GIMBE®
Gruppo Italiano per la Medicina Basata sulle Evidenze
Evidence-Based Medicine Italian Group

Decisioni Cliniche e Prove di Efficacia
Il Governo Clinico nelle Cure Primarie
Rimini, 3-4 ottobre 2008

Medicina e Persona

Workshop Clinici Interattivi (2)

I pazienti diabetici e la Medicina Generale Verso l'organizzazione di ambulatori dedicati?

Gianni Garozzo
Gabriele Forlani

Premessa

- La storia clinica del paziente si articola dal 1986 ad oggi
- Le decisioni cliniche riportate sono quelle reali
- Nella risposta ai quesiti fare sempre riferimento alle conoscenze oggi disponibili

Scenario Clinico

- Abramo è un ex piastrellista di 76 anni sposato con tre figlie
- Familiarità positiva per diabete (madre) e cardiopatia ischemica (padre)
- Forte fumatore (30 sigarette/die) e buon bevitore (1 bottiglia di vino/die)
- Iscritto nel 1983, lo conosco nel marzo 1986 quando viene in ambulatorio per lombalgia e gonalgia
- Rx: importante artrosi e osteofitosi in entrambi i distretti

Scenario Clinico

Dati obiettivi

- PAO 145/95 mmHg
- Modesta epatomegalia
- Peso 88 kg, BMI 31
- Glicemia 121 mg%, HbA1c 5.8%
- Colesterolo tot. 238 mg%, HDL 45 mg%, trigliceridi 251 mg%
- ECG: nei limiti di norma

Scenario Clinico

- Abramo rifiuta la curva da carico (dice che non ha tempo!), ma riesco ad ottenere un dignitoso profilo glicemico domenicale: glicemia basale 128 mg%, valori post-prandiali 144 mg% (2 ore dopo pranzo), 115 mg% (2 ore dopo cena)
- Propongo al sig. Abramo due obiettivi prioritari:
  - cessazione del fumo → ottenuta in 2 mesi
  - riduzione dell'alcool a 2-3 bicchieri/die →parzialmente raggiunta)
- Prescrivo dieta da 2.000 Kcal/die, riservandomi una restrizione calorica più decisa in tempi successivi

Scenario Clinico

1987

- Settembre: in occasione di meniscectomia consulenza diabetologica con diagnosi di IGT → prescritta dieta da 1800 Kcal/die. Non viene programmato alcun follow-up
- Novembre: PAO 160/100 mmHg dopo ripetuti controlli
- Inizio amlodipina 10 mg/die → 20 mg/die dopo 2 mesi
- La compliance è scarsa: il signor Abramo sospende ripetutamente la terapia, per riferiti episodi di ipotensione

Clinical Question

1. Condividi, come prima scelta, l'amlodipina per trattare l'ipertensione nei pazienti diabetici?

1. Sì
2. No, ACE inibitore
3. No, inibitore dell'angiotensina II
4. No, beta-bloccante
5. No, diuretico

NHS
National Institute for Health and Clinical Excellence

1.8.7 First-line blood-pressure-lowering therapy should be a once-daily, generic angiotensin-converting enzyme (ACE) inhibitor.

1.8.9 A calcium-channel blocker should be the first-line blood-pressure-lowering therapy for a woman for whom, after an informed discussion, it is agreed there is a possibility of her becoming pregnant.

1.8.10 For a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), substitute an angiotensin II-receptor antagonist for the ACE inhibitor.

American Diabetes Association®

• Pharmacologic therapy for patients with diabetes and hypertension should be with a regimen that includes either an ACE inhibitor or an ARB

• If one class is not tolerated, the other should be substituted

• If needed to achieve blood pressure targets, a thiazide diuretic should be added to those with an estimated GFR ≥50 and a loop diuretic for those with an estimated GFR < 50

Diabetes: treating hypertension

Search date February 2007
Sandeep Vijan

INTERVENTIONS

TREATMENTS

Beneficial

Angiotensin-converting enzyme inhibitors. 2

Diuretics. 4

Likely to be beneficial

Angiotensin II receptor antagonists (reduce cardiovascular events compared with beta-blockers). 6

Beta-blockers (similar reduction in cardiovascular and microvascular events to angiotensin-converting enzyme inhibitors, but may cause weight gain and increase the need for glucose-lowering therapy). 7

Calcium channel blockers (similar reduction in cardiovascular events to diuretics but less effective than angiotensin-converting enzyme inhibitors). 9

Unknown effectiveness

Alpha-blockers. 10

DIFFERENT BLOOD PRESSURE TARGETS

Beneficial

Lower blood pressure targets (more effective than higher targets). 11

Scenario Clinico

1988 – 1989

• Glicemia basale 115 - 130 mg%
• HbA1c 5.7% - 6.2%
• Profilo lipidico stabile
• PAO ben controllata: mediamente 140/85 mmHg
• Progressivo incremento ponderale sino a 95 kg, anche per la scarsa compliance al regime dietetico

Scenario Clinico

1990

• A febbraio inizio metformina: 500 mg/die, incrementando la dose in sei mesi sino a 2.500 mg/die (tre somministrazioni ai pasti principali)

• Autocontrollo glicemico quindicinale con valori basali intorno 130 mg%, postprandiali 140 – 160 mg%

• A fine anno Abramo pesa Kg 85

Clinical Question

2. L'autocontrollo della glicemia è efficace nel migliorare il compenso metabolico del DM II?

1. No
2. Sì, in tutti i pazienti
3. Sì, solo nei pazienti in trattamento insulinico

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1.4 Self-monitoring of plasma glucose

1.4.1 Offer self-monitoring of plasma glucose to a person newly diagnosed with type 2 diabetes only as an integral part of his or her self-management education. Discuss its purpose and agree how it should be interpreted and acted upon.

American Diabetes Association.

Self-monitoring of Blood Glucose (SMBG)

- SMBG should be carried out three or more times daily for patients using multiple insulin injections or insulin pump therapy. (A)

Diabetes: glycaemic control in type 2

Search date October 2006
Bala Srinivasan, Nick Taub, Kamlesh Khunti, and Melanie Davies.

OO **Unknown effectiveness**
Blood glucose self-monitoring. 21

Welschen LMC, Bloemendal E, Nijpels G,et al.

Self-monitoring of blood glucose in patients with type 2 diabetes mellitus who are not using insulin

Cochrane Database of Systematic Reviews 2008, Issue 3

RESULTS

- 6 RCT were included in the review: 4 compared SMBG with usual care, 1 compared SMBG with self-monitoring of urine glucose and there was 1 three-armed trial comparing SMBG with self-monitoring of urine glucose and usual care
- Because of heterogeneity between the studies, it was not possible to perform a meta-analysis
- The methodological quality of studies was low
- 2/6 studies reported a significant lowering effect of self-monitoring of blood glucose on HbA1c

Welschen LMC et al. CDSR 2008

CONCLUSION

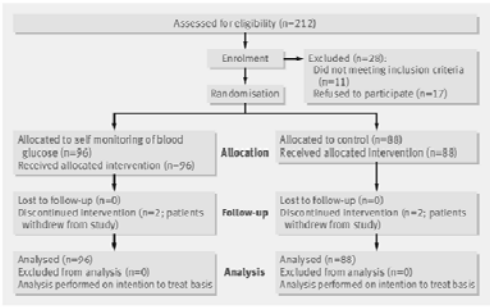
- Self-monitoring of blood glucose might be effective in improving glycaemic control in patients with type 2 diabetes who are not using insulin.
- To assess the potential beneficial effects of SMBG in these patients a large and well-designed randomised controlled trial is required.
- This long-term trial should also investigate patient-related outcomes like quality of life, well-being and patient satisfaction, and provide adequate education to the patient to allow SMBG to be effective.

Welschen LMC et al. CDSR 2008

Efficacy of self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes (ESMON study): randomised controlled trial

Maurice J O'Kane, consultant,[1] Brendan Bunting, professor,[2] Margaret Copeland, trial manager,[3] Vivien E Coates, professor,[3] on behalf of the ESMON study group

BMJ, 24 maggio 2008



WHAT IS ALREADY KNOWN ON THIS TOPIC

Self monitoring of blood glucose concentration in type 2 diabetes is widely advocated as an adjunct to achieving good glycaemic control

Randomised trials on self monitoring have given conflicting results, have been limited to patients with established diabetes, and have rarely considered quality of life

WHAT THIS STUDY ADDS

Self monitoring of blood glucose in patients with newly diagnosed type 2 diabetes did not result in improved glycaemic control but was associated with a 6% higher score on a depression index

Cost effectiveness of self monitoring of blood glucose in patients with non-insulin treated type 2 diabetes: economic evaluation of data from the DiGEM trial

Judit Simon, senior researcher,[1] Alastair Gray, professor,[1] Philip Clarke, senior international research fellow,[2] Alisha Wade, resident,[3] Andrew Neil, professor,[4] Andrew Farmer, lecturer,[3] on behalf of the Diabetes Glycaemic Education and Monitoring Trial Group

BMJ, 24 maggio 2008

WHAT IS ALREADY KNOWN ON THIS TOPIC

The clinical effects of blood glucose testing in non-insulin treated type 2 diabetes are unclear

Self monitoring of blood glucose is costly

A previous study suggesting that routine self monitoring could be cost effective for non-insulin treated diabetes was potentially confounded by heterogeneity

WHAT THIS STUDY ADDS

Self monitoring in non-insulin treated type 2 diabetes is unlikely to be cost effective and should not be recommended for routine use

The additional intervention costs of self monitoring of blood glucose are between £84 and £92 per patient over 12 months

Self monitoring has an initial negative impact on quality of life, in part associated with increased reported anxiety

Self monitoring of blood glucose in type 2 diabetes

May not be clinically beneficial or cost effective and may reduce quality of life

Scenario Clinico

1991- 95

- Benessere, ad eccezione dei dolori articolari
- PAO ben controllata
- Tre controlli di HbA1c tra 5.7 e 6.2%
- Funzionalità renale nella norma
- Profilo lipidico invariato
- ECG: blocco incompleto di branca dx
- Fundus oculi: normale

Scenario Clinico

1996 – 1998

- Arriva la sospirata pensione: pomeriggi al circolo e attività fisica scarsa portano Abramo ai 100 kg
- PAO ben controllata: mediamente 130/80 mmHg
- Visita oculistica: vitreopatia degenerativa, non retinopatia
- HbA1c 7.2 % → 8%

Clinical Question

2. DIABETE

3. Quale decisione terapeutica per migliorare il controllo metabolico del sig. Abramo?

1. Nessuna
2. ↑ dosaggio metformina
3. Aggiunta altro ipoglicemizzante orale
4. Insulina
5. Richiesta consulenza diabetologica

Scenario Clinico

1998

• Marzo: aggiungo glibenclamide 2.5 mg x 2 che nei mesi successivi aumento a 5 mg x 2

• Giugno: diagnosi di carcinoma vescicale a cellule transizionali → resezione endoscopica e BCG

• Abramo sospende per alcuni mesi il controllo glicemico

NHS National Institute for Health and Clinical Excellence

1.5.2 Insulin secretagogues

1.5.2.1 Consider a sulfonylurea as an option for first-line glucose-lowering therapy if:

- the person is not overweight
- the person does not tolerate metformin (or it is contraindicated) **or**
- a rapid response to therapy is required because of hyperglycaemic symptoms

1.5.2.2 Add a sulfonylurea as second-line therapy when blood glucose control remains or becomes inadequate (see 1.3.1) with metformin.

1.5.2.3 Continue with a sulfonylurea if blood glucose control remains or becomes inadequate (see 1.3.1) and another oral glucose-lowering medication is added.

1.5.2.4 **Prescribe a sulfonylurea** with a low acquisition cost (but not glibenclamide) when an insulin secretagogue is indicated (see 1.5.2.1 and 1.5.2.2).

Scenario Clinico

Ottobre 1998

• Nonostante la sospensione dei controlli, Abramo ha continuato metformina 3 gr/die e glibenclamide 5 mg x 3/die

• Abramo viene una mattina in ambulatorio senza appuntamento, accompagnato dal fratello: riferisce di sentirsi da circa una settimana molto astenico

• EO negativo, ECG immodificato

• Il giorno prima ha eseguito: glicemia basale 230 mg%, HbA1c 8.9%

Clinical Question

2. DIABETE

4. Quale decisione terapeutica per il sig. Abramo?

1. Nessuna
2. Consulenza diabetologica
3. Modifica tipo/dosi ipoglicemizzanti orali
4. Insulina

Scenario Clinico

• Decido in autonomia di iniziare l'insulina: due dosi di pronta ai pasti, associata a intermedia serale

• Sospendo glibenclamide e mantengo metformina

• Consiglio ad Abramo:
- autocontrollo quotidiano del profilo glicemico
- gestione telefonica
- educazione ad una certa autonomia: adattamento dosi della pronta in base ai valori di glicemia e all'entità di pasti
- attività fisica in programma

Scenario Clinico

Giugno 1999

• Glicemia 135 mg%, HbA1c 7.2%

• Colesterolo totale 259 mg%, HDL 44 mg%, TG 171 mg%

• Creatinina 1.31 mg%, microalbuminuria 24/h 359 mg

• Visita oculistica: quadro stabile

Scenario Clinico

2000

• Gennaio: sospende metformina per intolleranza intestinale →introduco insulina intermedia anche al mattino

• Febbraio: Abramo viene in ambulatorio per la recente comparsa di:
- dispnea per sforzi lievi-moderati (2 rampe di scale)
- segni di claudicatio: dolore alle gambe dopo marcia asintomatica in piano per 200 mt

Scenario Clinico

INDAGINI ESEGUITE

• Doppler arti inferiori: occlusione della tibiale ant. sx a 3 cm dall'origine a dx modeste note di sclerosi vasale

• Rx torace, ECG da sforzo massimale, ecocardiografia, doppler TSA nei limiti

Scenario Clinico

2000

• Maggio: HbA1c 7.8 mg, colesterolo tot. 256 mg%, HDL 37 mg%, trigliceridi 200 mg% → prescrivo pravastatina 20 mg/die e sostituisco amlodipina con valsartan 80 mg/die

• Creatinina 1.9 mg% → visita nefrologica

• Clearance creatinina 72 ml/min, microalbuminuria 24h 553 mg, proteinuria 1.35 gr/die → diagnosi di IRC

• Il nefrologo aggiunge idroclorotiazide 12,5 mg/die

• Visita oculista: quadro stabile

Scenario Clinico

2001 - 2003

• Esegue regolarmente profili glicemici, valori di HbA1C oscillano tra 7.5% e 8%

• Abramo segue regolare follow-up presso gli ambulatori di nefrologia e oncologia

Clinical Question

5. Quale target ottimale dell'HbA1c per la maggior parte dei pazienti con DM II?

1. ≤ 6.0%
2. ≤ 6.5%
3. ≤ 7.0%
4. ≤ 7.5%

Annals of Internal Medicine | CLINICAL GUIDELINES

Glycemic Control and Type 2 Diabetes Mellitus: The Optimal Hemoglobin A_{1c} Targets. A Guidance Statement from the American College of Physicians

Amir Qaseem, MD, PhD, MHA; Sandeep Vijan, MD, MS; Vincenza Snow, MD; J. Thomas Cross, MD, MPH; Kevin R. Weiss, MD, MPH; and Douglas K. Owens, MD, MS, for the Clinical Efficacy Assessment Subcommittee of the American College of Physicians*

Ann Intern Med. 2007;147:417-422

This guidance statement is derived from other organizations' guidelines and is based on an evaluation of the strengths and weaknesses of the available guidelines. We used the Appraisal of Guidelines, Research and Evaluation in Europe (AGREE) appraisal instrument to evaluate the guidelines from various organizations.

AGREE

Ann Intern Med. 2007;147:417-422

AGREE
Appraisal of Guidelines for Research & Evaluation

23 item in 6 dimensioni

1. obiettivi della LG
2. coinvolgimento delle parti in causa
3. rigore metodologico
4. chiarezza espositiva
5. applicabilità
6. indipendenza editoriale

Guidelines

AACE	AAFP	ADA	AGS	CDA	ICSI	NICE	SIGN	VHA
50.5	71	53	70	71.5	64.5	77	74	72

* AACE: American Association of Clinical Endocrinologists; AAFP: American Academy of Family Physicians; ADA: American Diabetes Association; AGS: American Geriatrics Society; CDA: Canadian Diabetes Association; ICSI: Institute for Clinical Systems Improvement; NICE: National Institute for Health and Clinical Excellence; SIGN: Scottish Intercollegiate Guidelines Network; VHA: Veterans Health Administration.

Ann Intern Med. 2007;147:417-422

Statement 1: To prevent microvascular complications of diabetes, the goal for glycemic control should be as low as is feasible without undue risk for adverse events or an unacceptable burden on patients. Treatment goals should be based on a discussion of the benefits and harms of specific levels of glycemic control with the patient. A hemoglobin A_{1c} level less than 7% based on individualized assessment is a reasonable goal for many but not all patients.

Statement 2: The goal for hemoglobin A_{1c} level should be based on individualized assessment of risk for complications from diabetes, comorbidity, life expectancy, and patient preferences.

Statement 3: We recommend further research to assess the optimal level of glycemic control, particularly in the presence of comorbid conditions.

Ann Intern Med. 2007;147:417-422

AMD diabete italia SID

STANDARD ITALIANI PER LA CURA DEL DIABETE MELLITO

RACCOMANDAZIONI

Il compenso glicemico e il trattamento ipoglicemizzante

- Nei diabetici anziani gli obiettivi glicemici dovrebbero essere individualizzati. Se le condizioni generali sono relativamente buone, il valore di HbA_{1c} potrà essere compreso tra 6,5% e 7,5% (**Livello della prova VI, Forza della raccomandazione B**)
- Negli anziani fragili (con complicanze, affetti da demenza, con pluripatologie, nei quali il rischio di ipoglicemia è alto e nei quali i rischi di un controllo glicemico intensivo superino i benefici attesi) è appropriato un obiettivo meno restrittivo, con valori di HbA_{1c} compresi tra 7,5% e 8,5%. (**Livello della prova VI, Forza della raccomandazione B**)
- Nei diabetici anziani lo schema di automonitoraggio dovrebbe essere commisurato al grado di autosufficienza e quindi alle singole capacità funzionali, affettive e cognitive. Lo schema deve essere basato sugli obiettivi glicemici e di HbA_{1c} programmati, sulle reali possibilità di modificare la terapia e sul rischio di ipoglicemia. (**Livello della prova VI, Forza della raccomandazione B**)
- Se in un soggetto anziano è indicata una terapia con antidiabetici orali, non è opportuno l'utilizzo di clorpropamide e glibenclamide. (**Livello della prova V, Forza della raccomandazione B**)

Scenario Clinico

2004-2008

- Nel 2005 Abramo viene preso in carico dall'ambulatorio diabetologico
- Vedo regolarmente i referti grazie al SISS: il controllo metabolico è discreto (HbA1c tra 8% e 9%)
- Non ricevo nessun contatto dall'ambulatorio diabetologico che, nel 4/08 ha prescritto un'associazione insulina glargine e glulisina, di cui mi limito a trascrivere le ricette (!)
- Abramo, intanto ha sfondato la barriera dei 100 kg (+ 20 kg dalla pensione), ha un BMI di 37 e una circonferenza addominale 115 cm…

Clinical Question

2. DIABETE

6. Nei pazienti con diabete di II tipo, le nuove insuline (glargine, detemir, glulisina) sono più efficaci dell'insulina tradizionale?

1. No
2. Sì, solo in specifiche categorie di pazienti
3. Sì, in tutti i pazienti

Canadian Agency for Drugs and Technologies in Health

Agence canadienne des médicaments et des technologies de la santé

OPTIMAL THERAPY REPORT

COMPUS

Volume 2, Issue 1
March 2008

Long-Acting Insulin Analogues for the Treatment of Diabetes Mellitus: Meta-analyses of Clinical Outcomes – Update of CADTH Technology Report No. 92

OBJECTIVE

• To identify and synthesize the available evidence on the clinical efficacy and safety of long-acting insulin analogues, specifically insulin glargine (IGlar) and insulin detemir (IDet), in the management of DM (type 1,type 2, and gestational)

CONCLUSION

• In patients with type 2 DM treated with IGlar or IDet, mean A1c levels were similar to those achieved with NPH

• Both IGlar and IDet significantly reduced the risk of nocturnal hypoglycemia in type 2 DM patients.

• There was limited comparative data for IGlar versus IDet.

• Long-term comparative studies of higher quality are needed to definitively determine the clinically relevant benefits and harms of long-acting insulin analogues compared with conventional insulins.

Diabetes: glycaemic control in type 2

Search date October 2006
Bala Srinivasan, Nick Taub, Kamlesh Khunti, and Melanie Davies.

Unknown effectiveness

Blood glucose self-monitoring. 21

Insulin analogues versus conventional insulin (insufficient evidence to assess how they compare) New 13

Insulin delivered by continuous subcutaneous infusion (probably as effective as multiple daily injections). . 10

NHS
National Institute for Health and Clinical Excellence

1.7.2.3 Insulin therapy should be initiated from a choice of a number of insulin types and regimens.

- Preferably begin with human NPH insulin, taken at bed-time or twice daily according to need.
- Consider, as an alternative, using a long-acting insulin analogue (insulin glargine) for a person who falls into one of the following categories[r].
  - Those who require assistance from a carer or healthcare professional to administer their insulin injections.
  - Those whose lifestyle is significantly restricted by recurrent symptomatic hypoglycaemic episodes.
  - Those who would otherwise need twice-daily basal insulin injections in combination with oral glucose-lowering medications.

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- Consider pre-mixed preparations of insulin analogues rather than pre-mixed human insulin preparations when:
  - immediate injection before a meal is preferred, or
  - hypoglycaemia is a problem, or
  - there are marked postprandial blood glucose excursions.

1.7.2.4 Offer a trial of insulin glargine if a person who has started with NPH insulin experiences significant nocturnal hypoglycaemia.

Scenario Clinico

• Da circa un anno l'organizzazione dell'assistenza ai diabetici è stata rivoluzionata, passando in modo deciso alla strategia di intervento, grazie alla collaborazione dell'infermiera che, tra le altre cose, si occupa della programmazione dei controlli

• La nuova gestione che prevede l'impegno di medico, infermiera e segretaria, impegna lo staff per 50' a settimana per paziente, dei quali circa 25' per il medico

Clinical Question

7. Nei pazienti con DM II, gli interventi organizzativi sono efficaci nel migliorare gli esiti assistenziali e l'utilizzo dei servizi sanitari?

1. No
2. Sì

Griffin S, Kinmonth AL

Systems for routine surveillance for people with diabetes mellitus

Cochrane Database of Systematic Reviews 2008, Issue 3

OBJECTIVE

• To assess the effects of involving primary care professionals in the routine review and surveillance for complications of people with established diabetes mellitus compared with secondary care specialist follow up.

Griffin S, et al. CDSR 2008

RESULTS

• Five trials involving 1.058 people were included

• In those schemes featuring more intensive support through a prompting system for general practitioners and patients, there was no difference in mortality between hospital and general practice care, HbA1c tended to be lower and losses to follow up were significantly lower in primary care

• Schemes with less well-developed support for family doctors were associated with adverse outcomes for patients

• Quality of life, CV risk factors, functional status and the development of complications were infrequently assessed

Griffin S, et al. CDSR 2008

CONCLUSION

• Unstructured care in the community is associated with poorer follow up, greater mortality and worse glycaemic control than hospital care

• Computerised central recall, with prompting for patients and their family doctors, can achieve standards of care as good or better than hospital outpatient care, at least in the short term

• The evidence supports provision of regular prompted recall and review of people with diabetes by willing general practitioners and demonstrates that this can be achieved, if suitable organisation is in place

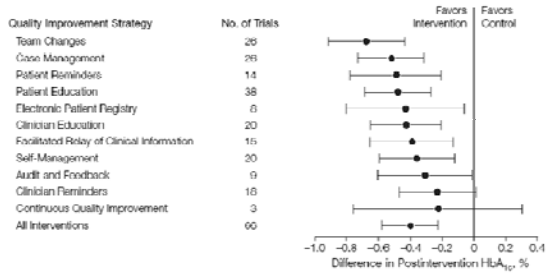
Griffin S, et al. CDSR 2008

Effects of Quality Improvement Strategies for Type 2 Diabetes on Glycemic Control

A Meta-Regression Analysis

JAMA. 2006;296:427-440

Figure 2. Postintervention Differences in Serum HbA_{1c} Values After Adjustment for Study Bias and Baseline HbA_{1c} Values



Shojania KG, et al. JAMA 2006

CONCLUSION

- Most QI strategies produced small to modest improvements in glycemic control
- Team changes and case management showed more robust improvements, especially for interventions in which case managers could adjust medications without awaiting physician approval
- Estimates of the effectiveness of other specific QI strategies may have been limited by difficulty in classifying complex interventions, insufficient numbers of studies, publication bias

Shojania KG, et al. JAMA 2006

Case Management. Any system for coordinating diagnosis, treatment, or ongoing patient management (eg, arrangement for referrals, follow-up of test results) by a person or multidisciplinary team in collaboration with or supplementary to the primary care clinician.

Team Changes. Changes to the structure or organization of the primary health care team, defined as present if any of the following applied:

- Adding a team member or "shared care," eg, routine visits with personnel other than the primary physician (including physician or nurse specialists in diabetic care, pharmacists, nutritionists, podiatrists).
- Use of multidisciplinary teams, ie, active participation of professionals from more than 1 discipline (eg, medicine, nursing, pharmacy, nutrition) in the primary, ongoing management of patients.
- Expansion or revision of professional roles (eg, nurse or pharmacist plays more active role in patient monitoring or adjusting medication regimens).

Shojania KG, et al. JAMA 2006