

EBM Presentation

2008-10-28

Speaker: Int. 戴逸昇

Supervisor: VS. 張毓弘 醫師

Clinical Scenario

- A 57-year-old woman was diagnosed of type 2 DM and she failed in sugar control with OAD.
 - Thus, basal insulin was suggested, but she afraid of **hypoglycemia event** and also want to know when is the **appropriate time** to receive basal insulin, morning or bed-time?
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Clinical Problem

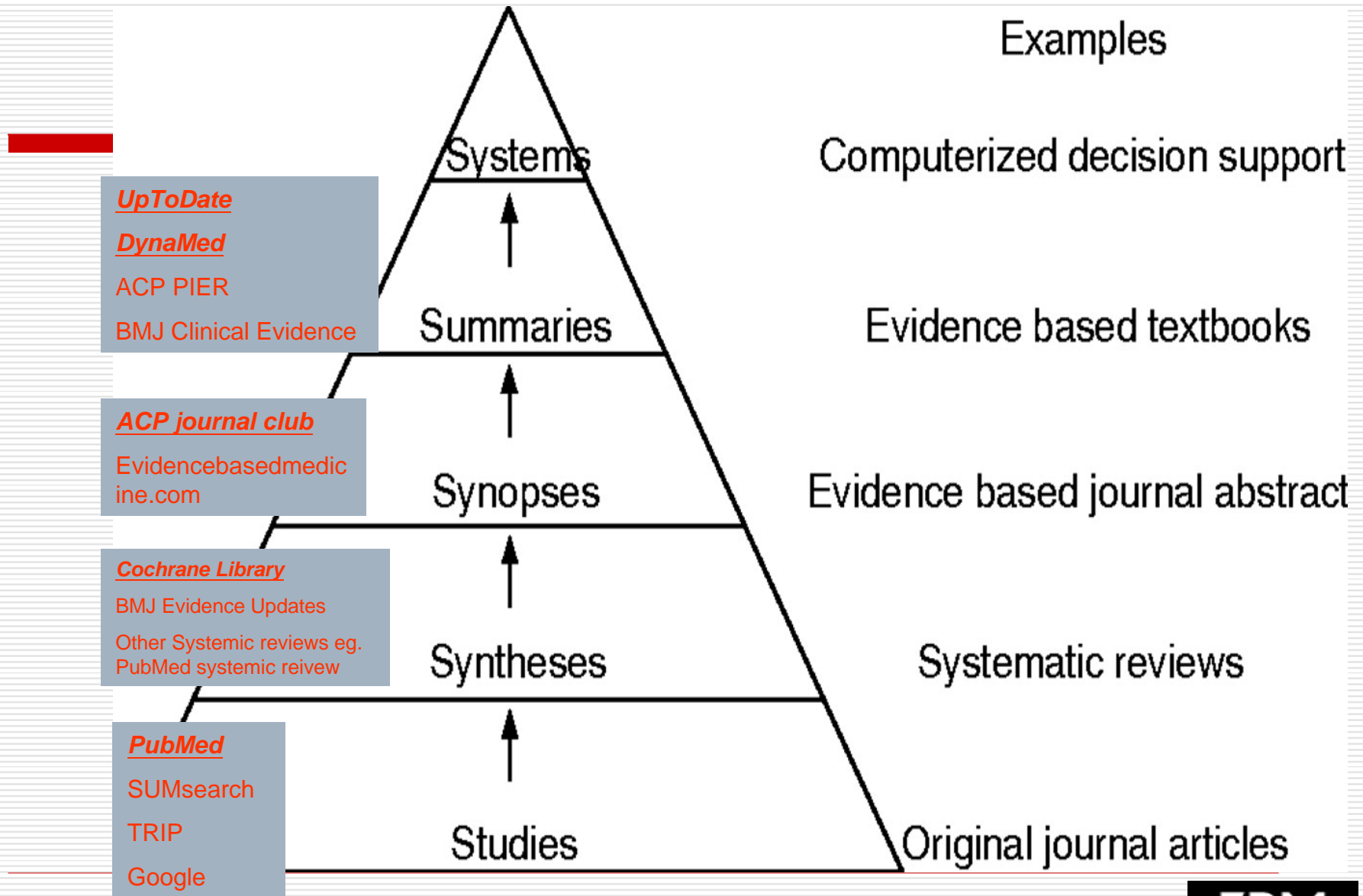
P	57 year-old woman with type 2 DM
I	Morning basal insulin
C	Bed time basal insulin
O	Hypoglycemia or sugar control

搜尋最有用的資料

先從已經過評讀的database開始找起
(system, summary, synopses, synthesis)
最後再找尚未經過嚴格評讀的study

The "5S" levels of organisation of evidence from healthcare research

Brian Haynes, R Evid Based Med 2006;11:162-164



SEARCH

- Key words:

type2 diabetes, insulin, basal insulin

- Data base: UpToDate

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Insulin therapy in type 2 diabetes mellitus - Mozilla Firefox
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Insulin therapy in type 2 diabetes mellitus

TOPIC OUTLINE

- INTRODUCTION
- NORMAL PATTERNS OF INSULIN SECRETION
- INSULIN PREPARATIONS
 - Premixed insulin preparations
- COMBINATION DRUG AND INSULIN THERAPY
 - Choice of insulin
 - Basal insulin
 - Pre-meal bolus insulin
 - Insulin dose
 - Optimal timing of insulin dose
- SWITCHING TO INSULIN MONOTHERAPY
 - Starting dose
 - Once-daily regimens
 - Twice-daily regimens
 - Intensive insulin
- INSULIN AS INITIAL THERAPY
- SUMMARY AND RECOMMENDATIONS
- REFERENCES
- GRAPHICS**
- ALGORITHMS
 - Insulin titration
- FIGURES
 - Microvasc endpoint and control
 - HbA1c with intensive therapy
 - Insulin glargine versus NPH
 - Time course of insulin action
- TABLES
 - Insulin pharmacokinetics
- RELATED TOPICS**
- Glycemic control and vascular complications in type 1 diabetes mellitus
- Glycemic control and vascular complications in type 2 diabetes

Insulin therapy in type 2 diabetes mellitus

Author
David K McCulloch, MD

Section Editor
David M Nathan, MD

Deputy Editor
Jean E Mulder, MD

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INTRODUCTION — The importance of glycemic control in minimizing complications related to diabetes has been well established in type 1 diabetes [1,2]. (See "Glycemic control and vascular complications in type 1 diabetes mellitus"). Similarly, the United Kingdom Prospective Diabetes Study (UKPDS) demonstrated that strict glycemic control in patients with type 2 diabetes results in a similar reduction in risk of microvascular disease (although the impact on prevention of macrovascular complications in type 2 diabetes remains uncertain) (show figure 1) [3]. (See "Glycemic control and vascular complications in type 2 diabetes mellitus").

Based upon the results of the UKPDS, normoglycemia is now the goal for many patients with type 2 diabetes. Initial therapy should begin with diet, weight reduction, and exercise, which may induce normoglycemia if compliance is optimal. Metformin therapy (in the absence of contraindications) may be initiated, concurrent with lifestyle intervention, at the time of diabetes diagnosis. (See "Initial management of blood glucose in type 2 diabetes mellitus", section on Medications for initial therapy).

Oral agents become less effective as beta cell function declines. After a successful initial response to oral therapy, patients fail to maintain target A1C levels (<7 percent) at a rate of 5 to 10 percent per year. In the UKPDS, 50 percent of patients originally controlled with a single drug required the addition of a second drug after three years and, by nine years, 75 percent needed multiple therapies to achieve the target hemoglobin A1C value (show figure 2) [4].

The therapeutic options for patients who fail therapy with an oral hypoglycemic drug are to add a second drug, add insulin, or discontinue the drug and switch to insulin. There is no consensus about which option is most effective. However, insulin is the preferred second-line medication for patients with A1C >8.5 percent or with symptoms of hyperglycemia despite metformin titration. Thus, many patients with type 2 diabetes will ultimately require treatment with insulin. (See "Management of persistent hyperglycemia in type 2 diabetes mellitus" section on Treatment options).

The role of insulin in achieving optimal glycemic control in patients with type 2 diabetes will be reviewed here. General principles of insulin therapy, insulin therapy in type 1 diabetes, and intensive insulin therapy for critically ill patients (who are not necessarily diabetic) are discussed elsewhere. (See "General principles of insulin therapy in diabetes mellitus" and see "Insulin therapy in type 1 diabetes mellitus" and see "Nutritional support in the critically ill" section on Glucose control).

An interactive case that highlights initiating insulin therapy in type 2 diabetes is found elsewhere. (See "Interactive diabetes case 2: Switching from oral agents to insulin in type 2 diabetes").

NORMAL PATTERNS OF INSULIN SECRETION — Insulin is secreted in a pulsatile manner; pulses occur under basal (unstimulated) conditions and in response to meals [5]. Basal insulin secretion represents approximately 50 percent of 24-hour insulin production, with the remainder accounted for by prandial (mealtime) excursions.

The term "intensive insulin therapy" has been used to describe complex regimens that separate basal insulin delivery (given as one to two daily injections of intermediate or long-acting insulin) with superimposed doses of short or rapid-acting insulins three or more times daily. Intensive regimens more nearly approximate normal insulin physiology. While intensive regimens were initially used for patients with type 1 diabetes, they are used for patients with type 2 diabetes as well.

INSULIN PREPARATIONS — In type 2 diabetes, Insulin is generally provided in two ways:

- As a basal supplement with an intermediate to long-acting preparation (NPH, glargine, or detemir) to suppress hepatic glucose production and maintain near normoglycemia in the fasting state.
- As a premeal bolus dose of short-acting (regular) or rapid-acting (lispro, aspart, glulisine) insulin to cover the extra requirements after food is absorbed. (See "General principles of insulin therapy in diabetes mellitus", section on Insulin preparations).

The approximate time of onset, peak activity, and duration of action of the most commonly used insulins are shown in the table (show table 1).

For many patients with type 2 diabetes, a basal supplement is often adequate for good glycemic control as endogenous insulin secretion will control the post-prandial excursions. Some patients with type 2

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完成

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- Basal insulin — While NPH has been used commonly at bedtime to supplement oral hypoglycemic drug therapy, longer acting insulins, such as [insulin glargine](#) (once daily) and detemir (once or twice daily), **added to oral agents are equally effective for reducing A1C values and may cause less nocturnal hypoglycemia, albeit at greater cost**
 - [Insulin detemir](#) is another available long-acting insulin analog; a fatty acid side chain that allows albumin binding results in prolongation in action. However, its duration of action appears to be substantially shorter than that of insulin glargine. As an example, in a 52-week study of supplementation of oral therapy with insulin glargine or detemir, there were similar improvements in glycemic control (mean A1C 7.1 and 7.2 percent, respectively), but over half of the participants (55 percent) required twice daily dosing with detemir, as opposed to once daily dosing with glargine .
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- Meta-analyses of trials in patients with type 2 diabetes comparing once-daily [insulin glargine](#) or detemir to once- or twice-daily NPH insulin report similar glycemic control between groups. However, the rates of **symptomatic overall and nocturnal hypoglycemia**, while relatively infrequent with either basal insulin, **were lower in patients treated with either insulin glargine or detemir compared with NPH**. Thus, insulin glargine and detemir may have some relatively modest clinical advantages over NPH (less symptomatic and nocturnal hypoglycemia) with the important disadvantage of high cost.
 - If once daily insulin is added to oral hypoglycemic therapy in patients with type 2 diabetes, a single daily dose of either [insulin NPH](#) or detemir given at bedtime or [insulin glargine](#) given in the morning or at bedtime is a reasonable initial regimen. If nocturnal hypoglycemia or symptomatic hypoglycemia occurs in patients taking bedtime NPH, we adjust the dose or switch to insulin glargine.
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Optimal timing of insulin dose

- In contrast, a **morning rather than a bedtime dose of [insulin glargine](#) may provide better glycemic control** in patients with type 2 diabetes who are also treated with an oral agent. This issue was addressed in a randomized, controlled trial of 695 patients with type 2 diabetes previously treated with oral agents [17]. The following findings were noted:
 - [Glimepiride](#) given with a morning dose of insulin glargine lowered A1C significantly more than a bedtime dose of NPH (-1.24 versus -0.84 percentage points; difference of 0.40 percent) or a bedtime dose of insulin glargine (-1.24 versus -0.96 percentage points, difference of 0.28 percent).
 - Nocturnal hypoglycemia was less frequent with morning and bedtime insulin glargine than with bedtime NPH.
 - In summary, for patients with type 2 diabetes taking an oral hypoglycemic agent, the optimal timing is once-daily NPH or detemir at bedtime or once-daily [insulin glargine](#) in the morning or bedtime.
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1. Review: Long-acting insulin analogues do not improve glycemic control but do reduce nocturnal hypoglycemia in diabetes
2. 2007 - Review: Long-acting insulin analogues reduce risk for hypoglycemia compared with NPH insulin in type 2 diabetes
3. OAN: 2005 - Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial.
4. OAN: 2005 - Improvement of glycemic control in subjects with poorly controlled type 2 diabetes: comparison of two treatment algorithms using insulin glargine.
5. OAN: 2005 - Effects of exercise on the absorption of insulin glargine in patients with type 1 diabetes.
6. OAN: 2005 - Continuous subcutaneous insulin infusion (CSII) of insulin aspart versus multiple daily injection of insulin aspart/insulin glargine in type 1 diabetic patients previously treated with CSII.
7. OAN: 2008 - Advancing insulin therapy in type 2 diabetes previously treated with glargine plus oral agents: prandial premixed (insulin lispro protamine suspension/lispro) versus basal bolus (glargine/lispro) therapy.
8. OAN: 2006 - Comparison of glargine insulin versus rosiglitazone addition in poorly controlled type 2 diabetic patients on metformin plus sulfonylurea.
9. OAN: 2006 - Triple therapy in type 2 diabetes: insulin glargine or rosiglitazone added to combination therapy of sulfonylurea plus metformin in insulin-naïve patients.

http://www.acpjic.org/Content/148/2/issue/ACFJC-2008-148-2-037.htm

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Review: Long-acting insulin analogues do not improve glycemic control but do reduce nocturnal hypoglycemia in diabetes

For correspondence: Dr. K. Tran, Canadian Agency for Drugs and Technologies in Health, Ottawa, Ontario, Canada. E-mail pubs@cadth.ca.

Long-acting insulin analogues (LAIAs) vs conventional insulin (HPH) in diabetes*

Outcomes	Number of trials (n)	Diabetes type: LAIA	Weighted mean difference (95% CI)†	RRR/RRI (CI)	HIIT/HHH (CI)
Change in HbA _{1c} level‡	8 (2937)	Type 1: detemir	-0.05% (-0.12 to 0.03)		
	2 (980)	Type 2: detemir	0.11% (-0.03 to 0.26)		
	7 (2967)	Type 2: glargine	0.05% (-0.07 to 0.16)		
Nocturnal hypoglycemia	7 (2590)	Type 1: detemir		RRR 11% (3 to 18)	15 (9 to 34)
	1 (505)	Type 2: detemir		RRR 34% (4 to 54)	13 (7 to 133)
	7 (2626)	Type 1: glargine		RRR 8% (-4 to 19)	Not significant
	5 (2099)	Type 2: glargine		RRR 43% (26 to 56)	9 (7 to 12)
Severe hypoglycemia§	8 (2708)	Type 1: detemir		RRR 25% (5 to 41)	50 (25 to 100)
	6 (2701)	Type 1: glargine		RRR 22% (-5% to 42)	Not significant
	4 (1885)	Type 2: glargine		RRI 9% (-44 to 112)	Not significant

*HbA_{1c} = hemoglobin A_{1c}; HPH = neutral protamine Hagedorn; other abbreviations defined in [Glossary](#). RRR, RRI, HIIT, HHH, and CI calculated from data in article; all data combined using a random-effects model.

†Negative values indicate a benefit for insulin glargine or insulin detemir over HPH.

‡Trials of insulin glargine vs HPH in type 1 diabetes were heterogeneous and not pooled.

§Trials of insulin detemir in type 2 diabetes did not report severe

□ **Main results**

Glargine and NPH insulin did not differ for glycemic control: weighted mean difference in decrease in HbA1c level was 0% (95% CI -0.10 to 0.09) (6 RCTs, $n = 2902$). NPH insulin reduced HbA1c level by 0.12% (CI 0.01 to 0.23) more than detemir (2 RCTs, $n = 967$). Compared with NPH insulin, **glargine reduced risks for symptomatic and nocturnal hypoglycemia, and detemir reduced risks for overall and nocturnal hypoglycemia** (Table). Groups did not differ for severe hypoglycemia with either drug (Table).

□ **Conclusion**

In patients with type 2 diabetes, the **long-acting insulin analogues glargine and detemir reduce risk for hypoglycemia** compared with human isophane insulin, without sacrificing glycemic control.



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- Glimepiride combined with morning insulin glargine, bedtime neutral protamine hagedorn insulin, or bedtime insulin glargine in patients with type 2 diabetes. A randomized, controlled trial [Ann Intern Med 2003 Jun 17;138\(12\):952-9.](#)
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- ❑ BACKGROUND: Patients with type 2 diabetes are often treated with oral antidiabetic agents plus a basal insulin.
 - ❑ OBJECTIVE: To investigate **the efficacy and safety of glimepiride combined with either morning or bedtime insulin glargine or bedtime neutral protamine Hagedorn (NPH) insulin** in patients with type 2 diabetes.
 - ❑ DESIGN: Open-label, randomized, controlled trial.
 - ❑ SETTING: 111 centers in 13 European countries.
 - ❑ PATIENTS: 695 patients with type 2 diabetes who were previously treated with oral antidiabetic agents.
 - ❑ INTERVENTION: Randomization to treatment with morning insulin glargine, bedtime NPH insulin, or bedtime insulin glargine for 24 weeks in addition to 3 mg of glimepiride. The insulin dose was titrated by using a predefined regimen to achieve fasting blood glucose levels of 5.56 mmol/L or lower (< or =100 mg/dL).
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□ RESULTS: Hemoglobin A(1c) levels improved by -1.24% (two-sided 90% CI, -1.10% to -1.38%) with morning insulin glargine, by -0.96% (CI, -0.81% to -1.10%) with bedtime insulin glargine, and by -0.84% (CI, -0.69% to -0.98%) with bedtime NPH insulin. **Hemoglobin A(1c) improvement was more pronounced with morning insulin glargine** than with NPH insulin (0.40% [CI, 0.23% to 0.58%]; P = 0.001) or bedtime insulin glargine (0.28% [CI, 0.11% to 0.46%]; P = 0.008). Baseline to end-point fasting blood glucose levels improved similarly in all three groups. **Nocturnal hypoglycemia was less frequent with morning** (39 of 236 patients [17%]) **and bedtime** insulin glargine (52 of 227 patients [23%]) than with bedtime NPH insulin (89 of 232 patients [38%]) (P < 0.001).

□ CONCLUSION: The **risk for nocturnal hypoglycemia was lower with glimepiride in combination with morning and bedtime** insulin glargine than with glimepiride in combination with bedtime NPH insulin in patients with type 2 diabetes. **Morning insulin glargine provided better** glycemic control than did bedtime insulin glargine or bedtime NPH insulin.

Appraisal

Level of evidence

Oxford Centre for Evidence-based Medicine Levels of Evidence (May 2001)

Level	Therapy/Prevention, Aetiology/Harm	Prognosis	Diagnosis	Differential diagnosis/symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR† validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR† with 1b studies from different clinical centres	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval‡)	Individual inception cohort study with ≥ 80% follow-up; CDR† validated in a single population	Validating** cohort study with good††† reference standards; or CDR† tested within one clinical centre	Prospective cohort study with good follow-up****	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none§	All or none case-series	Absolute SpPins and SnNouts††	All or none case-series	Absolute better-value or worse-value analyses †††
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR† or validated on split-sample§§§ only	Exploratory** cohort study with good††† reference standards; CDR† after derivation, or validated only on split-sample§§§ or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research; Ecological studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Non-consecutive study; or without consistently applied reference standards	Non-consecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies§§)	Case-series (and poor quality prognostic cohort studies***)	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on economic theory or "first principles"

Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998.

Grades of Recommendation

A	consistent level 1 studies
B	consistent level 2 or 3 studies <i>or</i> extrapolations from level 1 studies
C	level 4 studies <i>or</i> extrapolations from level 2 or 3 studies
D	level 5 evidence <i>or</i> troublingly inconsistent or inconclusive studies of any level

Will the Results Help Me in Caring for My Patients ?

- Are the people in the study like my patient ?
 - Age
 - General state of health
 - Type and severity of disease process
 - Time in the course of the disease
- Did the study cover all aspects of problem ?
 - eg treatment effect on symptom relief, quality of life, mortality etc
- Is the treatment feasible in my setting ?
- Will the potential benefits of treatment outweigh the potential harms of treatment for my patients ?
- Does it suggest a clear and useful plan of action ?
 - Help to clarify a patient's prognosis
 - Suggest a useful plan to improve patient's state of health

P

Validity	Article
所取樣本是否有臨床代表性，是否與我的病人差不多	yes
分組是否有隨機盲法分組	Open label, randomized, controlled trial No, not double blinded
失去追蹤個案數是否過多？ 5/20% rule	No, loss follow up <5%

I and C

Feasible?	Article 1
I是否清楚描述並且是可行的	yes
C是否清楚描述並且是可行的	yes

Cover all problems?	Article 1
是否包含提出的所有問題？	yes

Result

Table 2. Effect of Bedtime Neutral Protamine Hagedorn Insulin, Bedtime Insulin Glargine, or Morning Insulin Glargine on Glycemic Control*

Variable	Bedtime NPH Insulin Group	Bedtime Insulin Glargine Group	Morning Insulin Glargine Group	Overall P Value
Patients, <i>n</i>	232	227	236	
Mean improvement in HbA _{1c} level† (90% CI), %	-0.84 (-0.69 to -0.98)	-0.96‡ (-0.81 to -1.10)	-1.24§ (-1.10 to -1.38)	<0.001
HbA _{1c} level < 7.5%, <i>n</i> (%)	74 (32.5)	75 (33.6)	102 (43.4)¶	0.022

Table 3. Patients with Hypoglycemic Episodes Treated with Bedtime Neutral Protamine Hagedorn Insulin, Bedtime Insulin Glargine, or Morning Insulin Glargine*

Variable	Bedtime NPH Insulin Group	Bedtime Insulin Glargine Group	Morning Insulin Glargine Group	Overall P Value
Patients, <i>n</i>	232	227	236	
All episodes of hypoglycemia, <i>n</i> (%)	173 (75)	155 (68)	175 (74)	>0.2
All episodes of symptomatic hypoglycemia, <i>n</i> (%)	135 (58)	98† (43)	133 (56)	0.002
Nocturnal hypoglycemia, <i>n</i> (%)	89 (38)	52‡ (23)	39‡ (17)	<0.001
Severe hypoglycemia, <i>n</i> (%)	6 (2.6)	4 (1.8)	5 (2.1)	>0.2

* NPH = neutral protamine Hagedorn.

† *P* = 0.004 versus morning insulin glargine and *P* = 0.001 versus bedtime NPH insulin.

‡ *P* < 0.001 versus bedtime NPH insulin.

O

Result	Article1
測量方式是否客觀，有無雙盲	yes
是否是ITT analysis	yes
好處有多大，多精準ARR,NNT RRR(CI) HbA1c level < 7.5% (vs bedtime glargine)	ARR= 0.098 RRR= 0.29 NNT=10.20
副作用有多大，多精準 ARI,NNH RRI (CI) Nocturnal hypoglycemia (vs bedtime glargine)	ARI= -0.06 RRI= -0.217 NNH=15.63

總結與討論

- Insulin detemir and insulin glargine are safer than NPH in prevention of hypoglycemia event and effective in lowering HbA1C
 - Morning insulin glargine is more effective in lowering HbA1C than bed time insulin glargine
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Thank You for Your Attention
