, Lindsay A, Pryor TA, Brown WF, Walsh K. Application of a computerized medical decision-making process to the problem of digoxin intoxication. *Journal of the American College of Cardiology* 1984;**4**(3):571–6.

Willcourt 1994 *{published data only}*
Willcourt RJ, Pager D, Wendel J, Hale RW. Induction of labor with pulsatile oxytocin by a computer-controlled pump. *American Journal of Obstetrics and Gynecology* 1994; **170**(2):603–8.

Wilson 2002 *{published data only}*
Wilson WH, Grossbard ML, Pittaluga S, Cole D, Pearson D, Drbohlav N, et al. Dose-adjusted EPOCH chemotherapy for untreated large B-cell lymphomas: a pharmacodynamic approach with high efficacy. *Blood* 2002; **99**(8):2685–93. [0006–4971]

Yamamoto 2005 *{published data only}*
Yamamoto N, Tamura T, Murakami H, Shimoyama T, Nokihara H, Ueda Y, et al. Randomized pharmacokinetic and pharmacodynamic study of docetaxel: dosing based on body-surface area compared with individualized dosing based on cytochrome P450 activity estimated using a urinary metabolite of exogenous cortisol. *Journal of Clinical Oncology* 2005;**23**(6):1061–9. [0732–183X]

References to studies awaiting assessment

Anderson 2011 *{published data only}*
Anderson JL, Horne BD, Stevens SM, Woller SC, Samuelson KM, Mansfield JW, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing: CoumaGen-II. Proceedings of the American Heart Association; 2011 Nov 12-16; Orlando, FL. 2011.

Anderson 2012 *{published data only}*
Anderson JL, Horne BD, Stevens SM, Woller SC, Samuelson KM, Mansfield JW, et al. A randomized and clinical effectiveness trial comparing two pharmacogenetic algorithms and standard care for individualizing warfarin dosing (CoumaGen-II). *Circulation* 2012;**125**(16): 1997–2005. [PUBMED: 22431865]

Caduff 2013 *{published data only}*
Caduff Good A, Nobel D, Krahenbuhl S, Geisen C, Henz S. Randomised trial of a clinical dosing algorithm to start anticoagulation with phenprocoumon. *Swiss Medical Weekly* 2013;**143**:w13709. [PUBMED: 23299853]

Dumont 2012 *{published data only}*
Dumont C, Bourguignon C. Effect of a computerized insulin dose calculator on the process of glycemic control. *American Journal of Critical Care* 2012;**21**(2):106–15. [PUBMED: 22381987]

Horibe 2012 *{published data only}*
Horibe M, Nair BG, Yurina G, Neradilek MB, Rozet I. A novel computerized fading memory algorithm for glycemic control in postoperative surgical patients. *Anesthesia and Analgesia* 2012;**115**(3):580–7. [PUBMED: 22669346]

Jeanne 2012 *{published data only}*
Jeanne M, Clement C, De Jonckheere J, Logier R, Tavernier B. Variations of the analgesia nociception index during general anaesthesia for laparoscopic abdominal surgery. *Journal of Clinical Monitoring and Computing* 2012;**26**(4): 289–94. [PUBMED: 22454275]

Joerger 2012 *{published data only}*
Joerger M, Kraff S, Huitema AD, Feiss G, Moritz B, Schellens JH, et al. Evaluation of a pharmacology-driven dosing algorithm of 3-weekly paclitaxel using therapeutic drug monitoring: a pharmacokinetic-pharmacodynamic simulation study. *Clinical Pharmacokinetics* 2012;**51**(9): 607–17. [PUBMED: 22804749]

Kelly 2012 *{published data only}*
Kelly PJ, Kay-Lambkin FJ, Baker AL, Deane FP, Brooks AC, Mitchell A, et al. Study protocol: a randomized controlled trial of a computer-based depression and substance abuse intervention for people attending residential substance abuse treatment. *BMC Public Health* 2012;**12**:113. [PUBMED: 22325594]

Kim 2012 *{published data only}*
Kim S, Lee HW, Lee W, Um TH, Cho CR, Chun S, et al. New allele-specific real-time PCR system for warfarin dose genotyping equipped with an automatic interpretative function that allows rapid, accurate, and user-friendly reporting in clinical laboratories. *Thrombosis Research* 2012; **130**(1):104–9. [PUBMED: 21911247]

Magee 2012 *{published data only}*
Magee MC. Improving IV insulin administration in a community hospital. *Journal of Visualized Experiments* 2012;**64**:e3705. [PUBMED: 22710978]

Nieuwlaat 2011 *{published data only}*
Nieuwlaat R, Spyropoulos AC, Hubers L, Stehouwer A, Van Spall HG, Eikelboom JW, et al. Randomized comparison of the DAWN AC computer program and a simple manual nomogram for quality of warfarin dosing. 23rd Congress of the International Society on Thrombosis and Haemostasis. 2011; Vol. Proceedings of the 57th Annual SSC Meeting; 2011 Jul 23–28; Kyoto Japan;:302.

Nieuwlaat 2012 *{published data only}*
Nieuwlaat R, Hubers LM, Spyropoulos AC, Eikelboom JW, Connolly BJ, Van Spall HG, et al. Randomised comparison of a simple warfarin dosing algorithm versus a computerised anticoagulation management system for control of warfarin maintenance therapy. *Thrombosis and Haemostasis* 2012; **108**(6):1228–35. [PUBMED: 23015161]

Overgaard 2010 *{published data only}*
Overgaard K, Corell P, Madsen P, Rasmussen RS. Computer-aid improves oral anticoagulant therapy. Proceedings of the 19th European Stroke Conference; 2010 May 25-28; Barcelona, Spain. 2010.

Pielmeier 2012 *{published data only}*
Pielmeier U, Rousing ML, Andreassen S, Nielsen BS, Haure P. Decision support for optimized blood glucose control and nutrition in a neurotrauma intensive care unit: preliminary results of clinical advice and prediction accuracy of the Glucosafe system. *Journal of Clinical Monitoring and Computing* 2012;**26**(4):319–28. [PUBMED: 22581038]

Radhakrishnan 2012 *{published data only}*
Radhakrishnan A, Vido D, Tayur S, Akan M, Murali S. Genotype guided therapeutic dosing of warfarin in geriatric patients. *Journal of the American College of Cardiology* 2012; **59**(13 Suppl 1):E1696.

Rasmussen 2012 *{published data only}*
Rasmussen RS, Corell P, Madsen P, Overgaard K. Effects of computer-assisted oral anticoagulant therapy. *Thrombosis Journal* 2012;**10**(1):17. [PUBMED: 22935243]

Spaniel 2012 *{published data only}*
Spaniel F, Hrdlicka J, Novak T, Kozeny J, Hoschl C, Mohr P, et al. Effectiveness of the information technology-aided program of relapse prevention in schizophrenia (ITAREPS): a randomized, controlled, double-blind study. *Journal of Psychiatric Practice* 2012;**18**(4):269–80. [PUBMED: 22805901]

Tamblyn 2012 *{published data only}*
Tamblyn R, Eguale T, Buckeridge DL, Huang A, Hanley J, Reidel K, et al. The effectiveness of a new generation of computerized drug alerts in reducing the risk of injury from drug side effects: a cluster randomized trial. *Journal of the American Medical Informatics Association* 2012;**19**(4): 635–43. [PUBMED: 22246963]

Whitehead 2012 *{published data only}*
Whitehead J, Thygesen H, Jaki T, Davies S, Halford S, Turner H, et al. A novel phase I/IIa design for early phase oncology studies and its application in the evaluation of MK-0752 in pancreatic cancer. *Statistics in Medicine* 2012; **31**(18):1931–43. [PUBMED: 22495759]

Wiltshire 2012 *{published data only}*
Wiltshire HR, Kilpatrick GJ, Tilbrook GS, Borkett KM. A placebo- and midazolam-controlled phase I single ascending-dose study evaluating the safety, pharmacokinetics, and pharmacodynamics of remimazolam (CNS 7056): Part II. Population pharmacokinetic and pharmacodynamic modeling and simulation. *Anesthesia and Analgesia* 2012; **115**(2):284–96. [PUBMED: 22253270]

Additional references

Arditi 2012
Arditi C, Rège-Walther M, Wyatt JC, Durieux P, Burnand B. Computer-generated reminders delivered on paper to healthcare professionals; effects on professional practice and health care outcomes. *Cochrane Database of Systematic Reviews* 2012, Issue 12. [DOI: 10.1002/14651858.CD001175.pub3]

Baldwin 1995
Baldwin L. Calculating drug doses. *British Medical Journal* 1995;**310**(6988):1154.

Bates 2003
Bates DW, Kuperman GJ, Wang S, Gandhi T, Kittler A, Volk L, et al. Ten commandments for effective clinical decision support: making the practice of evidence-based medicine a reality. *Journal of the American Medical Informatics Association* 2003;**10**(6):523–30.

Brennan 1991
Brennan TA, Leape LL, Laird NM, Hebert L, Localio AR, Lawthers AG, et al. Incidence of adverse events and negligence in hospitalized patients. Results of the Harvard Medical Practice Study I. *New England Journal of Medicine* 1991;**324**(6):370–6.

Chatellier 1998
Chatellier G, Colombet I, Degoulet P. Computer-adjusted dosage of anticoagulant therapy improves the quality of anticoagulation. *Studies in Health Technology and Informatics* 1998;**52**(Pt 2):819–23.

CLINICIP
CLINICIP Project. CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients). www.clinicip.org (accessed 25 September 2013).

Deeks 2011
Deeks JJ, Higgins JPT, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Durieux 2005
Durieux P. Electronic medical alerts - so simple, so complex. *New England Journal of Medicine* 2005;**352**(10):1034–6.

EPOC 2009
EPOC. Risk of bias - EPOC specific. epoc.cochrane.org/sites/epoc.cochrane.org/files/uploads/Risk%20of%20Bias%2005-01-2009.doc (accessed 25 September 2013).

EPOC 2012
EPOC. What study designs should be included in an EPOC review and what should they be called?. epocoslo.cochrane.org/sites/epocoslo.cochrane.org/files/uploads/What%20study%20designs%20should%20be%20included%20in%20an%20EPOC%20reviews%20and%20what%20should%20they%20be%20called.pdf (accessed 25 September 2013).

Eslami 2009
Eslami S, Abu-Hanna A, de Jonge E, de Keizer NF. Tight glycemic control and computerized decision-support systems: a systematic review. *Intensive Care Medicine* 2009; **35**(9):1505–17.

Fitzmaurice 1998a
Fitzmaurice DA, Hobbs FD, Delaney BC, Wilson S, McManus R. Review of computerized decision support systems for oral anticoagulation management. *British Journal of Haematology* 1998;**102**(4):907–9.

Franke 2000
Franke L, Avery AJ, Groom L, Horsfield P. Is there a role for computerized decision support for drug dosing in general practice? A questionnaire survey. *Journal of Clinical Pharmacy and Therapeutics* 2000;**25**(5):373–7.

Garcia-Alamino 2010
Garcia-Alamino JM, Ward AM, Alonso-Coello P, Perera R, Bankhead C, Fitzmaurice D, et al. Self-monitoring and self-management of oral anticoagulation. *Cochrane Database of Systematic Reviews* 2010, Issue 4. [DOI: 10.1002/14651858.CD003839.pub2]

Garg 2005
Garg AX, Adhikari NK, McDonald H, Rosas-Arellano M, Devereaux PJ, Beyene J, et al. Effects of computerized clinical decision support systems on practitioner performance and patient outcomes: a systematic review. *JAMA* 2005;**293**(10):1223–38.

Guyatt 2008
Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *British Medical Journal* 2008;**336**(7650):924–6.

Guyatt 2011
Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, et al. GRADE guidelines: 7. Rating the quality of evidence - inconsistency. *Journal of Clinical Epidemiology* 2011;**64**:1294–302.

Higgins 2011
Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.

Hozo 2005
Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Medical Research Methodology* 2005;**5**:13.

Ioannidis 2007
Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *Canadian Medical Association Journal* 2007; **176**:1091–6.

Kawamoto 2005
Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. *British Medical Journal* 2005;**330**(7494): 765.

Kuperman 2003
Kuperman GJ, Gibson RF. Computer physician order entry: benets, costs, and issues. *Annals of Internal Medicine* 2003; **139**(1):31–9.

McDonald 1976a
McDonald CJ. Protocol-based computer reminders, the quality of care and the non-perfectability of man. *New England Journal of Medicine* 1976;**295**(24):1351–5.

Moher 2009
Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *PLOS Medicine* 2009;**6**:e1000097.

Mollon 2009
Mollon B, Chong J Jr, Holbrook AM, Sung M, Thabane L, Foster G. Features predicting the success of computerized decision support for prescribing: a systematic review of randomized controlled trials. *BMC Medical Informatics and Decision Making* 2009;**9**:11.

Moore 1984a
Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *American Journal of Medicine* 1984;**77**(4):657–62. [Moore 1984a]

Moore 1984b
Moore RD, Smith CR, Lietman PS. The association of aminoglycoside plasma levels with mortality in patients with gram-negative bacteremia. *Journal of Infectious Diseases* 1984;**149**(3):443–8. [Moore 1984b]

Moore 1987
Moore RD, Lietman PS, Smith CR. Clinical response to aminoglycoside therapy: importance of the ratio of peak concentration to minimal inhibitory concentration. *Journal of Infectious Diseases* 1987;**155**(1):93–9.

National Asthma 2002
National Asthma Education and Prevention Program. Expert Panel Report: guidelines for the diagnosis and management of asthma update on selected topics - 2002. *Journal of Allergy and Clinical Immunology* 2002;**110**(5 Suppl):S141–219.

Nieuwlaat 2011a
Nieuwlaat R, Connolly SJ, Mackay JA, Weise-Kelly L, Navarro T, Wilczynski N L, et al. Computerized clinical decision support systems for therapeutic drug monitoring and dosing: a decision-maker-researcher partnership systematic review. *Implementation Science* 2011;**6**:90.

Pearson 2009
Pearson SA, Moxey A, Robertson J, Hains I, Williamson M, Reeve J, et al. Do computerised clinical decision support systems for prescribing change practice? A systematic review of the literature (1990-2007). *BMC Health Services Research* 2009;**9**:154.

RevMan 2011 [Computer program]
The Nordic Cochrane Centre, The Cochrane Collaboration. Review Manager (RevMan). Version 5.1. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2012.

Robertson 2010
Robertson J, Walkom E, Pearson SA, Hains I, Williamsone M, Newby D. The impact of pharmacy computerised clinical decision support on prescribing, clinical and patient outcomes: a systematic review of the literature. *International Journal of Pharmacy Practice* 2010;**2**:69–87.

Rolfe 1995
Rolfe S, Harper NJ. Ability of hospital doctors to calculate drug doses. *British Medical Journal* 1995;**310**(6988): 1173–4.

Shojania 2009
Shojania KG, Jennings A, Mayhew A, Ramsay CR, Eccles MP, Grimshaw J. The effects of on-screen, point of care computer reminders on processes and outcomes of care. *Cochrane Database of Systematic Reviews* 2009, Issue 3. [DOI: 10.1002/14651858.CD001096.pub2]

Ukoumunne 1999
Ukoumunne OC, Gulliford MC, Chinn S, Sterne JA, Burney PG, Donner A. Methods in health service research. Evaluation of health interventions at area and organisation level. *British Medical Journal* 1999;**319**:376–9.

Yourman 2008
Yourman L, Concato J, Agostini JV. Use of computer decision support interventions to improve medication prescribing in older adults: a systematic review. *American Journal of Geriatric Pharmacotherapy* 2008;**6**(2):119–29.

References to other published versions of this review

Durieux 2008
Durieux P, Trinquart L, Colombet I, Nies J, Walton R, Rajeswaran A, et al. Computerized advice on drug dosage to improve prescribing practice. *Cochrane Database of Systematic Reviews* 2008, Issue 3. [DOI: 10.1002/14651858.CD002894.pub2]

Walton 2001
Walton R T, Harvey E, Dovey S, Freemantle N. Computerised advice on drug dosage to improve prescribing practice. *Cochrane Database of Systematic Reviews* 2001, Issue 1. [DOI: 10.1002/14651858.CD002894]

* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ageno 1998

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Episode of care Power calculation: Not reported
Participants	Profession: Mixed (physicians + nurses) Level of training: Accredited/licensed Clinical specialty: Other, anticoagulant clinic Country: Canada (Ontario) Centre: 1 general hospital (Hamilton General Hospital) Location of care: Outpatient care Participants: 101 outpatients on long-term oral anticoagulant therapy after mechanical heart valve replacement
Interventions	Clinical problem: Long-term warfarin therapy Intervention: Prediction rules, computer-assisted group (n = 50) vs. control group (n = 51) Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Proportion of doses adjustments (potential unit of analysis error) Serum concentrations and therapeutic range: None Physiological parameters: None (percentage of days in range with an INR of 2.5-3.5 according to the Duxburry method (reported as time spent in days per 100 patient-days of treatment), % of INRs > 5: reported, % of INRs < 2: reported, mean INR values: no dispersion data, % of INRs in range (2.3-3.7): not included, % of days in range (2.5-3.5): not included, % of days in range (2.3-3.7): not included) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	- The author confirm that none of the participants was included in both studies Ageno 1998 and Ageno 2000 - Therapeutic INR range: "Warfarin is administered with a therapeutic INR range of 2.5 to 3.5, according to the 1995 American College of Chest Physicians recommendations"

Risk of bias

Ageno 1998 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	"Consecutive patients who were discharged from the Hamilton General Hospital (Ontario, Canada) after mechanical heart valve replacement were randomized to be controlled by the computerized system or standard manual monitoring by trained personnel". No further information provided
Baseline outcome measurements similar	Low risk	No baseline measure of outcome
Baseline characteristics similar	Unclear risk	Participant randomization. "The two groups were similar with respect to age and gender." No further information provided Providers were 2 physicians and 3 registered nurses, all with several years of experience in the management of people on oral anticoagulants
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly specified in the paper
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Ageno 2000

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Other (dose, INR, participant) Power calculation: Not reported
Participants	Profession: Mixed (physicians + nurses) Level of training: Accredited/licensed

Ageno 2000 (*Continued*)

	Clinical specialty: General/family practice Country: Canada (Ontario) Centre: 1 general hospital (Hamilton General Hospital) Location of care: Inpatient care Participants: 101 participants who required oral anticoagulation (heart valve replacement, treatment of venous thromboembolism, atrial fibrillation, prophylaxis for deep vein thrombosis, acute myocardial infarction and vascular surgery)
Interventions	Clinical problem: Warfarin adjustment in hospitalized people Intervention: Computer-based control of oral anticoagulation (n = 50 participants) vs. standard manual dosing (n = 51 participants). The computerized induction treatment module (DAWN AC INDUCTION) calculated the daily dosage of warfarin based on algorithms that could be set at every centre according to the local clinical practice Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Proportion of doses adjustments (potential unit of analysis error) (daily dose of warfarin: no dispersion data) Serum concentrations and therapeutic range: None Physiological parameters: None (% of INRs > 5: reported, mean INR values: no dispersion data, % of participants with at least 1 INR > upper limit of therapeutic range: not included) Time to achieve therapeutic control: None Clinical events: Minor bleeding (major bleeding: not included) Healthcare costs: None Improvement: None
Notes	- There were different indications for oral anticoagulation: "heart valve replacement (n: 74), treatment of venous thromboembolism (n:16), atrial fibrillation (n:5), prophylaxis for deep vein thrombosis (n:4), acute myocardial infarction (n:1), and vascular surgery (n:1)" - The author confirm that none of the participants was included in both studies Ageno 1998 and Ageno 2000 - Therapeutic INR range: "Because of a higher risk of bleeding during the early days of treatment due to the presence of pacing wires which are usually removed between the fifth and seventh post operative day, the initial therapeutic INR for participants following heart valve replacement ranges between 1.5 to 2.6. After the wires are removed, the therapeutic INR is 2.5 to 3.5 for mechanical valves, and 2.0 to 3.0 for bioprosthetic valves. For all other indications, the therapeutic INR ranges between 2.0 and 3.0. In the algorithm set in the computer, we defined a low therapeutic regime for the first 5 days of treatment for all the participants following heart valve replacement"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Ageno 2000 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	"Consecutive patients who were hospitalized at the Hamilton General Hospital (Ontario, Canada) and who required oral anticoagulation were randomized to control by the computerized system or standard manual dosing until the seventh day of treatment or until discharge, whichever happened first". No further information provided
Baseline outcome measurements similar	Low risk	No baseline measure of outcome
Baseline characteristics similar	Low risk	Participant randomization. "The two groups were similar with respect to age (64. 6 manual group; 63.3 computer group), whereas the proportion of males was higher in the computer group (64%) than in the manual group (53%) [...] The proportion of participants following heart valve replacement was 78% in the computer group and 69% in the manual group.[...] The mean INR was 2.09 in the computer group, and 2.07 in the manual group" Providers were trained nurses or physicians (supposed to be the same providers at baseline and during intervention)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not clearly specified in the paper
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Outcomes included bleeding events. Minor and major bleeding events were not clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Anderson 2007

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Mixed (physicians + pharmacists) Level of training: Not reported Clinical specialty: Not reported Country: USA (Salt Lake City) Centre: 1 general urban hospital and surgical centre (LDS Hospital, Intermountain's outstanding heart network in the Salt Lake Valley) Location of care: Inpatient care Participants: 206 participants being initiated on oral anticoagulation. 200 participants analyzed
Interventions	Clinical problem: Warfarin initiation Intervention: Pharmacogenetic-guided dosing (n = 101) versus standard empirical dosing (n = 99). Pharmacogenetic-arm dosing was determined with a regression equation included CYP2C9 (*1, *2, *3) and VKORC1 (C1173T) genotypes, age, weight and sex. Standard dosing followed the 10-mg warfarin nomogram of Kovacs et al. Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Dose adjustments per participant Serum concentrations and therapeutic range: None Physiological parameters: Time (%) within therapeutic range (% of out-of-range INRs: not included, Number of INR measurements: not included, % participants reaching therapeutic INR on days 5 and 8: not included) Time to achieve therapeutic control: None (time to first supratherapeutic INR: not included) Clinical events: % participants with adverse events (clinical plus INR $\geq$ 4), % participants with serious adverse events (clinical only) Healthcare costs: None Improvement: None
Notes	- Therapeutic INR range: "Although the target INR range was 2 to 3, we prospectively defined an out-of-range INR value, for purposes of end-point analysis and for clinical dose adjustment, as 1.8 or 3.2 to allow for measurement error and to avoid problems inherent in overcorrection"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomization (in permuted blocks of 5) to the pharmacogenetic or standard arm"

Anderson 2007 (*Continued*)

Allocation concealment (selection bias)	Low risk	"The randomization arm assignment was blinded to patients and clinicians/investigators and known only to a designated research assistant and pharmacist"
Baseline outcome measurements similar	Low risk	Not applicable (initiation of warfarin therapy)
Baseline characteristics similar	High risk	"Clinical characteristics were balanced except for older age and greater prevalence of hypertension in pharmacogenetic patients. " The results on primary endpoint were unchanged by further adjustment for differences in age and hypertension
Incomplete outcome data (attrition bias) All outcomes	Low risk	No apparent missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective. "An independent Data and Safety Monitoring Committee tracked unblinded safety data. A separate independent Clinical Events Committee adjudicated key clinical adverse events blinded to study arm"
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomized. "The randomization arm assignment was blinded to patients and clinicians/investigators and known only to a designated research assistant and pharmacist"
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Anderson 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	- Same study as Anderson 2007

Asberg 2010

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Other (blood sample, participant) Power calculation: Not done "In this pilot study, the number of subjects needed to be included was empirically based"
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Nephrology Country: Norway (Oslo) Centre: 1 university hospital Location of care: Mixed (nephrology and standard clinical follow-up) Participants: 40 adult kidney transplant recipients on CsA, prednisolone and mycophenolate were included 2 weeks after transplantation (discharge from the surgical department) and followed for at least 8 weeks (standard clinical follow-up)
Interventions	Clinical problem: CsA in early post-transplant phase Intervention: Computer dosing of CsA doses (n = 20 participants) vs. standard practice (n = 20 participants). Individual CsA doses were calculated by a population pharmacokinetic model and suggested to the physician Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Indirect intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Daily CsA dose Serum concentrations and therapeutic range: None (% participants with a deviation from the targeted blood concentration > 50% on at least 1 occasion: not included) Physiological parameters: Glomerular filtration rate (renal function) (mL/min) (% of blood concentrations within the therapeutic window for an individual: reported, 2-hour plasma glucose (mmol/L): not included) Time to achieve therapeutic control: None Clinical events: Proportion of participants with cytomegalovirus infections Healthcare costs: None Improvement: Proportion of participants without biopsy-confirmed rejections
Notes	"The attending physician specified individual therapeutic C2 windows based on clinical evaluation of patient characteristics and risk factors. The standard protocol at our center is 900-1100 µg/L for the first month of transplant, followed by 700-900 µg/L up to month 3 in a normal risk patient; high-risk patients start with a therapeutic window of 1200-1600 µg/L followed by appropriate tapering"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified

Asberg 2010 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"A single center randomized prospective trial in adult kidney transplant recipients on CsA-based immunosuppression was performed." No further information provided
Baseline outcome measurements similar	Low risk	"There was no significant differences between the number of samples collected in the 2 groups (P=0.12) or in the percentage of C2 values obtained in each group (MAP-BE: 82%, CONTR: 78%, P=0.39)." No further information provided
Baseline characteristics similar	Unclear risk	Participant randomization. "There was no relevant demographic differences between groups" Providers were physicians (supposed to be the same providers at baseline and during intervention)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There was no significant differences between the number of samples collected in the 2 groups (P=0.12)"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Augstein 2007

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done. "Using a one-sided test at a 5% level of statistical significance, the trial was designed to have an 85% statistical power to detect a difference of 0.5% in change in A1C (A1C) from baseline to end of trial between the CGMS and CGMS/ KADIS group, with an assumed SD of 0.6"
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: General/family practice, diabetes specialty Country: Germany Centre: 5 outpatient centres (3 general and 2 diabetes specialist practices) Location of care: Outpatient care Participants: 49 insulin-treated outpatients. 46 subjects completed the study (3 subjects had incomplete first CGMS monitoring and were excluded)
Interventions	Clinical problem: Insulin in people with diabetes Intervention: CGMS + KADIS (n = 24 participants) vs. CGMS (n = 25 participants). CGMS provides information about glycaemic control by glucose readings every 5 min and was used as the source of glucose data. All participants were educated to use CGMS monitors and the CGMS data were downloaded and transferred to the centre (Institute of Diabetes) for analysis. Depending on the group to which the participant belonged, physicians received either CGMS data alone or CGMS data plus KADIS decision support report. KADIS is based on a mathematical model that describes the glucose/insulin metabolism in type 1 diabetes in the form of a coupled differential equation Computer advice: Not reported CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Insulin (IU/day) Serum concentrations and therapeutic range: None Physiological parameters: Mean sensor glucose (mmol/L), A1C (%) (duration of hypoglycaemic excursions (h/day): not included, duration of hyperglycaemic excursions (h/day): not included, Bread Exchange Unit: not included) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Augstein 2007 (*Continued*)

Random sequence generation (selection bias)	Low risk	"Patients with even random numbers, derived from a random number table, were assigned for the CGMS and patients with uneven random numbers for the CGMS/KADIS group"
Allocation concealment (selection bias)	Unclear risk	Random number table. No further information provided
Baseline outcome measurements similar	Low risk	"Both study groups included type 1 and type 2 diabetic subjects in equal proportions. There were no significant differences in age, sex, diabetes duration, BMI [body mass index], or insulin application between groups (Table 1)"
Baseline characteristics similar	Low risk	Participant randomization. "The two groups were similar with respect to age (64.6 manual group; 63.3 computer group), whereas the proportion of males was higher in the computer group (64%) than in the manual group (53%) [...] The proportion of participants following heart valve replacement was 78% in the computer group and 69% in the manual group.[...] The mean INR was 2.09 in the computer group, and 2.07 in the manual group" Providers were trained nurses or physicians (supposed to be the same providers at baseline and during intervention)
Incomplete outcome data (attrition bias) All outcomes	High risk	"Of the 49 subjects found eligible, 46 (24 in the CGMS and 22 in the CGMS/KADIS group) completed the study. Three subjects had incomplete first CGMS monitoring (one in the CGMS and two in the CGMS/KADIS group) and were excluded"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section

Augstein 2007 (*Continued*)

Other bias	Low risk	No evidence of other risk of biases

Begg 1989

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Not reported Country: New Zealand Centre: 1 general hospital (Christchurch Hospital) Location of care: Inpatient care Participants: 50 hospital inpatients (ICU excluded)
Interventions	Clinical problem: Aminoglycoside Intervention: Pharmacokinetic model, computer-assisted group (n = 24) vs. control group (n = 26) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Aminoglycoside (mg/day) Serum concentrations and therapeutic range: Aminoglycoside peak plasma concentration after 2 days (mg/L), % participants within drug therapeutic range (plasma peak concentrations of 6-10 mg/L and trough concentrations of 1-2 mg/L at 2 days), % participants with plasma peak concentrations of 6-10 mg/L at 2 days (peak concentration criterion alone) (peak concentrations after 5 days: not included, through concentrations: not included, number of dose alterations: not included) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: Death, nephrotoxicity (increase in creatinine clearance) Healthcare costs: None Improvement: None
Notes	"Patients in the intensive care unit were excluded, since they formed the basis of a similar study with a different control group being conducted concurrently" Hickling K, Begg E, Moore ML (1989): 32 adult patients in intensive care unit at Christchurch Hospital (New Zealand) who required gentamicin or tobramycin therapy for serious life threatening infections, other than those receiving haemodialysis for renal acute failure
Risk of bias	

Begg 1989 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated randomisation procedure"
Allocation concealment (selection bias)	Low risk	"Computer generated randomisation procedure"
Baseline outcome measurements similar	Low risk	No information provided
Baseline characteristics similar	Low risk	"There were no major differences between the groups in their demographic features (Table 1)"
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants randomized: 50 (24 in the computer-assisted group, 26 in the control group) Number of participants analyzed: 45 ("for the remaining patients aminoglycoside therapy was discontinued before analysis of plasma concentration"). Peak concentrations were available for 33 participants at 2 days, and 26 participants at 5 days. Trough concentrations were available for 32 participants at 2 days, and 26 participants at 5 days
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Blaha 2009

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported

Blaha 2009 (*Continued*)

Participants	Profession: Mixed (physicians + nurses) Level of training: Not reported Clinical specialty: Surgical ICU Country: Czech Republic (Prague) Centre: 1 university hospital (Charles University and General University Hospital) Location of care: Inpatient care Participants: 120 adults admitted to the postoperative ICU after elective cardiac surgery were randomly assigned into the Matias protocol based on the absolute glucose value (n = 40), the Bath protocol based on the relative glucose change (n = 40), or the computer-based model predictive control algorithm with variable sampling rate (eMPC) (n = 40)
Interventions	Clinical problem: Insulin in critically ill people (cardiac surgery patients) Intervention: Matias protocol based on the absolute glucose value (n = 40 participants) versus computer-based model predictive control algorithm with variable sampling rate (eMPC) (n = 40 participants). The eMPC is an enhanced version of the model predictive control algorithm (MPC), a model of the glucoregulatory system. Glucose concentration, insulin dosage, and carbohydrate content of enteral and parenteral input are the input variables for the eMPC. The insulin infusion rate and the time of the next glucose sample are the outputs. Group with the Bath protocol based on the relative glucose change (n = 40) was excluded since most of standard protocols use the absolute glucose value and this protocol had not been used in the Charles University and General University Hospital before the study Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: % of time within the target range for blood glucose during the study or the first 48 h (80-110 mg/dL or 4.4-6.1 mmol/L), mean blood glucose (mmol/L) Time to achieve therapeutic control: Time to target range (hours), mean sampling interval (hours) Clinical events: Proportion of participants with severe hypoglycaemic episodes (blood glucose level < 2.3 mmol/L) Healthcare costs: None Improvement: None
Notes	- "The target glucose range was 4.4 - 6.1 mmol/l, which has been demonstrated to reduce mortality and morbidity". "severe hypoglycemic episodes (blood glucose <2.3 mmol/l)" - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Risk of bias

Bias	Authors' judgement	Support for judgement

Blaha 2009 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	No significant differences on blood glucose at study start or number of participants with history of diabetes (Table 1)
Baseline characteristics similar	Low risk	No significant differences on baseline characteristics (Table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Because the duration of the ICU stay and the total monitoring time differed among patients, only data for up to 48 h were used for the comparison of the protocols. Forty-eight hours of ICU stay were accomplished in 109 of 120 patients included in the study"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Burton 1991

Methods	Design: RCT Unit of allocation: House staff team (a random number table was used to determine which of the house staff teams would be assigned to the intervention group. At the end of each 4 months, during the study, intervention groups were changed to control and vice versa to ensure equal allocation of participant types and infections to each group) Unit of analysis: Participant (cluster was not taken into account in the analysis) Power calculation: Not reported
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not reported Country: USA (Dallas) Centre: 1 Veterans Administration Medical Center (680-bed tertiary care - affiliated

Burton 1991 (*Continued*)

	institution) Location of care: Inpatient care Participants: 147 participants treated with aminoglycosides
Interventions	Clinical problem: Aminoglycoside Intervention: Dose advice based on Bayesian pharmacokinetic model (n = 72) vs. usual care (n = 75) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Beginning aminoglycoside dose (mg/day) , Ending aminoglycoside dose (mg/day) Serum concentrations and therapeutic range: Aminoglycoside peak serum concentration (mg/L), toxic drug level (% participants within peak concentration > 4 mg/L) (maximum trough concentration: not included, % participants within trough concentrations ≥ 2 mg/L: not included) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: Nephrotoxicity (rise in serum creatinine level of 0.5 mg/dL if the initial value was ≤ 1.5 mg/dL or a 30% rise in the serum creatinine value), death Healthcare costs: Length of stay Improvement: % of participants cured (afebrile for 4 consecutive days and without: recurrence of fever, leukocytosis, recurrence of infection, use of another effective antibiotic within 48 hours of stopping aminoglycoside)
Notes	"All initial and revised dosages in the intervention group were targeted to obtain peak and trough serum concentrations within the recognized therapeutic range of 5 to 10 mg/L for peak concentrations and less than 2 mg/L for through concentrations of gentamicin and tobramycin. The therapeutic range for amikacin was 20 to 30 mg/L for peak concentrations and less than 5 mg/L for through serum concentrations"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random number table to determine which 9 of the 17 house staff teams would be assigned as control groups"
Allocation concealment (selection bias)	Low risk	"Random number table to determine which 9 of the 17 house staff teams would be assigned as control groups"
Baseline outcome measurements similar	Low risk	No information provided

Burton 1991 (*Continued*)

Baseline characteristics similar	Low risk	"As shown in Table II, there were no significant differences in any of the patient characteristics between subjects in the control versus the intervention group." "In a similar manner, there were no significant differences in the clinical diagnosis between patients in each group (Table I)"
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants randomized: 147 (72 in intervention group and 75 in the control group) Number of participants analyzed: 136 for number of participants cured (68 in each groups), 143 for toxic drug levels (70 in intervention group and 73 in the control group) "Intervention patients were excluded from the study if recommended dosing was not implemented within 48 hours of the first dose of aminoglycoside"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective. Nephrotoxicity and % of participants cured were clearly defined in the methods section
Blinding of participants and personnel (performance bias) All outcomes	High risk	Teams were randomized in 1 site. At the end of each 4 months during the study, intervention groups were changed to control and vice versa
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of bias

Carter 1987

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Mixed (physicians + pharmacists) Level of training: Not reported Clinical specialty: Not reported Country: USA Centre: 1 Veterans Administration Medical Center Location of care: Inpatient care

Carter 1987 (*Continued*)

	Participants: 65 adult inpatients receiving warfarin sodium
Interventions	Clinical problem: Initiation of warfarin therapy Intervention: Pharmacokinetic concepts, analogue-computer program (n = 31) vs. empiric dosing (n = 34) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Indirect intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Warfarin stabilization dosage (mg/day) (for the 39 participants who achieved stable prothrombin ratios before discharge) Serum concentrations and therapeutic range: None Physiological parameters: None Time to achieve therapeutic control: Time to stabilization (for the 39 participants who achieved stable prothrombin ratios before discharge) Clinical events: None Healthcare costs: None Improvement: None
Notes	"A prothrombin time (PT) ratio (patient PT divided by control PT) between 1,3 and 2, 5 was considered to be in therapeutic range"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"The patients were randomly assigned to one of the three groups for warfarin dosage prediction". No further information provided
Allocation concealment (selection bias)	Unclear risk	"The patients were randomly assigned to one of the three groups for warfarin dosage prediction". No further information provided
Baseline outcome measurements similar	Low risk	Not applicable (initiation of warfarin therapy)
Baseline characteristics similar	High risk	Demographic data only available for the subgroup of participants who achieved stable prothrombin ratios before discharge (54/101 participants)
Incomplete outcome data (attrition bias) All outcomes	High risk	Number of participants randomized: 101 Number of participants analyzed: 87 (31 in the analogue-computer group, 22 in the

Carter 1987 (*Continued*)

		linear-regression group, 34 in the empiric-dosing group) "Fourteen randomized patients (3 analog computer, 7 linear regression, 4 empiric dosing) were removed from the study because they did not receive an initial warfarin dosage of 10 mg for three days or because the drug was discontinued before day 5" "33 patients were discharged before they met the stated criteria for a stable PT [prothrombin]"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Casner 1993

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not done
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Not reported Country: USA (El Paso, Texas) Centre: 1 general hospital Location of care: Inpatient care Participants: 35 participants with diagnoses of asthma or obstructive pulmonary disease
Interventions	Clinical problem: Theophylline maintenance for asthma Intervention: Suggestion based on linear 1 compartment model (n = 17) vs. usual care (n = 18) Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported

Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: Serum theophylline (mg/L) (at the 3rd level (C3) after adjustment and prior to discontinuation of infusion) Physiological parameters: None (PH and partial pressure of carbon dioxide (PCO_2) measurements: not included) Time to achieve therapeutic control: None Clinical events: Proportion of participants with theophylline toxicity (nausea, vomiting, tremor, tachycardia and seizures) Healthcare costs: Length of stay Improvement: None
Notes	"Physicians adjusting theophylline infusions were instructed to attain a therapeutic goal of 15mg/L theophylline level and to base this empirically on the C1 and C2 levels that had been obtained"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Each patient was randomized to one of two groups as determined by a computer-derived randomization list"
Allocation concealment (selection bias)	Low risk	"Each patient was randomized to one of two groups as determined by a computer-derived randomization list"
Baseline outcome measurements similar	Low risk	Not appropriate (theophylline maintenance for asthma)
Baseline characteristics similar	Low risk	"There were no significant differences between the kinetic group in age or height, although there was a significant difference in actual body weight (85.5 versus 69.0 kg; p<0.05), but the ideal weights of both groups was not significantly different (55.7 versus 54.1 kg). Theophilline infusion doses were based on ideal body weight" Table 1: 54.7 versus 54.1 kg
Incomplete outcome data (attrition bias) All outcomes	High risk	"Twelve patients were withdrawn from study because of incomplete data collection (i.e., either C1, C2, or C3 was missing or inadequate time interval between levels), which left 35 patients for analysis"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective. Theophylline toxicity was defined

Casner 1993 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Chertow 2001

Methods	Design: NRCT (alternating time series design with 4 consecutive 2-month period) Unit of allocation: Participant Unit of analysis: Episode of care Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Other mixed Country: USA (Boston, Massachusetts) Centre: 1 urban tertiary care academic medical centre (Brigham and Women's Hospital, 720 beds) Location of care: Inpatient care Participants: 17,828 inpatients with renal insufficiency
Interventions	Clinical problem: Renal insufficiency Intervention: CDSS periods (n = 7887 participants) vs. control periods (n = 9941 participants) Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: Proportion of appropriate orders (potential unit of analysis error) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None Healthcare costs: Length of stay Improvement: None
Notes	"The BICS order entry application provides the physician with a range of possible dose amounts for that medication (dose list) along with 1 dose that is highlighted as the default or recommended dose amount." "An expert panel [...] selected those medications that were renally cleared and/or nephrotoxic" "To smooth dose recommendations, renal insufficiency was divided into 3 categories: mild (estimated creatinine clearance, 50-80

	mL/min [0,84-1,34 mL/s]), moderate (estimated creatinine clearance, 16-49 mL/min [0,27-0,82 mL/s]), and advanced (estimated creatinine clearance, d15 mL/min [d0,25 mL/s])" "A selection was considered appropriate if the dose amount or frequency interval did not exceed the parameters set forth by the expert panel"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"The study periods consisted of 4 alternating 8-week blocks of intervention and control subperiods"
Allocation concealment (selection bias)	High risk	"The study periods consisted of 4 alternating 8-week blocks of intervention and control subperiods"
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Unclear risk	Mean age of participants and sex "were not significantly different across periods". The mean Diagnosis Related Group (DRG) weight "was higher during control periods" "The number of admissions and the hospital census were higher during the control periods"
Incomplete outcome data (attrition bias) All outcomes	Low risk	A log was kept of all instances
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Alternating 8-week blocks of intervention and control subperiods
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Unclear risk	"The Cockcroft-Gault formula may overestimate renal function when the serum creatinine is increasing, and underestimate renal function when the serum creatinine is decreasing"

Claes 2005

Methods	Design: RCT Unit of allocation: GP practice Unit of analysis: Participant (cluster was taken into account in statistical analysis) Power calculation: Done
Participants	Profession: Mixed (GP + pathologists) Level of training: Accredited/licensed Clinical specialty: General/family practice + laboratory medicine Country: Belgium Centre: 96 GPs regrouped in 66 GP practices, for whom the clinical laboratory of the Medical Centre for GPs in Tessenderlo determined the INRs on venous blood Location of care: Community-based care Participants: 834 participants on oral anticoagulation were included (out of 936 participants eligible). 91 participants who underwent a surgical intervention with an interruption of the anticoagulation during the study period were excluded from the analysis
Interventions	Clinical problem: Oral anticoagulation therapy at steady state (anticoagulation therapy for at least 28 days) Intervention: Multifaceted education and DAWN AC computer advice (n = 15 GP practices, n = 201 participants) vs. multifaceted education (n = 17 GP practices, n = 170 participants). The Grol's multifaceted education: summary of the guidelines printed on the cover of a folder containing the anticoagulation files; information booklets on anticoagulation for their patients; website with guidelines, study design, and general information; newsletter sent every 2 months to inform the GPs on the study progress and requested them to send the anticoagulation files for control Computer advice: Not reported (the pathologist reviewed the computer-generated advice and faxed it the same afternoon to the GP) CDSS integration in CPOE: No (advice faxed) Starter: User-initiated Type of intervention: Indirect intervention (the pathologist reviewed the computer-generated advice and faxed it to the GP) Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None (% of participants with treatment changes: reported, median number of tests per participant and per month: reported) Serum concentrations and therapeutic range: None Physiological parameters: None (mean % of time in range (0.5 INT-units from target) : reported, mean % of time in range (0.75 INT-units from target): not included, % of participants with at least 1 INR > 5: reported, % of participants with at least 1 INR < 2: reported) Time to achieve therapeutic control: None Clinical events: Number of bleeding events (minor + major) per patient-years, number of thromboembolic events per patient-years Healthcare costs: See Claes 2006 Improvement: None
Notes	- The practices were randomized into 4 groups: multifaceted education (group A), multifaceted education + feedback on the performance of the practice (group B), multifaceted education + a CoaguChek device to determine the INR on the spot using capillary blood (group C), multifaceted education + DAWN

	AC computer advice that generated a recommended dosing scheme and the time to next visit (group D). Only groups A and D were retained for the review - The target range were defined as within 0.5 INR-units and 0.75 INR-units from the chosen target INR of 2.5 or 3.5

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"The 66 GP-practices were divided into four different groups using a stratified block randomization. Six different strata of GP-practices were defined depending on the number of anticoagulated patients (5 patients, 6-14 patients, 15 patients) and the type of practice (single-handed GP or group practice). These six strata (numbered containers with cards) were divided blindly over the four intervention groups by a university staff member as follows: out of the first container a card was drawn and placed in box A, the next card in box B, C, D, A, B, etc. The same procedure was followed for the other five boxes"
Allocation concealment (selection bias)	Low risk	Unit of allocation: GP practice
Baseline outcome measurements similar	Low risk	"The 6 months retrospective analysis showed that the patients of the practices assigned to groups A, B, C, and D were 55, 49, 46, and 44% of time within 0.5 INR-units from target, respectively. There was no significant difference among the four groups in the per cent within 0.5 INR-units from target (P = 0.50) or within 0.75 INR-units from target (P = 0.70)"
Baseline characteristics similar	High risk	Baseline characteristics were not reported for GP practices, GPs or participants. Number of participants per group were not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants per group were not provided
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective

Claes 2005 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Low risk	GP practices were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Claes 2006

Methods	Design: RCT Unit of allocation: GP practice Unit of analysis: Participant (cluster was taken into account in statistical analysis) Power calculation: Done
Participants	Profession: Mixed (GP + pathologists) Level of training: Accredited/licensed Clinical specialty: General/family practice + laboratory medicine Country: Belgium Centre: 96 GPs regrouped in 66 GP practices, for whom the clinical laboratory of the Medical Centre for GPs in Tessenderlo determined the INRs on venous blood Location of care: Community-based care Participants: 834 participants on oral anticoagulation were included (out of 936 participants eligible). 91 participants who underwent a surgical intervention with an interruption of the anticoagulation during the study period were excluded from the analysis
Interventions	Clinical problem: Oral anticoagulation therapy at steady state (anticoagulation therapy for at least 28 days) Intervention: Multifaceted education and DAWN AC computer advice (n = 15 GP practices, n = 201 participants) vs. multifaceted education (n = 17 GP practices, n = 170 participants). The Grol's multifaceted education: summary of the guidelines printed on the cover of a folder containing the anticoagulation files; information booklets on anticoagulation for their participants; website with guidelines, study design, and general information; newsletter sent every 2 months to inform the GPs on the study progress and request them to send the anticoagulation files for checking Computer advice: Not reported (The pathologist reviewed the computer-generated advice and faxed it the same afternoon to the GP) CDSS integration in CPOE: No (advice faxed) Starter: User-initiated Type of intervention: Indirect intervention (the pathologist reviewed the computer-generated advice and faxed it to the GP) Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: See Claes 2005 Serum concentrations and therapeutic range: See Claes 2005 Physiological parameters: See Claes 2005 Time to achieve therapeutic control: See Claes 2005 Clinical events: See Claes 2005

Claes 2006 (*Continued*)

	Healthcare costs: None ((monthly cost per participant (in EUR): reported, incremental cost-effectiveness ratio (ICER): reported) Improvement: See Claes 2005
Notes	- This is a cost-effectiveness analysis conducted as a part of the Belgian Improvement Study on Oral Anticoagulation Therapy (BISOAT) study reported by Claes et al. (see Claes 2005)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The 66 GP-practices were divided into four different groups using a stratified block randomization. Six different strata of GP-practices were defined depending on the number of anticoagulated patients (5 patients, 6-14 patients, 15 patients) and the type of practice (single-handed GP or group practice). These six strata (numbered containers with cards) were divided blindly over the four intervention groups by a university staff member as follows: out of the first container a card was drawn and placed in box A, the next card in box B, C, D, A, B, etc. The same procedure was followed for the other five boxes"
Allocation concealment (selection bias)	Low risk	Unit of allocation: GP practice
Baseline outcome measurements similar	Low risk	"The 6 months retrospective analysis showed that the patients of the practices assigned to groups A, B, C, and D were 55, 49, 46, and 44% of time within 0.5 INR-units from target, respectively. There was no significant difference among the four groups in the per cent within 0.5 INR-units from target (P = 0.50) or within 0.75 INR-units from target (P = 0.70)"
Baseline characteristics similar	High risk	Baseline characteristics were not reported for GP practices, GPs or participants. Number of participants per group were not provided
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Number of participants per group were not provided

Claes 2006 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	Low risk	GP practices were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Cordingley 2009

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Nurses Level of training: Not reported Clinical specialty: ICU Country: UK (London), Belgium (Leuven) Centre: 1 large specialist heart and lung hospital affiliated with the university and NHS Foundation Trust (Royal Brompton Hospital (RBH)), 1 university hospital (University Hospital Gasthuisberg (KUL)) Location of care: Inpatient care Participants: 34 critically ill patients admitted to ICU with hyperglycaemia (glucose > 120 mg/dL)
Interventions	Clinical problem: Insulin in critically ill patients with hyperglycaemia Intervention: eMPC algorithm (n = 16 participants) vs. standard care (n = 18 participants) . The eMPC algorithm calculates the time of the next glucose sample and the optimum insulin infusion rate expected to achieve the target glucose concentration Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: % of time in target glucose range (hyperglycaemia index (area of the glucose-time concentration curve above 110 mg/dL (6.1 mmol/L) divided by the time of the study): not included (data differed between text, table 3, table 4 and table 5 and the author had not replied by January 2012), blood glucose: not included (sample mean), time-weighted mean glucose concentration (mg/dL) (area under the glucose-

	time curve for each participant divided by the elapsed time): not included) Time to achieve therapeutic control: Time to establish glucose control (T_{target}) (time from study entry until the plasma glucose concentration was in the target range of 80-110 mg/dL (4.4-6.1 mmol/L)) (minutes), mean sampling interval (hours) Clinical events: Proportion of participants with plasma glucose concentrations < 60 mg/dL, proportion of participants with plasma glucose concentrations < 40 mg/dL Healthcare costs: None Improvement: None
Notes	- "At KUL nursing staff (each taking care of 2 patients) aimed to maintain plasma glucose in the range 80-110 mg/dL (4.4-6.1 mmol/L) using a paper-based guideline that allows intuitive decisions to be taken. At RBH, nurses (each taking care of 1 patient) used a written dynamic insulin infusion protocol targeting a plasma glucose concentration of 72-108 mg/dL (4-6 mmol/L)" - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients entered into the trial were randomized [...]". No further information provided
Allocation concealment (selection bias)	Unclear risk	"Patients entered into the trial were randomized [...]". No further information provided
Baseline outcome measurements similar	Low risk	"Glucose concentration at study entry was similar in both groups (Table 3)"
Baseline characteristics similar	Low risk	No significant differences on main characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	18 participants vs 16 participants. No apparent missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section

Other bias	High risk	An erratum had been published because there were some inconsistencies in the text and tables; we found other inconsistencies in tables, full text, and abstract; the author was contacted (had not replied by January 2012).

Destache 1990

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Mixed (physicians + clinical pharmacists) Level of training: Mixed Clinical specialty: Internal medicine, surgery ICU Country: USA (Omaha, Nebraska) Centre: 1 tertiary care facility (Saint Joseph Hospital) Location of care: Inpatient care Participants: 145 participants treated with aminoglycosides for infection
Interventions	Clinical problem: Aminoglycoside Intervention: Participants whose doctors accepted recommendations based on a 1 compartment Bayesian pharmacokinetic model (n = 75) vs. those of doctors who did not (n = 70) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Indirect intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Number of doses adjustments (potential unit of analysis error) (number of serum aminoglycoside concentrations drawn/participant: not included) Serum concentrations and therapeutic range: proportion of participants with first peak aminoglycoside serum concentrations “adequate” 0.5 h after infusion Physiological parameters: None Time to achieve therapeutic control: None (time for elevated temperature to decrease to < 99.8 °F (37.7 °C): not included, time for elevated heart rate to decrease to < 90 beats/min: not included, time for respiratory rate to decrease to < 24/min: not included) Clinical events: Death, nephrotoxicity (≥ 0.5 mg/dL rise in serum creatinine) Healthcare costs: Length of hospital stay (h), direct cost per participant (USD) Improvement: None
Notes	“First peak concentrations were categorized as ”adequate“ (>=5.0 mcg/ml and >=20.0 mcg/ml for amikacin [an aminoglycoside]), ”low“ (<5.0 mcg/ml and <20.0 mcg/ml for amikacin), or not drawn”

Destache 1990 (*Continued*)

	"The target trough therapeutic ranges are concentrations of <2.0 mcg/ml for gentamicin and tobramycin and 5-10 mcg/ml for amikacin"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization assignments were determined by a table of random numbers"
Allocation concealment (selection bias)	Low risk	"Assignments were individually placed in sealed envelopes"
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Low risk	No significant differences except for weight (table 3)
Incomplete outcome data (attrition bias) All outcomes	High risk	Many participants excluded from analysis: 20 of the 90 participants from the control group (monitored by other clinical pharmacists), 35 of the 110 participants from the computer advice group (recommendations were not always followed)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective. Nephrotoxicity was clearly defined in the methods section
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Fitzmaurice 2000

Methods	Design: RCT Unit of allocation: Primary care practice and participant (2 control populations: participants individually randomized as controls in the intervention practices and all participants in the control practices, which allow an estimate of the Hawthorn effect) Unit of analysis: Participant, INR (cluster was taken into account in statistical analysis) Power calculation: Done

Fitzmaurice 2000 (*Continued*)

Participants	Profession: Mixed (physicians + nurses) Level of training: Not reported Clinical specialty: General/family practice Country: UK (Birmingham) Centre: 12 practices Location of care: Community-based care Participants: 224 outpatients with cardiovascular disease
Interventions	Clinical problem: Warfarin adjustment for long-term therapy Intervention: CDSS group (n = 122) vs. routine care (n = 102) Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: Proportion of INR measurements within therapeutic range (unit of analysis error) Time to achieve therapeutic control: None Clinical events: Death, number of haemorrhagic events (epistaxis) per patient-years, number of thrombotic events per patient-years Healthcare costs: None Improvement: None
Notes	There were 2 levels of randomization. Practices were randomly tagged as intervention or control practices. Then, in intervention practices, participants were individually randomized to intervention or control. We did not analyze 'control practices' because of a potential unit of analysis error "Dosing recommendations made by the CDSS were based on the current INR in relation to individual therapeutic range, based on the British Society of Haematology guidelines, with the 2 main ranges being 2.0 to 3.0 and 3.0 to 4.5"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Practices were randomly selected by means of random numbers from a list of 21 practices that had expressed interest in the study
Allocation concealment (selection bias)	Low risk	Practices were randomly selected by means of random numbers from a list of 21 practices that had expressed interest in the study
Baseline outcome measurements similar	Low risk	Not appropriate

Fitzmaurice 2000 (*Continued*)

Baseline characteristics similar	Low risk	No apparent differences (table 2)
Incomplete outcome data (attrition bias) All outcomes	High risk	224 participants were recruited. 40 participants discontinued the study before 12 months, including 11 participants randomized to intervention who returned to hospital care Only participants with 3 or more INR results (n = 202) were included in the analysis of proportion of time spent in the target INR range
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcomes were objective. Monitoring for haemorrhagic and thrombotic events is not clearly defined
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Practices were randomized and participants individually randomized as controls in the intervention practices (intrapractice controls) and all participants in the control practices (interpractice controls)
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Gonzalez 1989

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not done
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Not reported Country: USA (Virginia, Richmond) Centre: 1 emergency department (Medical College of Virginia) Location of care: Inpatient care Participants: 82 participants with asthma treated with aminophylline
Interventions	Clinical problem: Theophylline Intervention: Bayesian 1 compartment pharmacokinetic model (n = 37) vs. population-based guidelines (n = 30) Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated

Gonzalez 1989 (*Continued*)

	Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Theophylline loading dose (mg/kg), theophylline maintenance dose (mg/kg/h) Serum concentrations and therapeutic range: Theophylline concentration (4 hours post load) (mg/L) (theophylline concentration at 1 and 2 hours post load: not included) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: Proportion of participants with adverse reactions (including nausea and vomiting) Healthcare costs: None Improvement: None
Notes	"Patients in group 1 received an IV bolus of aminophylline to achieve a serum theophylline concentration of 10 to 20 mg/L" "Patients in group 2 received and IV aminophylline bolus followed by a maintenance infusion to achieve a serum theophylline concentration of 15 mg/L"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"A random-numbers table was used to preassign 82 patients to either group 1 or group 2"
Allocation concealment (selection bias)	Low risk	"A random-numbers table was used to preassign 82 patients to either group 1 or group 2"
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Unclear risk	No apparent differences on patient demographics (table 2). No further information provided
Incomplete outcome data (attrition bias) All outcomes	High risk	"Fifteen patients were excluded because of protocol violations (three left the ED against medical advice; 12 had insufficient blood level data)"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcomes were objective. Adverse events are not clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized

Gonzalez 1989 (*Continued*)

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Hickling 1989

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Not reported Level of training: Not reported Clinical specialty: Other (intensive care) Country: New Zealand Centre: 1 general hospital (Christchurch Hospital) Location of care: Inpatient care Participants: 32 ICU patients who required aminoglycoside therapy for serious life threatening infections
Interventions	Clinical problem: aminoglycoside (gentamicin or tobramycin) Intervention: Pharmacokinetic model, computer-assisted group (n = 15) vs. control group (n = 17) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: Aminoglycoside mean peak concentration at 48-72 h, % participants within drug therapeutic range after 2 days (peak plasma concentrations 6-10 mg/L measured 1 h after the start of the infusion, and peak trough concentrations 1-2 mg/L within 30 min of the next dose), % participants achieving peak plasma concentrations at 48-72 h > 6 mg/L (peak concentration criterion alone) (proportion of participants achieving peak plasma concentrations at 48-72 h > 5 mg/L: not included, proportion of participants achieving peak plasma concentrations at 48-72 h > 7 mg/L: not included) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	"The program was designed to predict the dose and dose interval required to achieve any desired peak and trough concentration. For the purpose of the study the specific target concentrations were a peak of 8 mg/l and a trough of 1.5 mg/l"

Hickling 1989 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was carried out by computer using a random number generator"
Allocation concealment (selection bias)	Low risk	"Randomisation was carried out by computer using a random number generator"
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants (out of 32) were excluded because a dose change was made on clinical grounds before the 4th dose of aminoglycoside
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Hovorka 2007

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Other (Department of Cardiovascular Surgery) Country: Czech Republic (Prague) Centre: 1 university hospital (Charles University and General University Hospital) Location of care: Inpatient care Participants: 60 adults admitted for major elective cardiac surgery

Hovorka 2007 (*Continued*)

Interventions	Clinical problem: Insulin in critically ill patients (cardiac surgery patients) Intervention: Laptop-based algorithm eMPC (n = 30 participants) vs. standard protocol treatment (n = 30 participants). The eMPC is an enhanced version of the model predictive control algorithm (MPC), a model of the glucoregulatory system. Glucose concentration, insulin dosage, and carbohydrate content of enteral and parenteral input are the input variables for the eMPC. The insulin infusion rate and the time of the next glucose sample are the outputs Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Total Insulin dose (insulin units/24 h) Serum concentrations and therapeutic range: None Physiological parameters: % of time within the target range for blood glucose in the first 24 h (80-110 mg/dL or 4.4-6.1 mmol/L), blood glucose levels at ICU (mmol/L) (blood glucose levels at operating theatre: not included, time (h) above the target range for blood glucose in the first 24 h (>110 mg/dL): not included, time (h) under the target range for blood glucose in the first 24 h (>110 mg/dL): not included) Time to achieve therapeutic control: Mean sampling interval (hours) Clinical events: Proportion of participants with hypoglycaemic episodes (blood glucose level < 2.9 mmol/L) Healthcare costs: None Improvement: None
Notes	- "The target range for blood glucose levels, as defined by the study protocol, was 4.4-6.1 mmol/liter, which has reduced mortality and morbidity in post-cardiac surgery patients. " "Severe hypoglycemia was defined as blood glucose less than 2.9 mmol/liter" - The authors were contacted and confirmed that none of the participants from Kremen 2007 was included in Hovorka 2007 - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	No significant differences on blood glucose at study start or number of participants treated with diabetes before study start (table 1)

Hovorka 2007 (*Continued*)

Baseline characteristics similar	Low risk	No significant differences on baseline characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The number of glucose values used for calculation varied in each hour (figure 2) but the blood glucose was measured in 1- to 4-h intervals as requested by each algorithm during surgery and postoperatively over 24 h
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Hurley 1986

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Other (emergency) Country: Australia (Victoria) Centre: 1 community hospital (Preston and Northcote Community Hospital (PANCH)) Location of care: Inpatient care Participants: 91 participants admitted to hospital with asthma
Interventions	Clinical problem: Theophylline Intervention: Doctors given estimate of theophylline clearance based on 1 compartment linear pharmacokinetic model (n = 48) vs. usual care based on theophylline levels (n = 43). Computer gave advice on dose each day based on estimates of theophylline clearance Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Not reported

Hurley 1986 (*Continued*)

Outcomes	Dose of drug administered to the participant: Initial and maintenance daily dose of theophylline (mg/day) Serum concentrations and therapeutic range: serum concentration at day 2 (μg/mL), proportions of participants with serum trough concentrations in the therapeutic range, proportions of participants with serum concentrations in the toxic range Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None Healthcare costs: Death, length of stay Improvement: None
Notes	"Ideally theophylline serum concentrations should be within a relatively narrow therapeutic range of 10 to 20 µg/ml"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Low risk	No apparent differences (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	96 participants enrolled, 91 participants analyzed (1 participant because of intolerance to aminophylline, 1 because of lack of cooperation, 3 because of previous enrolment in the trial) Loading doses were available for 72 participants, infusion rate at day 1 for 91 participants, infusion rate at day 2 for 74 participants. Missing values were equally distributed and unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized

Hurley 1986 (*Continued*)

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Jowett 2009

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: INR Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not reported Country: Europe, Israel, Australia Centre: 32 centres in 13 countries (Europe: 29, Israel: 2, Australia: 1) Location of care: Outpatient care Participants: 13,219 anticoagulation patients randomized at each centre into manual-dosed or computer-assistant dosed arm (DAWN AC or PARMA 5). 13,052 participants analyzed (167 participants without INR results): 2631 for the DAWN AC study and 10,421 for the PARMA 5 study
Interventions	Clinical problem: Oral anticoagulation (warfarin, nicoumalone (acenocoumarol), phenprocoumon) Intervention: Computer-assisted dosage program (PARMA5 (n = 5290 participants)) versus manual dosage (n = 5131 participants). Computer-assisted dosage program (DAWN AC (n = 1315 participants)) versus Manual dosage (n = 1316 participants). Recruitment was restricted to new patients initiated oral anticoagulation. 2 subroutines: induction and steady-state monitoring; the aim of the dosage algorithm was to maintain the INR value as close as possible to the mean target INR and to provide the next appointment date Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Not reported Calculated dose given as a recommendation: No
Outcomes	Dose of drug administered to the participant: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC Serum concentrations and therapeutic range: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC Physiological parameters: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC Time to achieve therapeutic control: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC Clinical events: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC Healthcare costs: None (total cost per participant (Euros, base 2006) for all INR visits during the time period of the study (4.5 years) (dosing cost (staff time and the software

	for computer dosing), clinical event cost): reported) Improvement: See Poller 2008 PARMA 5 and Poller 2009 DAWN AC
Notes	- This is a cost-effectiveness analysis conducted as a part of the European Action on Anticoagulation's (EEA) randomized multicentre study of computer-assisted oral anticoagulant dosage vs. manual dosing reported by Poller et al (see Poller 2008 PARMA 5 and Poller 2009 DAWN AC) - Costs were available for 28/32 clinics. There was no distinct results for PARMA 5 and DAWN AC systems

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics of the 13,052 participants (see table 1 of Poller 2008 PARMA 5 and Poller 2009 DAWN AC)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Both cost and outcome data were available for 6218/6447 in manual-dosed group and 6366/6605 in computer-assisted dosage group
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Events were adjudicated by a committee
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Kremen 2007

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Other (Department of Cardiovascular Surgery ICU) Country: Czech Republic (Prague) Centre: 1 university hospital (Charles University and General University Hospital) Location of care: Inpatient care Participants: 20 adults who underwent a planned-cardiac surgery (coronary artery bypass or valve replacement) with glycaemia higher than 6.7 mmol/L at the time of admission to ICU
Interventions	Clinical problem: Insulin in critically ill patients (cardiac surgery patients) with hyperglycaemia Intervention: Laptop-based algorithm MPC (n = 10 participants) vs. routine blood glucose management protocol (n = 10 participants). The MPC is a model representing the glucoregulatory system. Glucose concentration, insulin dosage, and carbohydrate intake are the input variables for the MPC. The insulin infusion rate is the output parameter and was adjusted hourly as suggested by the algorithm Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Total Insulin dose (insulin units/48 h) Serum concentrations and therapeutic range: None Physiological parameters: Mean blood glucose (mmol/L) (Time (h) within the target range for blood glucose in the first 24 h (80-110 mg/dL or 4.4-6.1 mmol/L): reported, duration of hyperglycaemia (> 8.3 mmol/L) (h): not included) Time to achieve therapeutic control: Time to establish glucose control (T_{target}) (time from study entry until the plasma glucose concentration was in the target range of 80-110 mg/dL (4.4-6.1 mmol/L)) (min), time to target range (hours) Clinical events: Proportion of participants with hypoglycaemic episodes (blood glucose level < 2.9 mmol/L) Healthcare costs: None Improvement: None
Notes	- "The target range for blood glucose levels, as defined by the study protocol, was 4.4-6.1 mmol/liter, which has reduced mortality and morbidity in post-cardiac surgery patients. " "Severe hypoglycemia was defined as blood glucose less than 2.9 mmol/liter" - The authors were contacted and confirmed that none of the participants from Kremen 2007 was included in Hovorka 2007 - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Kremen 2007 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	No significant differences on blood glucose at study start (table 2)
Baseline characteristics similar	High risk	5 men/5 women in MPC group, 9 men/1 women in standard group (table 2)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The blood glucose was measured in 1- to 2-h intervals as requested by each algorithm during surgery and postoperatively over 48 h
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Unclear risk	Pilot study. Outcomes were not defined in the methods section
Other bias	Unclear risk	Pilot study with 10 participants in each groups. Article in Czech language. Authors were contacted but had not replied by February 2012

Le Meur 2007

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Nephrology Country: France Centre: 11 centres

Le Meur 2007 (*Continued*)

	Location of care: Inpatient care Participants: 137 renal allograft recipients receiving basiliximab, CsA, MMF and corticosteroids. 130 participants analyzed
Interventions	Clinical problem: MMF dosing in renal transplant patients Intervention: Concentration-controlled (CC) regimen (n = 65 participants) vs. fixed-dose (FD) MMF (n = 65 participants). In the CC group, MMF dose adjustments were calculated by a computer program to reach an MPA AUC target of 40 mg.h/L and were proposed to the physician. In the FD group, MMF dose adjustments were based on clinical experience Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None (MMF dose: not included (fixed dose in control group)) Serum concentrations and therapeutic range: None (serum creatinine level (μmol/L): not included) Physiological parameters: None (% participants within therapeutic range at day 14 (MPA AUC > 30 mg.h/L): reported) Time to achieve therapeutic control: None Clinical events: Death, proportion of participants with cytomegalovirus infections, proportion of participants with adverse events (anaemia, leukopenia, gastrointestinal adverse effects, infections) Healthcare costs: None Improvement: Proportion of participants without treatment failure (a composite of death, graft loss, acute rejection and MMF discontinuation), proportion of participants without biopsy-confirmed rejections
Notes	Primary outcome: Treatment failure (a composite of death, graft loss, acute rejection and MMF discontinuation) "In the CC group, MMF dose adjustments were calculated by a computer program (available at www.chu-limoges.fr/stp/stpacces.htm, June 21, 2007) to reach an MPA AUC target of 40 mg.h /L. The minimum dose change was 250 mg twice a day. Each dose adjustment of at least 250 mg twice a day that was able to result in an AUC closer to 40 mg.h /L was proposed by the program to the physician"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Within the first 3 days posttransplant, patients were randomized by an interactive voice response system administered by a private company; randomization was balanced within centers in blocks of 4 patients, and patients were enrolled and assigned to

Le Meur 2007 (*Continued*)

		one of the two groups by physicians at each center"
Allocation concealment (selection bias)	Low risk	"Within the first 3 days posttransplant, patients were randomized by an interactive voice response system administered by a private company; randomization was balanced within centers in blocks of 4 patients, and patients were enrolled and assigned to one of the two groups by physicians at each center"
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	High risk	"The sex ratio differed between groups in that there were a larger percentage of males in the CC-treated group (Table 1)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were seven withdrawals (CC, n = 5; FD, n = 2) due to death, primary non functioning graft or because MMF was not administered." In most of tables, only percentages are reported and according to the first decimal of percentages, there were missing data in the denominator. However, missing values were unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Acute rejection was diagnosed by renal biopsy except in patients with contraindications and were graded according to the Banff classification, in which case diagnosis was based on clinical and laboratory criteria (in particular, any unexplained increase in serum creatinine)." No committee reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Le Meur 2007 extract

Methods	
Participants	
Interventions	
Outcomes	
Notes	Text extracted from original article Le Meur 2007

Leehey 1993

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Mixed (physicians + pharmacists) Level of training: Not reported Clinical specialty: Not applicable Country: USA (Hines, Illinois) Centre: 1 Veterans Affairs Hospital Location of care: Inpatient care Participants: 324 participants receiving aminoglycosides for suspected or confirmed infection were enrolled and randomly assigned to 1 of 3 groups: usual physician-directed dosing (group 1), pharmacist-assisted dosing (group 2), or pharmacist-directed dosing (group 3). 81 participants were dropped from the study because they received < 72 h of therapy, leaving 243 study participants (73 in group 1, 90 in group 2, 80 in group 3)
Interventions	Clinical problem: Aminoglycoside in participants with suspected or confirmed infection Intervention: Pharmacist-directed dosing (group 3, n = 80) vs. usual physician-directed dosing (group 1, n = 73). Participants randomized to group 1 (customary dosing) had no intervention from study personnel other than the placement of an order in the hospital chart for the determination of serum creatinine levels post-therapy. In participants randomized to group 3 (pharmacist-directed dosing), all orders for aminoglycoside dosing were written by a pharmacist (with countersignature by 1 of the 2 study physicians) specially trained in the Bayesian dosing methods used in the study). Group 2 (pharmacist-assisted dosing) was excluded: dosing and monitoring recommendations were written by a pharmacist in the progress note section of the hospital chart, and the physicians caring for the participant were notified of these suggestions (the pharmacist served as a consultant) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Indirect intervention Calculated dose given as a recommendation: Yes

Outcomes	Dose of drug administered to the participant: Mean total aminoglycoside doses (mg) (duration of therapy: not included) Serum concentrations and therapeutic range: Mean peak serum aminoglycoside levels (μg/mL) (mean serum trough concentrations (μg/mL): reported) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: Need for dialysis, nephrotoxicity Healthcare costs: None Improvement: Proportion of participants with response to treatment
Notes	Nephrotoxicity was defined as a ≥ 100% increase in serum creatinine concentration with at least a 44 μmol/L (0.5 mg/dL) increment in this value

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	High risk	Sex gender not reported. There were differences on use of contrast media and the presence of lung disease
Incomplete outcome data (attrition bias) All outcomes	Low risk	81 participants were dropped from the study because they received < 72 h of therapy, leaving 243 study participants (73 in group 1, 90 in group 2, 80 in group 3). Incomplete data were unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Study data were reviewed by one of the authors who was blinded as to group assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Lesourd 2002

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Obstetrics and gynaecology Country: France (Toulouse, Rouen, Paris) Centre: 3 centres (private and university teaching hospitals) Location of care: Outpatient care Participants: 164 women undergoing ovarian stimulation to treat infertility
Interventions	Clinical problem: Ovarian stimulation by gonadotropins Intervention: CDSS group (n = 82) vs. control group (n = 82) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Number of follicle-stimulating hormone units administered Serum concentrations and therapeutic range: None Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None (cancelled cycles of ovarian stimulation: not included) Healthcare costs: None Improvement: Proportion of participants with clinical pregnancies (ongoing pregnancies: not included, mean number of follicles ≥ 18 mm: not included)
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	High risk	Participants in the group with the decision by software were younger than in the group with the decision by clinicians (31.7 ± 4.5 years versus 33.1 ± 4.2 years, P value < 0. 05 (table 2))

Lesourd 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	No details
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes (pregnancies) are objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Unclear risk	Few results reported (1 sentence in the results). Not enough information to evaluate the bias of the study

Manotti 2001

Methods	Design: NRCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not reported Country: Italy Centre: 5 anticoagulant clinics, all federated with the FCSA (Italian Federation of Anticoagulation Clinics) Location of care: Outpatient care Participants: 335 participants on oral anticoagulants
Interventions	Clinical problem: initiation of oral anticoagulant therapy (warfarin and acenocoumarol) Intervention: Computer-aided dosing (n = 145) vs. manual dosing (n = 190) Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None (maintenance dose (mg/week): not included (number of appointments, available only for warfarin)) Serum concentrations and therapeutic range: None Physiological parameters: None (% of participants reaching a stable state of anticoagulation (3 INR measurements within therapeutic range): reported) Time to achieve therapeutic control: None

	Clinical events: None Healthcare costs: None Improvement: None
Notes	"The use of only two separate therapeutic ranges was suggested: Low Intensity = INR 2.0 to 3.0; target value 2.5. People with deep venous thrombosis/ pulmonary embolism, atrial fibrillation, heart valve disease, biological valve prosthesis. High Intensity = INR 3.0 to 4.5 ; target value 3.5. People with a mechanical heart valve prosthesis, coronary or other arterial disease"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Patients were randomized into two arms. " No further information provided
Allocation concealment (selection bias)	Unclear risk	"Patients were randomized into two arms. " No further information provided
Baseline outcome measurements similar	Low risk	Not applicable (initiation of oral anticoagulant therapy)
Baseline characteristics similar	Low risk	No apparent differences (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Data were provided with patient-years. No details for follow-up
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Mihajlovic 2003

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Not reported Level of training: Not reported Clinical specialty: Psychiatry Country: Serbia Centre: 1 psychiatric clinic of a clinical hospital centre (Clinical Hospital Center Kragujevac) Location of care: Not reported Participants: 60 participants with major depressive disorder (according to ICD-10)
Interventions	Clinical problem: Amitriptyline in the treatment of major depressive episode Intervention: Computer-aided dosing of amitriptyline (n = 30 participants) vs. usual dose regimen (n = 30 participants). The individualization of amitriptyline dose was calculated using the modified Bayesian method (on the basis of therapeutic steady-state concentration of 80 ng/mL, participant's sex, weight, age, creatinine plasma concentration, albumin plasma concentration and volume of the liquid on the 'third space') Computer advice: Not reported CDSS integration in CPOE: Not reported Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Drug daily doses of amitriptyline + nortriptyline at day 14 (mg) (at day 28, day 42, day 56: not included) Serum concentrations and therapeutic range: None Physiological parameters: Steady-state plasma concentration of amitriptyline + nortriptyline at J14 (during the treatment course) (at day 28, day 42, day 56: not included) Time to achieve therapeutic control: None Clinical events: Proportion of participants with adverse effects of amitriptyline per days of research at day 14 (at day 28, day 42, day 56: not included) Healthcare costs: None Improvement: Hamilton Depression Rating scale scores at day 28 (at day 14, day 42, day 56: not included, Clinical Global Impression scale: not included)
Notes	Among the 60 participants included in the study, 15 were also included in Jankovic 1999 (excluded study)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Random table, in blocks of 10"

Mihajlovic 2003 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"Random table, in blocks of 10". No further information provided
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Low risk	"In general, the demographic characteristics of the patients were similar in the experimental and control groups (table 1)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated. Denominator not reported in tables
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcomes were objective. Hamilton scale is an hetero-questionnaire
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	High risk	Selection bias/opportunistic series: - Mihajlovic 2003: 60 participants admitted during 1997 - Mihajlovic 2010: Safety analysis of the study reported by Mihajlovic 2003 All 15 participants from the Jankovic study were included in the Mihajlovic study (confirmed by the author S. Jankovic)

Mihajlovic 2010

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Not reported Level of training: Not reported Clinical specialty: Psychiatry Country: Serbia Centre: 1 psychiatric clinic of a clinical hospital centre (Clinical Hospital Center Kragujevac) Location of care: Not reported Participants: 60 participants with major depressive disorder (according to ICD-10)

Interventions	Clinical problem: Amitriptyline in the treatment of major depressive episode Intervention: Computer-aided dosing of amitriptyline (n = 30 participants) vs. usual dose regimen (n = 30 participants). The individualization of amitriptyline dose was calculated using the modified Bayesian method (on the basis of therapeutic steady-state concentration of 80 ng/mL, participant's sex, weight, age creatinine plasma concentration, albumin plasma concentration and volume of the liquid on the 'third space') Computer advice: Not reported CDSS integration in CPOE: Not reported Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: See Mihajlovic 2003 Serum concentrations and therapeutic range: See Mihajlovic 2003 Physiological parameters: See Mihajlovic 2003 Time to achieve therapeutic control: See Mihajlovic 2003 Clinical events: None Healthcare costs: See Mihajlovic 2003 Improvement: See Mihajlovic 2003
Notes	This is a safety analysis conducted as a part of the randomized multicentre study of computer-aided dosing of amitriptyline vs. usual dose regimen reported by Mihajlovic et al. (see Mihajlovic 2003)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Random table, in blocks of 10"
Allocation concealment (selection bias)	Unclear risk	"Random table, in blocks of 10". No further information provided
Baseline outcome measurements similar	Low risk	Not appropriate
Baseline characteristics similar	Unclear risk	"In general, the demographic characteristics of the patients were similar in the experimental and control groups"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated. Denominator not reported in tables
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Main outcomes were objective. Clinical Global Impression Scale is an hetero-questionnaire

Mihajlovic 2010 (*Continued*)

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants were randomized
Selective reporting (reporting bias)	Unclear risk	All relevant outcomes were reported in the results section
Other bias	Unclear risk	Selection bias/Opportunistic series: - Mihajlovic 2003: 60 participants admitted during 1997 - Mihajlovic 2010: Safety analysis of the study reported by Mihajlovic 2003 All 15 participants from the Jankovic study were included in the Mihajlovic study (confirmed by the author S. Jankovic)

Mitra 2005

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant, dose of treatment Power calculation: Not done
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Rehabilitation Country: USA Centre: 1 free-standing, 288-bed, academic rehabilitation centre Location of care: Inpatient care Participants: 280 hospitalized rehabilitation patients who were prescribed warfarin for anticoagulation
Interventions	Clinical problem: Warfarin (Coumadin) to maintain hospitalized rehabilitation patients within a therapeutic INR (2.0-3.0) Intervention: Computer-aided dosing of warfarin (n = 14 participants) vs. physician dosing (n = 16 participants). The computer-generated program (DAWN AC) gave instructions to the physicians for warfarin dosing and for timing and frequency of blood draws Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: None (time spent in days per 100 patient-days of treatment: reported)

	Time to achieve therapeutic control: None Clinical events: Proportion of participants with thromboembolism (pulmonary embolism, deep vein thrombosis) (number of blood draws: not included) Healthcare costs: Length of stay (days) Improvement: None
Notes	"The goal of both groups was to maintain patients within a target INR of 2.0 - 3.0"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Subjects were randomized using a random number table into one of two groups: group P (physician dosing) or group C (computer dosing)"
Allocation concealment (selection bias)	Unclear risk	"Subjects were randomized using a random number table into one of two groups: group P (physician dosing) or group C (computer dosing)." No further information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	High risk	"A larger percentage of patients in group C had a history of atrial fibrillation (28% vs. 6%), and group P had a larger proportion of patients with a history of DVT [deep vein thrombosis] (50% vs. 7%)"
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	"The total number of data points (INR values) was 1014, excluding 36 days during which the INR score could not be imputed. " The original group of 32 patients was reduced to 30 through loss of data sheets. It is unclear if missing values could overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Pulmonary embolism, deep vein thrombosis: No committee reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section

Mitra 2005 (*Continued*)

Other bias	Low risk	No evidence of other risk of biases

Mungall 1994

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Mixed physicians + pharmacists) Level of training: Not reported Clinical specialty: Other (coronary care unit) Country: USA (Michigan) Centre: 2 medical centres (McLaren Regional Medical Center, Midland Regional Medical Center) Location of care: Inpatient care Participants: 51 participants needing anticoagulation with heparin after myocardial infarction
Interventions	Clinical problem: Heparin adjustment Intervention: Bayesian computer-generated starting doses (n = 25) vs. doctors using nomogram (n = 26) Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Indirect intervention (dosage determined by pharmacy using) Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: mean heparin dose (units/h) Serum concentrations and therapeutic range: None Physiological parameters: None (activated partial thromboplastin time ratio (compared with baseline activated partial thromboplastin time before heparin therapy): not included, number of activated partial thromboplastin time measurements per day of therapy: not included) Time to achieve therapeutic control: None Clinical events: Proportion of participants with clinical adverse events (recurrent chest pain, recurrent chest pain and readministration of thromboplastin, development of congestive heart failure, thrombotic stroke, arterial embolization, pulmonary embolus, transient ischaemic attack), proportion of participants with bleeding events Healthcare costs: None Improvement: None
Notes	- The therapeutic range was 1.2-2.5 times the participant's baseline activated partial thromboplastin time

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Mungall 1994 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No significant differences on main characteristics (table II)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Mean length of stay was 8 days. According to denominator in tables, there were no missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Bleeding and clinical events are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Pachler 2008

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported (non-inferiority trial but no margin addressed)
Participants	Profession: Nurses Level of training: Not reported Clinical specialty: ICU Country: Austria (Graz) Centre: 1 x 9-bed medical ICU in a tertiary teaching hospital Location of care: Inpatient care Participants: 50 mechanically ventilated medical ICU patients
Interventions	Clinical problem: Insulin in critically ill patients with hyperglycaemia Intervention: Laptop-based algorithm eMPC (n = 25 participants) vs. routine nurse-based protocol (n = 25 participants). The eMPC is an enhanced version of the MPC, a model of the glucoregulatory system. Glucose concentration, insulin dosage and carbohydrate content of enteral and parenteral input are the input variables for the eMPC. The insulin infusion rate and the time of the next glucose sample are the outputs

	Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Insulin (IU/h) (change of insulin rate (number of times in 72 h): reported, carbohydrate administration (g/h): not included) Serum concentrations and therapeutic range: None Physiological parameters: Hyperglycaemia index (mmol/L) (blood glucose (mmol/L): not included (unit of analysis error)) Time to achieve therapeutic control: Mean sampling interval (hours) Clinical events: Proportion of participants with hypoglycaemic episodes (blood glucose levels lower than 2.2 mM) Healthcare costs: None Improvement: None
Notes	- Hyperglycaemic index was used as primary endpoint for the assessment of glucose control. The hyperglycaemic index developed by Vogelzang et al. is defined as the AUC above the upper limit of normal (glucose level 6.1 mmol/L, modified from the original 6.0 mmol/L) divided by the total length of stay (time in study) - Non-inferiority trial analyzed like superiority trial - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Participants fulfilling the inclusion criterion were randomly assigned using serially numbered, sealed envelopes to either the intervention group (BG control by the eMPC) or the control group (routine BG management protocol)
Allocation concealment (selection bias)	Low risk	Participants fulfilling the inclusion criterion were randomly assigned using serially numbered, sealed envelopes to either the intervention group (BG control by the eMPC) or the control group (routine BG management protocol)
Baseline outcome measurements similar	Low risk	No significant differences on blood glucose at study start or number of participants treated with insulin before study start (table 1)

Pachler 2008 (*Continued*)

Baseline characteristics similar	Low risk	No significant differences on baseline characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated. Denominator not reported in tables. The treatment was discontinued ahead of schedule in 2 participants of the control group and in 5 participants assigned to the eMPC group. It is not clear if these participants were excluded from analysis
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Plank 2006

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant, time under treatment Power calculation: Not reported
Participants	Profession: Not reported Level of training: Not reported Clinical specialty: ICU Country: Europe (Austria, Czech Republic, UK) Centre: 3 ICUs across Europe (Graz, Prague, London) Location of care: Inpatient care Participants: 60 participants undergoing cardiac surgery with postsurgery hyperglycaemia (glucose > 120 mg/dL)
Interventions	Clinical problem: Insulin in critically ill patients with hyperglycaemia Intervention: Laptop-based algorithm MPC (n = 30 participants) vs. routine blood glucose management protocol (n = 30 participants). The MPC is a model representing the glucoregulatory system. Glucose concentration, insulin dosage and carbohydrate intake are the input variables for the MPC. The insulin infusion rate is the output parameter and was adjusted hourly as suggested by the algorithm Computer advice: Given in real time CDSS integration in CPOE: No

	Starter: User-initiated Type of intervention: Indirect intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Insulin dosages used for the first 24 h (insulin units/24 h) Serum concentrations and therapeutic range: None Physiological parameters: % of time within the target range for blood glucose in the first 24 h (80-110 mg/dL or 4.4-6.1 mmol/L), mean glucose levels (mg/dL) (% of time above the target range for blood glucose in the first 24 h (> 110 mg/dL): not included, % of time between 54 and 79 mg/dL for blood glucose in the first 24 h (2.9 to < 4.4 mmol/L): not included) Time to achieve therapeutic control: Mean sampling interval (h) Clinical events: Proportion of participants with hypoglycaemic episodes (blood glucose level < 54 mg/dL or < 3 mmol/L) Healthcare costs: None Improvement: None
Notes	- "The target range for blood glucose levels, as defined by the study protocol, was 80-110 mg/dl (4.4-6.1 mmol/l), which has been demonstrated to reduce mortality and morbidity in postcardiac surgery patients. The MPC algorithm and the routine care management protocol in Graz are aiming for exactly the same target range, while in Prague a slightly higher level for the upper limit (81-117 mg/dl [4.5-6.5 mmol/l]) and in London a slightly lower level for the lower limit (72-108 mg/dl [46 mmol/l]) is implemented in the routine glucose protocol. Likewise, small differences in the definition of hypoglycemia can be found among the routine management protocols (London: 54 mg/dl [3.0 mmol/l], Graz: 60 mg/dl [3.3 mmol/l], and Prague: 63 mg/dl [3.5 mmol/l]). For the study protocol, blood glucose levels 54 mg/dl (3.0 mmol/l) were defined as hypoglycemic events" - The author was contacted and confirmed that the algorithm gave advice to the ICU personnel (nurses and physicians), who input the glucose values and changed the infusion rate - The study is part of CLINICIP (Closed Loop Insulin Infusion for Critically Ill Patients; www.clinicip.org), an integrated project funded by the European Community

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"60 patients were randomized by individual centers in blocks of 10"
Allocation concealment (selection bias)	Unclear risk	"60 patients were randomized by individual centers in blocks of 10". No further information provided
Baseline outcome measurements similar	Unclear risk	Blood glucose at entry was reported by ICU (Graz, Prague, London) but not across study groups (table 1)

Plank 2006 (*Continued*)

Baseline characteristics similar	High risk	Baseline characteristics of participants were reported by ICU (Graz, Prague, London) but not across study groups (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated. Denominator not reported in tables
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes are clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Poller 1998 pop1

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Episode of care Power calculation: Not reported
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not applicable Country: Europe (Manchester (UK), London (UK), Oslo (Norway), Esbjerg (Denmark) , Gaia (Portugal)) Centre: 5 centres Location of care: Outpatient care Participants: 79 inpatients needing anticoagulant therapy (stabilized patients)
Interventions	Clinical problem: Warfarin therapy maintenance Intervention: Computer-generated-dose group (n = 39) or traditional-dose group (n = 40) Computer advice: Not reported CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None (proportion of doses adjustments: unknown denominator) Serum concentrations and therapeutic range: None

Poller 1998 pop1 (*Continued*)

	Physiological parameters: Proportion of time spent within target (INR) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	The proportion of time within target INR range was determined according to the Rosendaal method "The program has two main modules - the induction module for starting warfarin therapy over the first 4 days to reach a dose within 1 mg of eventual maintenance dose, and the maintenance module (version 4 only was used) for finely tuning the dose to the therapeutic range and sustaining it" "The INR target ranges were decided by the individual centre, based on one of: the guidelines on oral anticoagulation of the British Society of Haematology, the Leuven Group, and the ACCP Consensus. Three different ranges of INR resulted; 2.0-3.0, 3.0-4.5, and 2.5-3.5"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Randomisation was done according to computer-generated order at each centre"
Allocation concealment (selection bias)	Low risk	"Randomisation was done according to computer-generated order at each centre"
Baseline outcome measurements similar	Low risk	Not appropriate (warfarin therapy maintenance)
Baseline characteristics similar	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	285 randomized, 254 analyzed (16 excluded vs. 15)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Poller 1998 pop2

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Episode of care Power calculation: Not reported
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not applicable Country: Europe (Manchester (UK), London (UK), Oslo (Norway), Esbjerg (Denmark) , Gaia (Portugal)) Centre: 5 centres Location of care: Outpatient care Participants: 175 outpatients needing anticoagulant therapy (in the stabilization period)
Interventions	Clinical problem: Warfarin therapy stabilization Intervention: Computer-generated-dose group (n = 83) or traditional-dose group (n = 92) Computer advice: Not reported CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None (proportion of doses adjustments: unknown denominator) Serum concentrations and therapeutic range: None Physiological parameters: Proportion of time spent within target (INR) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	The proportion of time within target INR range was determined according to the Rosendaal method "The program has two main modules - the induction module for starting warfarin therapy over the first 4 days to reach a dose within 1 mg of eventual maintenance dose, and the maintenance module (version 4 only was used) for finely tuning the dose to the therapeutic range and sustaining it" "The INR target ranges were decided by the individual centre, based on one of: the guidelines on oral anticoagulation of the British Society of Haematology, the Leuven Group, and the ACCP Consensus. Three different ranges of INR resulted; 2.0-3.0, 3.0-4.5, and 2.5-3.5"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomisation was done according to computer-generated order at each centre"

Poller 1998 pop2 (*Continued*)

Allocation concealment (selection bias)	Low risk	"Randomisation was done according to computer-generated order at each centre"
Baseline outcome measurements similar	Low risk	Not appropriate (Warfarin therapy maintenance)
Baseline characteristics similar	High risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	285 randomized, 254 analyzed (16 excluded versus 15)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Poller 2002

Methods	
Participants	
Interventions	
Outcomes	
Notes	- Same data as Poller 1998 pop1; Poller 1998 pop2

Poller 2003

Methods	
Participants	
Interventions	
Outcomes	
Notes	- Abstract corresponding to the Protocol of the study published in 2008 (Poller 2008)

Poller 2008

Methods	
Participants	
Interventions	
Outcomes	
Notes	- Clinical endpoint report from the European Action on Anticoagulation (EAA), which gave the combined results using 2 currently marked computer-assisted dosage programs (DAWN AC and PARMA 5). The subgroup analyses were included (Poller 2009 DAWN AC, Poller 2008 PARMA 5)

Poller 2008 PARMA 5

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: INR Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not reported Country: Europe, Israel, Australia Centre: 32 centres in 13 countries (Europe: 29, Israel: 2, Australia: 1) Location of care: Outpatient care Participants: 13,219 anticoagulation patients randomized at each centre into manual-dosed or computer-assistant dosed arm (DAWN AC or PARMA 5). 13,052 participants analyzed (167 participants without INR results): 2631 for the DAWN AC study and 10,421 for the PARMA 5 study
Interventions	Clinical problem: Oral anticoagulation (warfarin, nicoumalone (acenocoumarol), phenprocoumon) Intervention: Computer-assisted dosage program (PARMA5 (n = 5290 participants)) versus manual dosage (n = 5131 participants). Recruitment was restricted to new patients initiated oral anticoagulation. 2 subroutines: induction and steady state monitoring; the aim of the dosage algorithm was to maintain the INR value as close as possible to the mean target INR and to provide the next appointment date Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: Time in target INR range (INR: not included) Time to achieve therapeutic control: None Clinical events: Death, number of bleeding events (major + minor) (events per 100 patient-years), number of thrombotic events (events per 100 patient-years) (number of

	events (minor bleeding events, major bleeding events, thrombotic events, deaths): not included) Healthcare costs: None Improvement: None
Notes	- Time in target INR range = proportion of time for which participants were maintained within the locally decided target INR ranges - This report is a subgroup analysis of the previous clinical endpoint report from the European Action on Anticoagulation (EAA) (Poller 2008b), which gave the combined results using 2 currently marked computer-assisted dosage programs (DAWN AC and PARMA 5) (Poller 2009 DAWN AC, Poller 2008 PARMA 5) - There were some incoherences between the number of events adjudicated in Poller 2008b (table 2) and the sum of number of events in Poller 2008 PARMA 5 (table II) and in Poller 2009 DAWN AC (table 2). The author confirmed the numbers in Poller 2008b and Poller 2008 PARMA 5 and corrected those in Poller 2009 DAWN AC

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics of the 10,421 participants (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	44/5175 in manual-dosed group and 87/5377 in computer-assisted dosage group did not receive allocated intervention
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Events were adjudicated by a committee
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Poller 2009 DAWN AC

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: INR Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Not reported Country: Europe, Israel, Australia Centre: 32 centres in 13 countries (Europe: 29, Israel: 2, Australia: 1) Location of care: Outpatient care Participants: 13,219 anticoagulation patients randomized at each centre into manual-dosed or computer-assistant dosed arm (DAWN AC or PARMA 5). 13,052 participants analyzed (167 participants without INR results): 2631 for the DAWN AC study and 10,421 for the PARMA 5 study
Interventions	Clinical problem: Oral anticoagulation (warfarin, nicoumalone (acenocoumarol), phenprocoumon) Intervention: Computer-assisted dosage program (DAWN AC (n = 1315 participants)) versus manual dosage (n = 1316 participants). Recruitment was restricted to new patients initiated oral anticoagulation. 2 modules: induction and maintenance; the time to the next test was set by the program using a table of variables Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: Time in target INR range (INR: not included) Time to achieve therapeutic control: None Clinical events: Death, number of bleeding events (major + minor) (events per 100 patient-years), number of thrombotic events (events per 100 patient-years) (number of events (minor bleeding events, major bleeding events, thrombotic events, deaths): not included) Healthcare costs: None Improvement: None
Notes	- Time in target INR range = proportion of time for which participants were maintained within the locally decided target INR ranges - This report is a subgroup analysis of the previous clinical endpoint report from the European Action on Anticoagulation (EAA) (Poller 2008b), which gave the combined results using 2 currently marked computer-assisted dosage programs (DAWN AC and PARMA 5) (Poller 2009 DAWN AC, Poller 2008 PARMA 5) - There were some incoherences between the number of events adjudicated in Poller 2008b (table 2) and the sum of number of events in Poller 2008 PARMA 5 (table II) and in Poller 2009 DAWN AC (table 2). The author confirmed the numbers in Poller 2008b and Poller 2008 PARMA 5 and corrected those in Poller 2009 DAWN AC

Poller 2009 DAWN AC (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics of the 2631 participants (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	12/1328 in manual-dosed group and 24/1339 in computer-assisted dosage group were excluded because no INR results were reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Events were adjudicated by a committee
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Poller 2009 erratum

Methods	
Participants	
Interventions	
Outcomes	
Notes	- Erratum from original article Poller 2009 DAWN AC

Rodman 1984

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not done
Participants	Profession: Not reported Level of training: Not reported Clinical specialty: Not reported Country: USA Centre: 1 medical centre (University of Southern California Medical Center) Location of care: Inpatient care Participants: 20 participants admitted to medical ICU or coronary care unit needing lignocaine therapy
Interventions	Clinical problem: Lidocaine therapy Intervention: Advice on initial therapy using individualized linear 2 compartment pharmacokinetic model (n = 9) vs. usual care (n = 11) Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: mean first hour infusion rate (μg/kg/min) , mean final infusion rate (μg/kg/min), mean overall infusion rate Serum concentrations and therapeutic range: serum concentrations (lidocaine) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: proportion of participants with adverse reactions (monitoring of rhythm, intermittent hard-copy rhythm strips, serial electrocardiographs, daily measurements of electrolyte and cardiac enzyme levels, liver function tests) Healthcare costs: None Improvement: None
Notes	Objective: "To achieve and maintain plasma concentrations in the approximate middle of the usual therapeutic range of 1.5 to 5.0 μg/mL"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Low risk	Sealed envelope
Baseline outcome measurements similar	Low risk	Not appropriate

Rodman 1984 (*Continued*)

Baseline characteristics similar	High risk	There were 6/9 men in the computer-assisted therapy group and 11//11 in the conventional lidocaine therapy group
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Unclear risk	Outcomes were not defined in the methods section
Other bias	Unclear risk	Only 20 participants were included

Rousseau 2010

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Nephrology Country: France Centre: 11 centres Location of care: Inpatient care Participants: 137 renal allograft recipients receiving basiliximab, CsA, MMF and corticosteroids. 130 participants analyzed
Interventions	Clinical problem: MMF dosing in renal transplant patients Intervention: Concentration-controlled (CC) regimen (n = 65 participants) vs. fixed-dose (FD) MMF (n = 65 participants). In the CC group, MMF dose adjustments were calculated by a computer program to reach an MPA AUC target of 40 mg.h/L and were proposed to the physician. In the FD group, MMF dose adjustments were based on clinical experience Computer advice: Given in real time CDSS integration in CPOE: No Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes

Outcomes	Dose of drug administered to the participant: See Le Meur 2007 Serum concentrations and therapeutic range: See Le Meur 2007 Physiological parameters: See Le Meur 2007 Time to achieve therapeutic control: See Le Meur 2007 Clinical events: See Le Meur 2007 Healthcare costs: Cost per participant during the first year of transplantation based on diagnosis-related groups reimbursements (EUR, base 2007) (hospital stays, drugs, biological tests and medical transportation) Improvement: See Le Meur 2007
Notes	This is a cost-effectiveness analysis conducted as a part of the APOMYGRE randomized multicentre study of concentration-controlled dosing regimen of MMF vs. fixed-dose reported by Le Meur et al. (see Le Meur 2007)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Within the first 3 days posttransplant, patients were randomized by an interactive voice response system administered by a private company; randomization was balanced within centers in blocks of 4 patients, and patients were enrolled and assigned to one of the two groups by physicians at each center"
Allocation concealment (selection bias)	Low risk	"Within the first 3 days posttransplant, patients were randomized by an interactive voice response system administered by a private company; randomization was balanced within centers in blocks of 4 patients, and patients were enrolled and assigned to one of the two groups by physicians at each center"
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	High risk	"The sex ratio differed between groups in that there were a larger percentage of males in the CC-treated group (table 1)"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"There were seven withdrawals (CC, n = 5; FD, n = 2) due to death, primary non functioning graft or because MMF was not administered." In most of tables, only percentages were reported and according to the first decimal of percentages, there were

Rousseau 2010 (*Continued*)

		missing data in the denominator. However, missing values were unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"Acute rejection was diagnosed by renal biopsy except in patients with contraindications and were graded according to the Banff classification, in which case diagnosis was based on clinical and laboratory criteria (in particular, any unexplained increase in serum creatinine)." No committee reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Saager 2008

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Done
Participants	Profession: Mixed (trained healthcare professionals) Level of training: Not reported Clinical specialty: Not reported Country: USA Centre: 1 large academic medical centre Location of care: Inpatient care Participants: 40 participants with diabetes mellitus scheduled for cardiac surgery (cardiothoracic ICU)
Interventions	Clinical problem: Insulin in people with diabetes undergoing cardiac surgery Intervention: Computer-guided glucose management system (n = 20 participants) vs. standard paper-based insulin protocol (n = 20 participants). The computer system (EndoTool Glucose Management System (MD Scientic)) used the previous 4 dose responses to recommend the insulin dose, glucose determination frequency, and a 50% dextrose dose (when appropriate) for hypoglycaemia Computer advice: Given in real time CDSS integration in CPOE: No Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes

Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: Mean blood glucose (mg/dL) in ICU (available in operating room: not included, time in blood glucose range in operating room: reported, time in blood glucose range in ICU: reported) Time to achieve therapeutic control: None Clinical events: Proportion of participants with side effects (hypoglycaemia: < 60 mg/dL at any time) in ICU (available in operating room: not included) Healthcare costs: None Improvement: None
Notes	"The standard paper-based ICU insulin protocol was developed at this institution with the goal of targeting blood sugar concentrations between 90 and 150 mg/dL"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Baseline outcome measurements similar	Low risk	No significant differences on baseline characteristics (table 1)
Baseline characteristics similar	Low risk	No significant differences on blood glucose (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Sato 2011

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant, blood glucose measurements Power calculation: Done
Participants	Profession: Anaesthesiologists Level of training: Not reported Clinical specialty: Other (anaesthesiology/cardiology) Country: Canada (Montreal) Centre: 1 university hospital (Royal Victoria Hospital, McGill University Health Centre) Location of care: Inpatient care Participants: 42 participants without diabetes undergoing elective cardiac surgery were randomized. 36 participants were analyzed. All studies were conducted by 6 anaesthesiologists, each anaesthesiologist was assigned to 3 manual and 3 GINCS studies in random order
Interventions	Clinical problem: Glucose and insulin administration in cardiac surgical patients Intervention: GIN Computer Software (GINCS) (n = 18) versus manual control group (n = 18). The computer program uses an algorithm based on the original clamp equation (DeFronzo et al.) and modified for its use during cardiac surgery requiring extracorporeal circulation. It takes account of the characteristic of glucose dynamics during cardiac surgery and CPB, including plasma glucose fluctuation, alterations in glucose utilization, transfusion of blood products, and rewarming of the patients Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: Not reported Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: mean amount of insulin infused (IU) (mean amount of glucose administered (g): reported) Serum concentrations and therapeutic range: None Physiological parameters: Mean blood glucose (mmol/L), % of participants with all measurements within the target range for blood glucose (4-6 mmol/L) (% of time within the target range for blood glucose (4-6 mmol/L) (unit of analysis error): reported, % of time below the target range for blood glucose (4-6 mmol/L) (unit of analysis error): not included, % of time above the target range for blood glucose (4-6 mmol/L) (unit of analysis error): not included, time (min) within the target range for blood glucose (4-6 mmol/L): not included, time (min) below the target range for blood glucose (4-6 mmol/L): not included, time (min) above the target range for blood glucose (4-6 mmol/L): not included) Time to achieve therapeutic control: Mean sampling interval (min) Clinical events: Proportion of participants with hypoglycaemic episodes (blood glucose level < 2.9 mmol/L) Healthcare costs: None Improvement: None
Notes	"Target glycemia was defined as BG [blood glucose] between 4.0 to 6.0 mmol/L. Hyperglycemia was defined as BG 7.0 mmol/L. Hypoglycemia was defined as a BG 2.9 mmol/L. Time within, above and below target range was calculated by assuming the linearity

Sato 2011 (*Continued*)

	of BG level over time"	
Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Consenting patients were allocated according to a computer-generated randomization schedule into the computer-assisted or manual group (Plan procedure, SAS software, SAS Institute, Cary, NC)"
Allocation concealment (selection bias)	Low risk	"Consenting patients were allocated according to a computer-generated randomization schedule into the computer-assisted or manual group (Plan procedure, SAS software, SAS Institute, Cary, NC)"
Baseline outcome measurements similar	Low risk	No significant differences on preoperative blood glucose (table 1)
Baseline characteristics similar	Low risk	No significant differences on participants demographic (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	The blood glucose was measured in short intervals as requested by each algorithm before, during and after cardiopulmonary bypass (over maximum 320 min)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Main outcomes were objective. Hypoglycaemic episodes were clearly defined
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Terrell 2010

Methods	Design: RCT Unit of allocation: Provider Unit of analysis: Medication, participant visit (cluster was taken into account in statistical analysis) Power calculation: Not reported
Participants	Profession: Physicians Level of training: Mixed Clinical specialty: Emergency Country: USA Centre: 1 urban public hospital Location of care: Inpatient care Participants: 42 emergency medicine faculty and resident physicians randomized (intern physicians excluded). Subjects were adults with renal insufficiency who were being discharged home from the emergency department. 6015 participant visits with prescription initially written for a targeted medication. Among the 2783 visits in which creatinine level was estimated, 113 (4%) participant visits (corresponded to 119 prescriptions) resulted in prescription of at least 1 medication that required dosage adjustment (3232 participant visits excluded because of insufficient information in the electronic medical record to estimate the creatinine clearance)
Interventions	Clinical problem: 10 high-use medications that require adjustments for renal impairment (amoxicillin, amoxicillin/clavulanate, cephalexin, ciprofloxacin, colchicine, hydrochlorothiazide, levofloxacin, lisinopril, ranitinide, trimethoprim/sulfamethoxazole) Intervention: Computerized decision support (21 physicians) vs. control group (21 physicians). Decision support was provided when an intervention physician prescribed a targeted medication to a person whose creatinine level was below the threshold for dosage adjustment for that particular medication. The physician could either accept or reject the decision support's recommendation. Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None (% excessively dosed prescriptions: reported, % visits with excessively dosed prescriptions: not included) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement

Terrell 2010 (*Continued*)

Random sequence generation (selection bias)	Low risk	"A biostatistician randomly assigned physicians in blocks of 2, stratified by stage of training (i.e., faculty status and by year of residency training) into the intervention or control group"
Allocation concealment (selection bias)	Low risk	"A biostatistician randomly assigned physicians in blocks of 2, stratified by stage of training (i.e., faculty status and by year of residency training) into the intervention or control group"
Baseline outcome measurements similar	Low risk	Not stated
Baseline characteristics similar	Low risk	"There were no important differences in the characteristics of intervention and control physicians or the 2 groups of patients who received their care" (table 1)
Incomplete outcome data (attrition bias) All outcomes	High risk	46% of participant visits excluded because of insufficient data to estimate creatinine clearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Physicians were randomized but the study was carried out in a single site and included a small sample of residents and academic emergency physicians
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Unclear risk	46% participant visits were excluded, only prescription that required dosage adjustment were analyzed and there was no adjustment for within-patient correlation "Providers in the intervention group initially prescribed targeted medications more often than control physicians did and consequently had substantially more opportunities to adjust dosing"

Theil 1993 fentanyl

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Other (anaesthesia) Country: USA (Durham, North Carolina) Centre: 1 University Medical Center (Duke University Medical Center) Location of care: Inpatient care Participants: 24 participants undergoing cardiac surgery with continuous infusion of IV anaesthetics
Interventions	Clinical problem: Fentanyl Intervention: Computer-controlled pump using pharmacokinetic model to achieve target serum level (n = 12) vs. infusion controlled by doctor (n = 12) Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: None (fentanyl loading dose (μg/kg): reported, fentanyl maintenance infusion dose during cardiopulmonary bypass (μg/kg): reported, fentanyl total dose (μg/kg): reported, mean number of infusion changes during cardiopulmonary bypass (potential unit of error analysis): reported) Serum concentrations and therapeutic range: None (mean plasma fentanyl concentration during cardiopulmonary bypass (ng/mL): reported) Physiological parameters: None (haemodynamic values: not included) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	"The primary objective for all patients was to maintain heart rate (HR) and mean arterial pressure (MAP) within 20% of baseline values. If possible, hemodynamic control was achieved by altering only the anesthetic infusions. Hypertension (MAP>20% baseline) and tachycardia (HR>20%) were initially treated by incremental increases in fentanyl or midazolam.[...] Hypotension (MAP>20%) prior to and during cardiopulmonary bypass (CPB) was treated by intravenous volume expansion, and a decrease in anesthetic delivery"

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No details

Theil 1993 fentanyl (*Continued*)

Allocation concealment (selection bias)	Unclear risk	No details
Baseline outcome measurements similar	Low risk	Not applicable (people undergoing cardiac surgery)
Baseline characteristics similar	Low risk	No significant differences on participants demographic (table 3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were reported for all participants included
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomized but blinded ("Both systems were attached to each patient by an independent operator")
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Theil 1993 midazolam

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Physicians Level of training: Not reported Clinical specialty: Other (anaesthesia) Country: USA (Durham, North Carolina) Centre: 1 University Medical Center (Duke University Medical Center) Location of care: Inpatient care Participants: 24 participants undergoing cardiac surgery with continuous infusion of IV anaesthetics
Interventions	Clinical problem: Midazolam Intervention: Computer-controlled pump using pharmacokinetic model to achieve target serum level (n = 12) vs. infusion controlled by doctor (n = 12) Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported

Theil 1993 midazolam (*Continued*)

Outcomes	Dose of drug administered to the participant: None (midazolam loading dose (μg/kg) : reported, midazolam maintenance infusion dose during cardiopulmonary bypass (μg/kg): reported, midazolam total dose (μg/kg): reported, mean number of infusion changes during cardiopulmonary bypass (potential unit of error analysis): reported) Serum concentrations and therapeutic range: None (mean plasma midazolam concentration during cardiopulmonary bypass (ng/mL): reported) Physiological parameters: None (haemodynamic values: not included) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	"The primary objective for all patients was to maintain heart rate (HR) and mean arterial pressure (MAP) within 20% of baseline values. If possible, hemodynamic control was achieved by altering only the anesthetic infusions. Hypertension (MAP>20% baseline) and tachycardia (HR>20%) were initially treated by incremental increases in fentanyl or midazolam.[...] Hypotension (MAP>20%) prior to and during cardiopulmonary bypass (CPB) was treated by intravenous volume expansion, and a decrease in anesthetic delivery"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No details
Allocation concealment (selection bias)	Unclear risk	No details
Baseline outcome measurements similar	Low risk	Not applicable (people undergoing cardiac surgery)
Baseline characteristics similar	Low risk	No significant differences on participants demographic (table 3)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were reported for all participants included
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were randomized but blinded ("both systems were attached to each patient by an independent operator")
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section

Theil 1993 midazolam (*Continued*)

Other bias	Low risk	No evidence of other risk of biases

Vadher 1997

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Mixed (physicians + nurses) Level of training: In training Clinical specialty: Not reported Country: UK (London) Centre: 1 district general hospital (Whittington Hospital) Location of care: Mixed Participants: 148 inpatients requiring start of warfarin therapy
Interventions	Clinical problem: Warfarin therapy initiation Intervention: CDSS group (n = 72) vs. control group (n = 76) Computer advice: Not reported CDSS integration in CPOE: No Starter: Not reported Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: None (time spent in days per 100 patient-days of treatment: reported) Time to achieve therapeutic control: Median time to reach therapeutic prothrombin ratio (days), median to reach stable dose (days) Clinical events: Thromboembolism, haemorrhage, death Healthcare costs: None Improvement: None
Notes	"We developed an initiation regimen aiming for a therapeutic range of international normalised ratio of 2 to 3"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"We used simple randomization with a table of random numbers to assign the patients to management by doctors aided by the decision support system (intervention group) or to management by doctors alone (control group)"

Vadher 1997 (*Continued*)

Allocation concealment (selection bias)	Unclear risk	"We used simple randomization with a table of random numbers to assign the patients to management by doctors aided by the decision support system (intervention group) or to management by doctors alone (control group)." No further information provided
Baseline outcome measurements similar	Low risk	Not appropriate (warfarin therapy initiation)
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	High risk	64/76 participants in the control group were followed up as outpatients and 53/72 in the intervention group. There was no description of missing data
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Vadher 1997 pop1

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant, participant time Power calculation: Not reported
Participants	Profession: Mixed (physicians + nurses) Level of training: Mixed Clinical specialty: Other (cardiology) Country: UK (London) Centre: 1 district general hospital (Whittington Hospital) Location of care: Outpatient care Participants: Participants who had been initiated on warfarin therapy as inpatients and followed in the outpatient clinic. Most of these participants required anticoagulation for deep vein thrombosis, pulmonary embolus or atrial fibrillation

Vadher 1997 pop1 (*Continued*)

Interventions	Clinical problem: Warfarin long-term therapy (therapeutic range 2-3) Intervention: CDSS group (n = 37) vs. control group (n = 44) Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Maintenance dose (mg/day) Serum concentrations and therapeutic range: None Physiological parameters: None (time spent in days per 100 patient-days of treatment: reported) Time to achieve therapeutic control: None Clinical events: Thromboembolism, haemorrhage Healthcare costs: None Improvement: None
Notes	The therapeutic range of INR was 2-3

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	"Simple randomization using random number tables was used"
Allocation concealment (selection bias)	Unclear risk	"Simple randomization using random number tables was used." No further information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section

Vadher 1997 pop1 (*Continued*)

Other bias	High risk	- The nurse-practitioners used the computer-decision support system and were compared to the clinician group of 3 junior doctors undergoing general professional training in general medicine - The was a risk of contamination due to logistical problems ("it was difficult to shield the clinicians from the CDSS suggestions")

Vadher 1997 pop2

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant, participant time Power calculation: Not reported Concealment of allocation: Not reported
Participants	Profession: Mixed (physicians + nurses) Level of training: Mixed Clinical specialty: Other (cardiology) Location of care: Outpatient care Country: UK (London) Centre: 1 district general hospital (Whittington Hospital) Participants: Participants who had been on warfarin for more than 1 year. Most of the participants required anticoagulation for heart valve disease, valve replacement or recurrent thromboembolism
Interventions	Clinical problem: Warfarin long term (therapeutic range 3-4.5) Intervention: CDSS group (n = 50) vs. control group (n = 46) Computer advice: Given in real time CDSS integration in CPOE: Not reported Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Maintenance dose (mg/day) Serum concentrations and therapeutic range: None Physiological parameters: None (time spent in days per 100 patient-days of treatment: reported) Time to achieve therapeutic control: None Clinical events: Thromboembolism, haemorrhage Healthcare costs: None Improvement: None
Notes	The therapeutic range of INR was 3-4.5
Risk of bias	

Vadher 1997 pop2 (*Continued*)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Simple randomization using random number tables was used"
Allocation concealment (selection bias)	Unclear risk	"Simple randomization using random number tables was used." No further information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	No apparent differences on baseline characteristics (table 1)
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not stated
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	High risk	- The nurse-practitioners used the computer-decision support system and were compared to the clinician group of 3 junior doctors undergoing general professional training in general medicine - The was a risk of contamination due to logistical problems ("it was difficult to shield the clinicians from the CDSS suggestions")

Verner 1992

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not done
Participants	Profession: Physicians Level of training: Accredited/licensed Clinical specialty: Internal medicine Country: Israel (Tel Hashomer)

Verner 1992 (*Continued*)

	Centre: A 1400 bed regional teaching hospital (Sheba Medical Center) Location of care: Inpatient care Participants: 25 participants needing aminophylline therapy for acute asthma
Interventions	Clinical problem: Theophylline Intervention: Computer suggested dose based on individualized pharmacokinetic model to doctor (n = 10) vs. usual care (n = 15) Computer advice: Not reported CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: Loading dose of theophylline (mg) Serum concentrations and therapeutic range: Serum theophylline concentration 20 minutes after completion of loading dose infusion (μg/mL) (% of time spent in therapeutic range (serum theophylline concentrations in 10-20 µg/mL): reported) Physiological parameters: None Time to achieve therapeutic control: None Clinical events: None Healthcare costs: Mean hospitalization time (days) Improvement: None
Notes	"The computer program was used to estimate the predicted admission serum theophylline concentration, and the partial loading dose needed to achieve the target concentration which was set at 16 g/ml"

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	High risk	"Randomization was based on the final digit in the patient's identification card number (odds versus even)"
Allocation concealment (selection bias)	High risk	Odd versus even identification card number
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	High risk	There were significant differences between the groups (age, asthma/chronic obstructive lung disease and associated medical conditions)
Incomplete outcome data (attrition bias) All outcomes	Low risk	Data were reported for all participants included

Verner 1992 (*Continued*)

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

Wexler 2010

Methods	Design: RCT Unit of allocation: Provider (physicians team) Unit of analysis: Participant (cluster was not taken into account in statistical analysis) Power calculation: Done
Participants	Profession: Physicians Level of training: In training Clinical specialty: Internal medicine Country: USA (Boston) Centre: 1 tertiary care medical centre (Massachusetts General Hospital Diabetes Center) Location of care: Inpatient care Participants: 144 insulin-treated people with type 2 diabetes enrolled. 128 participants analyzed
Interventions	Clinical problem: Insulin in general medical inpatients with type 2 diabetes Intervention: Electronic basal-bolus insulin order template (n = 65 participants) vs. usual insulin ordering (n = 63 participants). The total daily dose of insulin required for the participant (basal (long-acting) and prandial (short-acting)) was calculated by multiplying the weight of the participant by 0.5 units/kg. A button to use insulin-dose calculator was available Computer advice: Given in real time CDSS integration in CPOE: Yes Starter: System-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: Basal insulin dose (units) Serum concentrations and therapeutic range: None Physiological parameters: Mean blood glucose (mg/dL) Time to achieve therapeutic control: None Clinical events: Proportion of participants with hypoglycaemia (< 60 mg/dL at any time) (severe hypoglycaemia (< 40 mg/dL at any time): not included, prolonged hyperglycaemia (3 consecutive glucose values > 240 mg/dL): not included) Healthcare costs: Length of stay (days)

	Improvement: None
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Using a computerized coin toss, we randomly assigned seven teams of providers (42 internal medicine residents) working in general medical acute care units to have the option to use the order template (intervention group) or to use usual insulin ordering (control group)"
Allocation concealment (selection bias)	Low risk	"Using a computerized coin toss, we randomly assigned seven teams of providers (42 internal medicine residents) working in general medical acute care units to have the option to use the order template (intervention group) or to use usual insulin ordering (control group)"
Baseline outcome measurements similar	Unclear risk	It is unclear if the mean blood glucose values given at the beginning of the results were baseline data or results with all randomized participants (186 ± 56 mg/dL in intervention participants versus 206 ± 61 mg/dL in control participants (P value = 0.004))
Baseline characteristics similar	Low risk	There was no significant differences on participants demographic or primary diagnosis (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	144 insulin-treated people with type 2 diabetes were admitted, 16 participants whose point-of-care glucose values were between 60 and 180 mg/dL were excluded (non-target population)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Team of providers were randomized but the study was carried out in a single site

Wexler 2010 (*Continued*)

Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

White 1987

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not done
Participants	Profession: Mixed (physicians + pharmacists) Level of training: Accredited/licensed Clinical specialty: Other (anticoagulant clinic) Country: USA (California) Centre: 2 university hospitals (Veterans Administration Medical Center, Davis Medical Center) Location of care: Inpatient care Participants: 75 participants requiring anticoagulation with warfarin
Interventions	Clinical problem: Warfarin initiation Intervention: Initial dose suggested by Bayesian computer pharmacokinetic and pharmacodynamic model (n = 39) vs. usual care (n = 36) Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Not reported Calculated dose given as a recommendation: Yes
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None (participant with supratherapeutic prothrombin ratio (PR) at any time: not included) Physiological parameters: Days on warfarin PR therapeutic Time to achieve therapeutic control: Time to reach a therapeutic PR, time to reach a therapeutic dose Clinical events: Proportion of participants with a bleeding complication, death Healthcare costs: Length of stay Improvement: None
Notes	The therapeutic range was defined as PR = 1.8 ± 0.4, or, using a generalized formula, PR±(0.22)*(PR)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

White 1987 (*Continued*)

Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	Not applicable
Baseline characteristics similar	Low risk	There was no significant differences on demographic and clinical characteristics of participants (table 1)
Incomplete outcome data (attrition bias) All outcomes	Low risk	There were 4/36 participants in the physician-dosed group and 3/39 in the computer-dosed group which data could not be analyzed. Incomplete data were unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Low risk	All relevant outcomes were reported in the results section
Other bias	Low risk	No evidence of other risk of biases

White 1991

Methods	Design: RCT Unit of allocation: Participant Unit of analysis: Participant Power calculation: Not reported
Participants	Profession: Nurses Level of training: Mixed Clinical specialty: Not reported Country: USA (California) Centre: 1 university hospital (Davis Medical Center) Location of care: Outpatient care Participants: 50 participants needing anticoagulation with warfarin (long-term oral therapy)

White 1991 (*Continued*)

Interventions	Clinical problem: Long-term warfarin adjustment Intervention: Maintenance dose suggested by Bayesian computer pharmacokinetic model (n = 24) vs. usual care (n = 26) Computer advice: Given in real time CDSS integration in CPOE: No Starter: User-initiated Type of intervention: Direct intervention Calculated dose given as a recommendation: Not reported
Outcomes	Dose of drug administered to the participant: None Serum concentrations and therapeutic range: None Physiological parameters: None (proportion of participants within target (final prothrombin time): reported) Time to achieve therapeutic control: None Clinical events: None Healthcare costs: None Improvement: None
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Random sequence generation not specified
Allocation concealment (selection bias)	Unclear risk	No information provided
Baseline outcome measurements similar	Low risk	"There were no significant differences between the groups with respect to age, gender, target prothrombin times, percentage of patients initially below the target, percentage of patients initially above the target, or the mean of the absolute value of the differences between initial prothrombin times and the corresponding target prothrombin times (Table 1)"
Baseline characteristics similar	Low risk	"There were no significant differences between the groups with respect to age, gender, target prothrombin times, percentage of patients initially below the target, percentage of patients initially above the target, or the mean of the absolute value of the differences between initial prothrombin times and the corresponding target prothrombin times (Table 1)"

White 1991 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	2/26 participants in the nurse-specialist group and 1/24 participant in the computer group did not return for follow-up. Incomplete data were unlikely to overturn the study results
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcomes were objective
Blinding of participants and personnel (performance bias) All outcomes	High risk	Participants were randomized
Selective reporting (reporting bias)	Unclear risk	Outcomes were not described in the methods section
Other bias	Low risk	No evidence of other risk of biases

CDSS: clinical decision support system; CGMS: continuous glucose monitoring system; CPOE: computer physician order entry; CsA: cyclosporine A; eMPC: Enhanced software Model Predictive Control; GP: general practitioner; ICU: intensive care unit; INR: international normalized ratio; IU: international unit; IV: intravenous; KADIS: KArlsburg Diabetes Management System; MMF: mycophenolate mofetil; MPA: mycophenolic acid (MPA); NRCT: non-randomized controlled trial; RCT: randomized controlled trial.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbrecht 1982	- Not computerized drug dosage (computer controlled pump not under physician control)
Absalom 2003	- Not computerized drug dosage (automatic control of the propofol infusion using closed-loop system)
Albisser 2007	- Not computerized drug dosage (prediction of future glycaemia and future risks of hypoglycaemia and hyperglycaemia)
Alvis 1985	- Design
Barletta 2009	- Design (before and after study without control group)
Barras 2008	- Not computerized drug dosage (trial comparing individualized dosing of enoxaparin based on participa nt weight and renal function to conventional dosing)

(*Continued*)

Barras 2010	- Not computerized drug dosage (dose calculated from an equation including the weight of the participa nt)
Bartal 2003	- Not computerized drug dosage (utility of pharmacokinetic monitoring of aminoglycoside levels in the context of once-daily treatment (primary endpoint: renal toxicity))
Berg 2009	- Not computerized drug dosage (individually tailored treatment duration)
Burger 2003	- Not computerized drug dosage (t able with therapeutic drug monitoring rules depending on the concentration ratio method (standardized pharmacokinetic curve))
Bury 2005	- Not computerized drug dosage
Caraballo 2008	- Not computerized drug dosage (alerts)
Carter 1987a	- Not computerized drug dosage
Cavalcanti 2009	- Design (the target range for blood glucose was different according to the interventions or the conventional treatment)
Chan 2006	- Design (before and after study without control group)
Chiarelli 1990	- Participa nt aid not under physician control
Cohen 2007	- Not computerized drug dosage (trial comparing growth hormone dosing using a prespecified algorithm to conventional growth hormone dose)
Collins 2004	- Not computerized drug dosage (alerts)
Cupissol 1996	- Not computerized drug dosage (control of the cisplatin infusion using automatic pump)
Demakis 2000	- Not computerized drug dosage (reminder to standard of care)
Dillon 1989	- Design (some participa nts in the standardized dosing arm crossed-over to pharmacokinetic dosing arm)
Donovan 2010	- Not computerized drug dosage (alerts)
Doran 2004	- Design (cohort with 4 participa nts)
Dortch 2008	- Design (retrospective study)
Evans 1998	- Design (before and after study without control group)
Evans 1998a	- Not computerized drug dosage (no recommendation to the healthcare professional: chemotherapy protocol)

(*Continued*)

Evans 1999	- Design (before and after study without control group)
Faber 2006	- Not computerized drug dosage (individualize d dosing concerned the day of administration)
Feldstein 2006	- Not computerized drug dosage (alert for prescribing laboratory monitoring test)
Fety 1998	- Not computerized drug dosage (no recommendation to the healthcare professional: chemotherapy protocol)
Field 2009	- The dose advice was not individualized (maximal suggested dose)
Field 2009a	- The dose advice was not individualized (maximal suggested dose)
Fihn 1994	- Absence of relevant data for primary outcome
Fitzmaurice 1996	- Absence of relevant data for primary outcome
Fitzmaurice 1998	- Design
Flanders 2009	- Design (before and after study without control group)
Fritsch 2009	- Not computerized drug dosage (target-controlled inhalation induction)
Fukudo 2009	- Design (control group without random or quasi-random allocation)
Gamelin 2008	- Not computerized drug dosage (table with dose-adjustment algorithm according to plasma concentration)
Ghazal-Aswad 1997	- Conference publication (contact author failed due to erroneous email)
Gopakumaran 2004	- Discussion
Griffey 2012	- The dose advice was not individualized (most commonly used dose)
Guarracino 2001	- Not computerized drug dosage (evaluation of automated protamine dose assay)
Guarracino 2003	- Design (n ot a comparative study)
Hermayer 2007	- Design (before and after study without control group)
Hobbs 1996	- Absence of relevant data for primary outcome
Hoffman 2004	- Not computerized drug dosage (dose adjustment based on the occurrence of adverse events)
Horn 2002	- Design

(*Continued*)

Hwang 2004	- Design
Jankovic 1999	- The 15 participa nts from the Jankovic study were included in the Mihajlovic study (60 participa nts)
Jannuzzi 2000	- Not computerized drug dosage (dosage based on serum drug level monitoring)
Jellinek 2005	- Not computerized drug dosage (decision support algorithm)
Judge 2006	- Not computerized drug dosage (alerts)
Jung 2009	- Not computerized drug dosage (no individualized dose recomme nded to the healthcare professional: protocol for adjustment of growth hormone dosage)
Kazemi 2011	- Design (before and after study without control group)
Kirk 2005	- Design (cohort study)
Koide 2000	- Design (before after study)
Kristrom 2009	- The dose advice was not individualized (dose selection within an interval using a predicted response)
Kroese 2005	- Design (n ot a comparative study)
la Cour Freiesleben 2009	- Not computerized drug dosage (paper nomogram)
Lester 2006	- Not computerized drug dosage (email with low-density lipopr o tein therapeutic goal)
Ligtenberg 2006	- Not a study but a comment on Plank 2006
Lillis 2003	- Design (case history)
Liu 2006	- Not computerized drug dosage (closed-loop system)
Manotti 2001 maintenance	- Absence of relevant data for primary outcome
Mar Fernandez 1996	- Not computerized drug dosage (no recommendation to the healthcare professional: pharmacokinetic model used for drug monitoring)
Mar Fernandez 2009	- Not computerized drug dosage (predictive performance of population models)
Matheny 2008	- Not computerized drug dosage (reminders for annual intervals for laboratory monitoring)
Maurizi 2011	- Participa nt aid not under physician control (advice delivered directly to the participa nt: self monitor glucose)
McCluggage 2010	- Design (historical control group)

(*Continued*)

McCowan 2001	- Not computerized drug dosage (software that implements guidelines during consultations)
McCoy 2008	- Not computerized drug dosage (alerts)
McCoy 2010	- Not computerized drug dosage (alerts)
McDonald 1976	- Not computerized drug dosage (reminders)
McDonald 1980	- Not computerized drug dosage (dose prescribing rather than drug dosage)
McMichael 1993	- Absence of relevant data for primary outcome (n o professional behaviour change or participa nt outcomes)
McMullin 1997	- Design (n ot a comparative study)
McMullin 2004	- Not computerized drug dosage (list of prescriptions most appreciate)
McMullin 2005	- Not computerized drug dosage (list of prescriptions most appreciate)
Motykie 1999	- Design (historical control group)
Mullett 2001	- Design (before and after study without control group)
Murchie 1989	- Absence of relevant data for primary outcome
Nash 2005	- Not computerized drug dosage (thresholds)
Newby 2002	- Not computerized drug dosage (automated adjustment)
Nieuwenhuyze 1995	- Participa nt aid not under physician control
Nightingale 2000	- Not computerized drug dosage (dose prescribing rather than drug dosage)
Oppenheim 2002	- Design (not a comparative study)
Overhage 1997	- The dose advice was not individualized (' response orders')
Palen 2006	- Not computerized drug dosage (alert for prescribing laboratory monitoring test)
Pea 2002	- Absence of relevant data for primary outcome
Peck 1973	- Absence of relevant data for primary outcome
Peters 1996	- Participa nt aid not under physician control
Peterson 1986	- Participa nt aid not under physician control

(*Continued*)

Peterson 2005	- Not computerized drug dosage (screen showing the most commo nly used dose)
Peterson 2007	- Not computerized drug dosage (screen showing a default dose and minimum/maximum dose)
Phillips 2008	- Design (n ot a comparative study)
Piazza 2009	- Not computerized drug dosage (alerts)
Poller 1993	- Absence of relevant data for primary outcome
Popovic-Todorovic 2003	- Not computerized drug dosage (rules without calculation)
Proost 2003	- Discussion (p resentation of the project PharmDIS-e+)
Roberts 2010	- Design (before and after study without control group)
Rochon 2006	- Discussion
Rood 2005	- Absence of relevant data for primary outcome
Rothschild 2002	- Absence of relevant data for primary outcome (survey)
Rothschild 2003	- Not computerized drug dosage (feedback)
Rothschild 2005	- Not computerized drug dosage (smart infusion pumps providing decision support feedback)
Rotman 1996	- Not computerized drug dosage
Roumie 2005	- Not computerized drug dosage (alert with guidelines or goal blood pressure)
Ruiz 1993	- Not computerized drug dosage (closed-loop system)
Ryff-de Leche 1992	- Not computerized drug dosage (infusion not under physician control)
Santana 2003	- Not computerized drug dosage (treatment plan in 2 cohorts)
Santana 2005	- Design (n ot a comparative study)
Schneider 2005	- Not computerized drug dosage (organizational computer program)
Schrezenmeir 2002	- Participa nt aid not under physician control (advice delivered directly to the participa nt)
Shiach 2002	- Not computerized drug dosage (comparison of 2 systems of prothrombin time measurement)
Shieh 2006	- Not computerized drug dosage (comparison of 2 protocols for drug controller)

(*Continued*)

Soper 2006	- Design (historical control group)
Sparano 2006	- Not computerized drug dosage (trial comparing 2 therapies)
Strack 1985	- Design
Tamblyn 2003	- Not computer drug dosage
Tamblyn 2008	- Not computerized drug dosage (adherence calculation)
Tamblyn 2010	- Not computerized drug dosage (adherence calculation)
Terrell 2009	- Not computerized drug dosage (recommendation on substitute therapies)
Thomson 2011	- Design (before and after study without control group)
Tierney 2005	- Not computerized drug dosage (reminders)
Tomek 2011	- Conference publication (the author was contacted by January 201 2 but the message could not be delivered because the recipient ad d ress was rejected))
Traugott 2011	- Design (before and after study without control group)
Trivedi 2007	- Design (discussion)
Trivedi 2007a	- Not computerized drug dosage (decision support tool without calculation)
van der Bol 2010	- Not computerized drug dosage (dose calculated from an equation)
van Leeuwen 2005	- Abstract corresponding to the study published in 2007 (excluded study: van Leeuwen 2007)
van Leeuwen 2007	- Design (n o control group: comparison of 2 computer algorithms)
van Lent-Evers 1999	- Design (historical control group)
Van Wyk 2008	- Not computerized drug dosage (screening and treatment of dyslipidaemia)
Verstappen 2007	- Not computerized drug dosage (CAMERA study: comparison of 2 strategies of management in early rheumatoid arthritis)
Verstappen 2010	- Not computerized drug dosage (CAMERA study: comparison of 2 strategies of management in early rheumatoid arthritis)
Wasmuth 2007	- Design (cohort study)
Wasmuth 2007a	- Not computerized drug dosage (trial comparing 2 doses of treatment)

(*Continued*)

Whipple 1991	- Not computerized drug dosage (the clinical pharmacist calculated the dose and interval of aminoglycoside concentration)
White 1984	- Absence of relevant data for primary outcome
Willcourt 1994	- Participa nt aid not under physician control
Wilson 2002	- Design (cohort study)
Yamamoto 2005	- Not computerized drug dosage (dose calculated from an equation)

Characteristics of studies awaiting assessment *[ordered by study ID]*

Anderson 2011

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Anderson 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Caduff 2013

Methods	
Participants	
Interventions	
Outcomes	

Caduff 2013 (*Continued*)

Notes	Not yet assessed

Dumont 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Horibe 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Jeanne 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Joerger 2012

Methods	
Participants	
Interventions	
Outcomes	

Joerger 2012 (*Continued*)

Notes	Not yet assessed

Kelly 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Kim 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Magee 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Nieuwlaat 2011

Methods	
Participants	
Interventions	

Nieuwlaat 2011 (*Continued*)

Outcomes	
Notes	Not yet assessed

Nieuwlaat 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Overgaard 2010

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Pielmeier 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Radhakrishnan 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Rasmussen 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Spaniel 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Tamblyn 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Whitehead 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

Wiltshire 2012

Methods	
Participants	
Interventions	
Outcomes	
Notes	Not yet assessed

DATA AND ANALYSES

Comparison 1. Serum concentrations and therapeutic range

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Serum concentrations (mg/L) - part A (SMD > 0 in favour of the intervention)	9		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Aminoglycoside antibiotics: peak concentration	4	372	Std. Mean Difference (IV, Random, 95% CI)	0.79 [0.46, 1.13]
1.2 Theophylline	4	201	Std. Mean Difference (IV, Random, 95% CI)	0.41 [-0.20, 1.02]
1.3 Lidocaine	1	20	Std. Mean Difference (IV, Random, 95% CI)	1.32 [0.33, 2.32]
2 Serum concentrations (ng/L) - part B (SMD < 0 in favour of the intervention)	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Midazolam	1	24	Std. Mean Difference (IV, Random, 95% CI)	-1.43 [-2.34, -0.51]
2.2 Fentanyl	1	24	Std. Mean Difference (IV, Random, 95% CI)	0.27 [-0.53, 1.08]
2.3 Antidepressants: steady-state plasma concentration	1	60	Std. Mean Difference (IV, Random, 95% CI)	-0.68 [-1.20, -0.16]
3 Proportion of participants within therapeutic range	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 Aminoglycoside antibiotics: % of participants with peak concentrations adequate after 2 days	2	72	Risk Ratio (M-H, Random, 95% CI)	4.44 [1.94, 10.13]
3.2 Anti-rejection drugs	1	125	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.38, 1.32]
4 Proportion of participants with toxic drug levels	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 Theophylline	2	109	Risk Ratio (M-H, Random, 95% CI)	0.53 [0.25, 1.13]

Comparison 2. Physiological parameters

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Oral anticoagulants: % time in target INR range	6	13581	Mean Difference (IV, Random, 95% CI)	3.68 [0.90, 6.45]
2 Insulin: % time in target glucose range	4	234	Mean Difference (IV, Random, 95% CI)	22.18 [9.94, 34.43]
3 Insulin: mean blood glucose (mg/dL)	9	520	Std. Mean Difference (IV, Random, 95% CI)	-0.72 [-1.03, -0.42]

Comparison 3. Time to achieve therapeutic control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Time to achieve therapeutic range	5		Mean Difference (IV, Random, 95% CI)	Subtotals only
1.1 Oral anticoagulants: time to achieve therapeutic prothrombin ratio (days)	2	223	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.84, 0.69]
1.2 Insulin: time to achieve therapeutic control (h)	3	134	Mean Difference (IV, Random, 95% CI)	0.53 [-1.22, 2.27]
2 Time to stabilization	3		Std. Mean Difference (IV, Random, 95% CI)	Subtotals only
2.1 Oral anticoagulants: time to stabilization (days)	3	255	Std. Mean Difference (IV, Random, 95% CI)	-0.56 [-1.07, -0.04]

Comparison 4. Clinical improvement

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Aminoglycoside antibiotics	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Number of participants cured	2	271	Risk Ratio (M-H, Random, 95% CI)	1.12 [1.02, 1.22]
2 Anti-rejection drugs	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
2.1 No biopsy-confirmed rejections	2	170	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [1.00, 1.32]

Comparison 5. Clinical adverse events

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death	10	14046	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.80, 1.45]
1.1 Oral anticoagulants	5	13499	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.78, 1.51]
1.2 Aminoglycoside antibiotics	3	326	Risk Ratio (M-H, Random, 95% CI)	0.66 [0.14, 3.10]
1.3 Theophylline	1	91	Risk Ratio (M-H, Random, 95% CI)	0.18 [0.01, 3.64]
1.4 Cyclosporine	1	130	Risk Ratio (M-H, Random, 95% CI)	1.0 [0.06, 15.65]
2 Anticoagulants: events	7		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Bleeding	6	552	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.30, 1.41]
2.2 Thromboembolism	4	355	Risk Ratio (M-H, Random, 95% CI)	3.25 [0.66, 16.03]
3 Anticoagulants: event rates	4		Rate Ratio (Random, 95% CI)	Subtotals only
3.1 Bleeding	4	18902	Rate Ratio (Random, 95% CI)	0.81 [0.60, 1.08]
3.2 Thromboembolism	4	18902	Rate Ratio (Random, 95% CI)	0.68 [0.49, 0.94]
4 Insulin	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

4.1 Hypoglycaemia (< 60 mg/dL)	7	378	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.35, 1.48]
4.2 Severe hypoglycaemia (< 40 mg/dL)	4	292	Risk Ratio (M-H, Random, 95% CI)	0.69 [0.11, 4.31]
5 Aminoglycoside antibiotics	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 Nephrotoxicity	4	493	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.42, 1.06]
6 Anti-rejection drugs	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 Cytomegalovirus infections	2	170	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.58, 1.40]

Comparison 6. Healthcare resources

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Length of stay (days)	9	18507	Std. Mean Difference (IV, Random, 95% CI)	-0.15 [-0.33, 0.02]
1.1 Oral anticoagulants	2	105	Std. Mean Difference (IV, Random, 95% CI)	-0.12 [-1.10, 0.86]
1.2 Insulin	1	128	Std. Mean Difference (IV, Random, 95% CI)	0.18 [-0.17, 0.53]
1.3 Theophylline	3	151	Std. Mean Difference (IV, Random, 95% CI)	-0.20 [-0.56, 0.16]
1.4 Aminoglycoside antibiotics	2	295	Std. Mean Difference (IV, Random, 95% CI)	-0.35 [-0.58, -0.12]
1.5 Anti-rejection drugs	1	17828	Std. Mean Difference (IV, Random, 95% CI)	-0.04 [-0.07, -0.01]

WHAT'S NEW

Date	Event	Description
6 November 2013	New citation required but conclusions have not changed	A new search for studies was conducted January 2012.
12 December 2012	New search has been performed	Search strategies were significantly revised and databases searched from 1996 to January 2012

CONTRIBUTIONS OF AUTHORS

PD, IC, LT and FG prepared the protocol. All authors applied the inclusion criteria, assessed the quality and extracted the data for the included studies. FG and LT conducted the quantitative analyses and qualitative analyses. FG and EC drafted the manuscript with input from all authors. RW conducted the initial review and provided comments on the revised manuscript.

DECLARATIONS OF INTEREST

None.

INDEX TERMS

Medical Subject Headings (MeSH)

*Drug Therapy, Computer-Assisted; *Practice Patterns, Physicians'; Dosage Forms; Medication Errors [prevention & control]; Randomized Controlled Trials as Topic

MeSH check words

Humans