The new NICE NG28 Type 2 Diabetes Guidelines

How do they help me understand which medicine to prescribe?

Disclaimer

- Dr Sarah Jarvis has received honoraria for lecturing, chairing meetings and attending advisory boards for Astra Zeneca, Janssen, MSD, Sanofi and Takeda

Who's at risk in your practice?

The State of the Nation says:

- **Every 3 minutes** someone in the UK learns that they have diabetes
- There are about **3.2 million** people in England living with the condition
  - >2,700,000 diagnosed (90% with type 2 diabetes)
  - Approximately 500,000 people have undiagnosed type 2 diabetes
- A 38% increase in diagnosed diabetes was seen between 2001 and 2013
- Another 9.8 million people could be at high risk of developing type 2 diabetes
- If current trends continue:
  - **By 2025**: 4 million people in the UK will have diabetes
  - **By 2030**: diabetes prevalence could be 14% in some areas

Diabetes UK (2014) *State of the Nation: challenges for 2015 and beyond.* Available at: http://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/State%20of%20the%20nation%202014.pdf accessed 04.03.2015

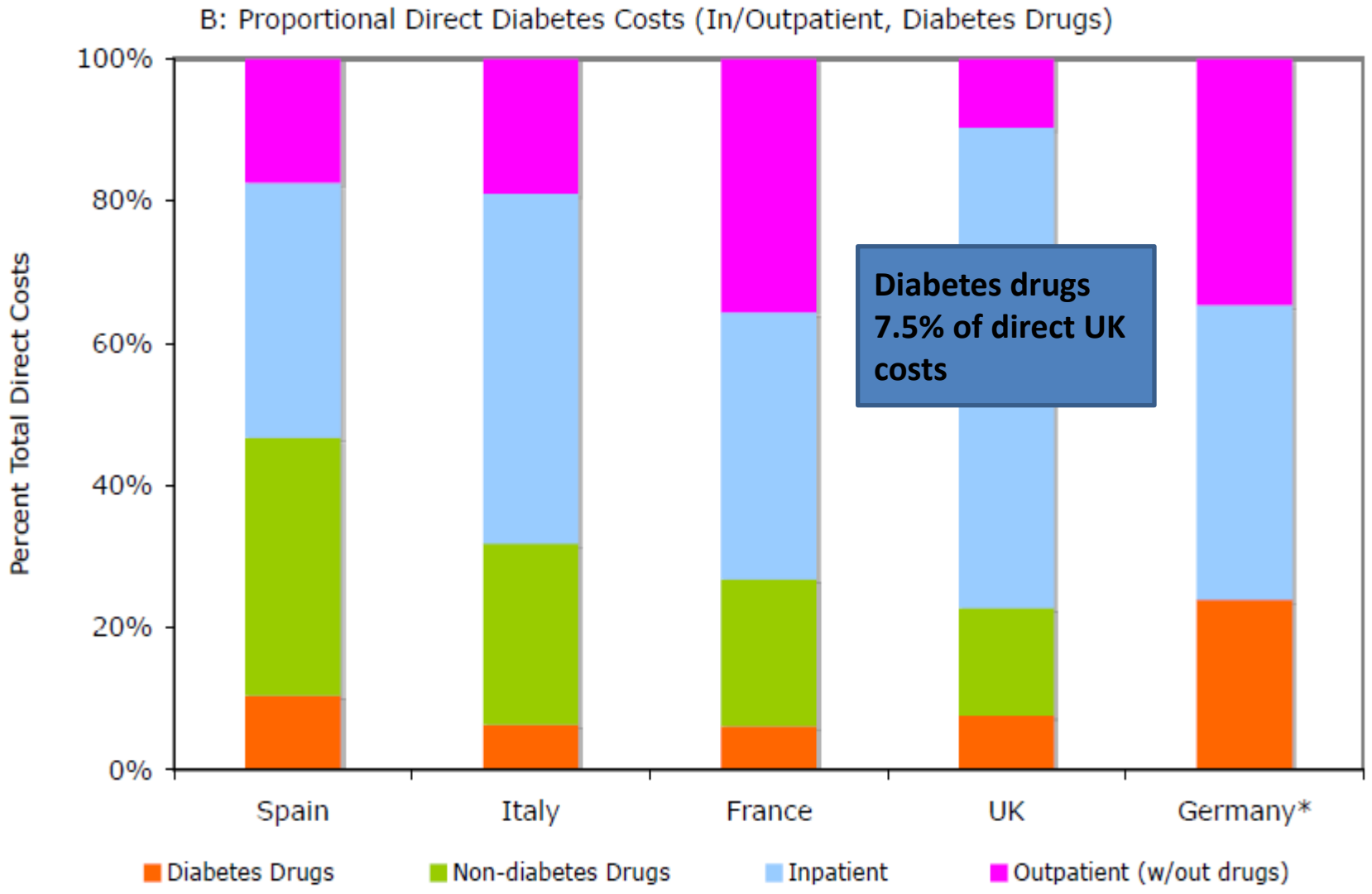
But first appearances can be deceptive

Lookalike

Wayne

Ena

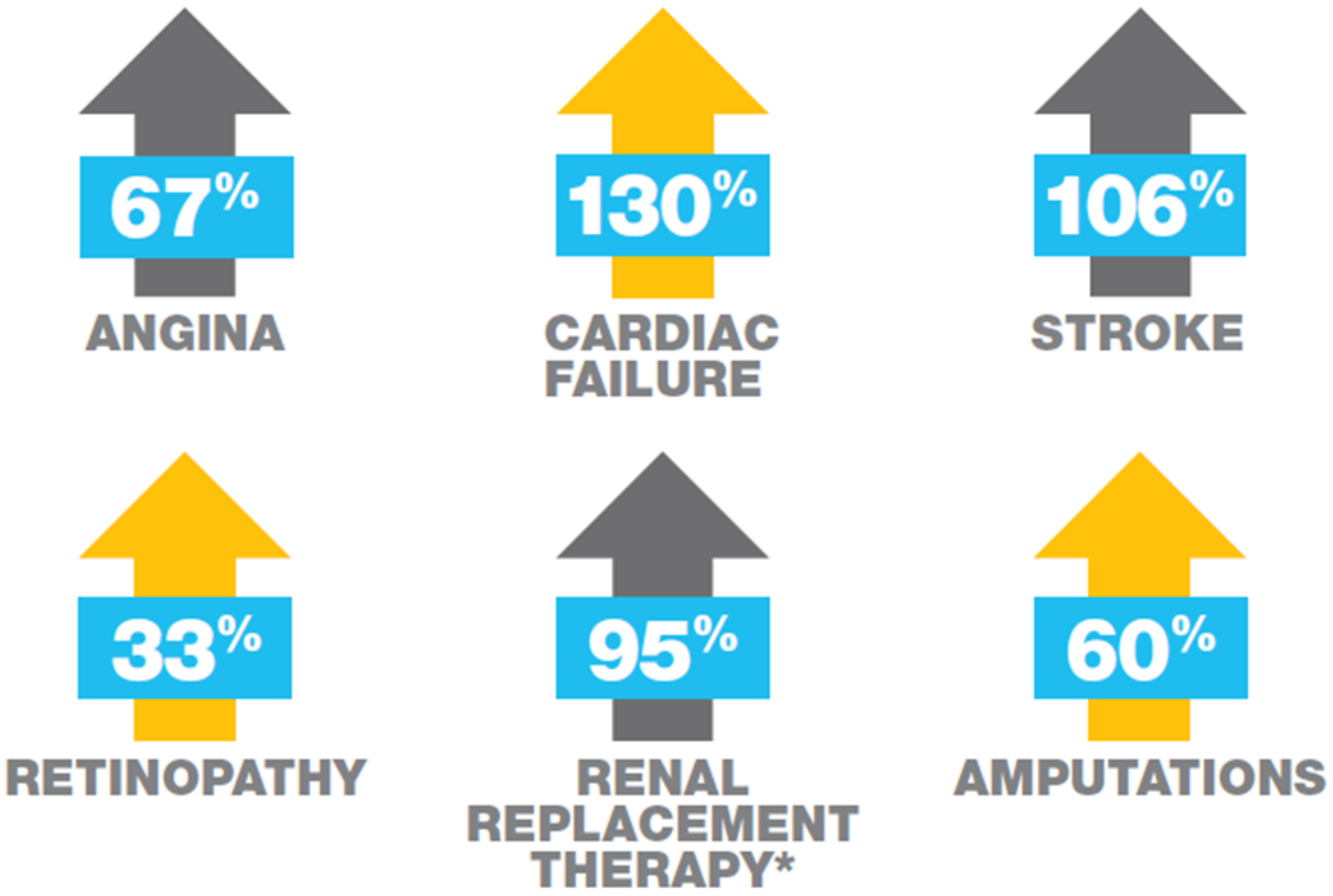
As a proportion of NHS costs



http://www2.lse.ac.uk/LSEHealthAndSocialCare/research/LSEHealth/MTRG/LSEDiabetesReport26Jan2012.pdf

Complications cost

Between 2007 and 2012, avoidable complications increased significantly[14]

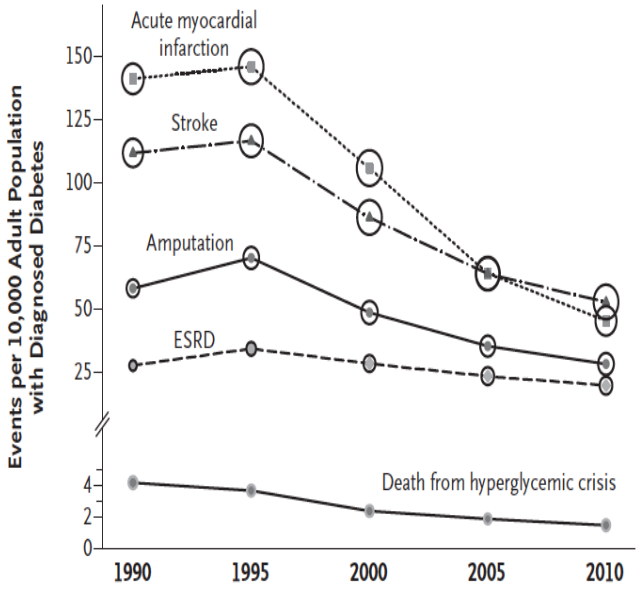


*Term used for life-supporting treatments required to treat end stage kidney disease

Diabetes UK. State of the Nation: challenges for 2015 and beyond. Available at iahttps://www.diabetes.org.uk/Documents/About%20Us/What%20we%20say/State%20of%20the%20nation%202014.pdfv Last accessed 9th March 2016

Incidence of diabetes-related complications has decreased for the past 20 years[1]

Age standardized event rates



Adapted from Gregg et al. 2014.

Prevalence of diabetes in the USA

1990	**2010**
6.5 millions	20.7 millions (population +27%)

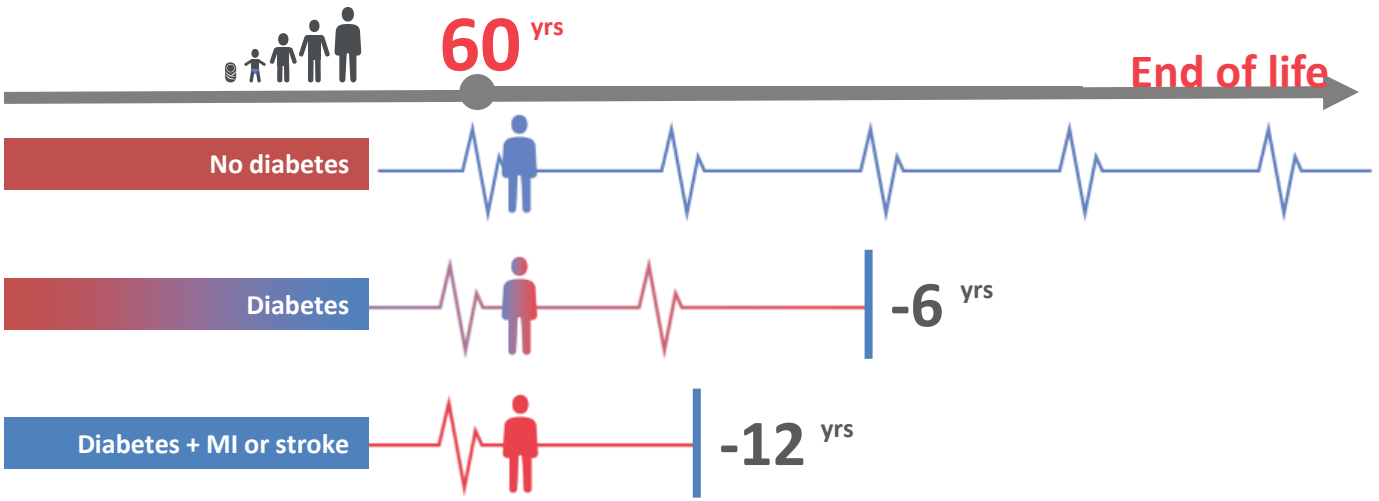
INCIDENCE/10,000 (USA)	**1990**	**2010**	
MI	140	46	**-67%**
Stroke	112	53	**-53%**
Amputation	58	28	**-51%**

ABSOLUTE NUMBERS (USA)	**1990**	**2010**	
MI	140,122	135,743	**-4,379**
Stroke	127,016	186,719	**+59,703**
Amputation	50,364	73,067	**+22,703**

1. Gregg et al.New Engl J Med, 2014.

But there’s still a long way to go

Life expectancy reduced by 12 years in patients with T2D and CVD compared to general population*[1]



In this case, CVD is represented by MI or stroke
*Male, 60 years of age with history of MI or stroke
CVD, cardiovascular disease; MI, myocardial infarction

1. The Emerging Risk Factors Collaboration. JAMA 2015;314:52

We’re doing pretty well in some respects

National Diabetes Audit
2013-2014 and 2014-2015

Care Pr d Trea

hscic Health & Social Care Information Centre

HQIP Healthcare Quality Improvement Partnership

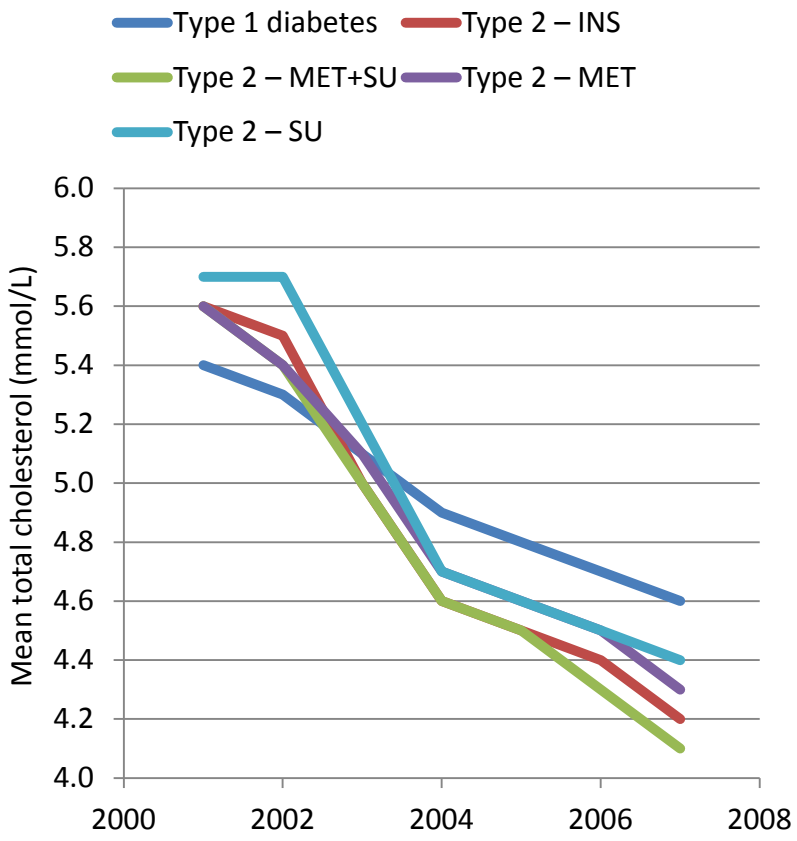
DIABETES UK CARE. CONNECT. CAMPAIGN.



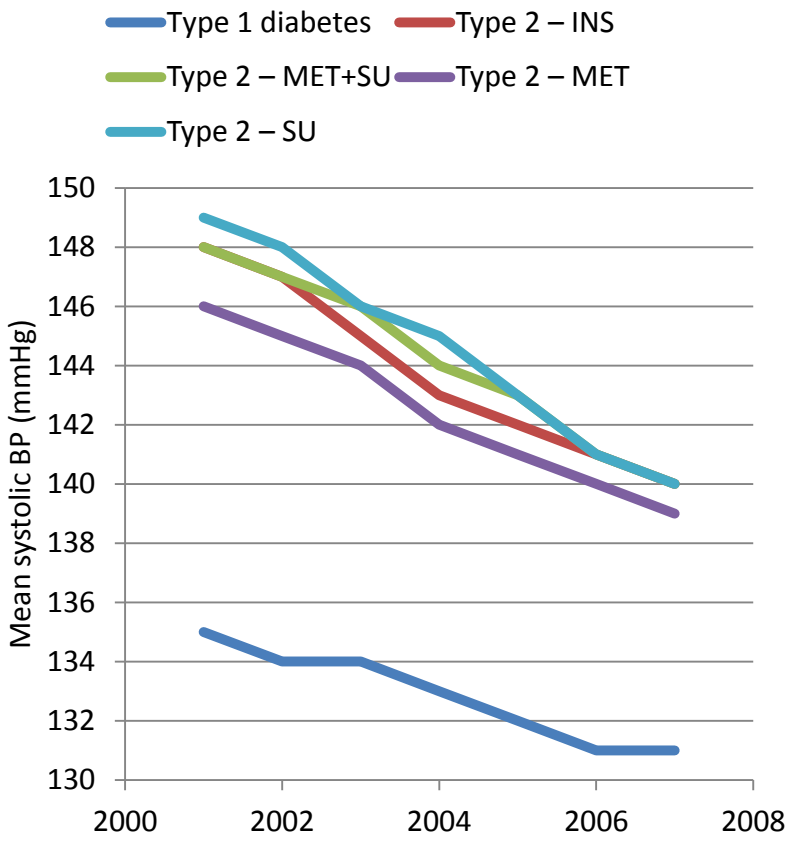
- Version 1.0
- Published: 28 January 2016

Risk factor trends over time in people with type 2 diabetes managed in primary care

Change in mean total cholesterol levels



Change in mean systolic BP levels



BP=blood pressure; INS=insulin; MET=metformin; SU=sulphonylurea

Adapted from: Currie CJ et al (2010) *Diabet Med* **27**: 938–48

But not so well in others

- % in England and Wales receiving all 8 NICE recommended care processes has declined - at its lowest since the NDA began 6 years ago.
- 58.7% of those with Type 2 diabetes achieved all 8 targets (down from 67.6% in 2013-14)

- National Diabetes Audit 2013-2014 and 2014-2015 Report 1: Care Processes and Treatment Targets
  NDA Data Quality statement

Getting it right across the board saves live

- Randomisation to intensified, target-driven therapy for a median of 7.8 years yielded the following benefits compared with conventional multifactorial treatment when patients were observed after a further 5.5 years (STENO2):

Mortality rate:	Cardiovascular event rate:
20% absolute risk reduction	29% absolute risk reduction
(50% vs. 30%; *P*=0.02)	(60% vs. 31%; *P*<0.001)

- Participants (n=160) had type 2 diabetes and persistent microalbuminuria
- Intensive treatment included the following targets:
  - HbA_{1c} <48 mmol/mol (<6.5%)
  - Total cholesterol <4.5 mmol/L
  - Triglycerides <1.7 mmol/L
  - Systolic BP <130 mmHg
  - Diastolic BP <80 mmHg

Gaede P et al (2008) *N Engl J Med* **358**: 580–91

The curate's egg: macrovascular outcomes

Glucose-lowering therapies

Study[1]	Baseline HbA1c control vs. intensive	Mean duration of diabetes at baseline (years)	Microvascular		CVD		Mortality	
UKPDS[2]	9%→7.9% vs 7%	Newly diagnosed	↓	↓	↔	↓	↔	↓
ACCORD[3]	8.3%→7.5% vs 6.4%	10.0	↓*		↔		↑	
ADVANCE[4]	7.5 %→7.3% vs 6.5%	8.0	↓	↔†	↔	↔	↔	↔
VADT[5]	9.4 %→8.4% vs 6.9%	11.5	↓	?	↔	↓	↔	↔

*No change in primary microvascular composite, but significant decreases in micro/macroalbuminuria[2,3]

†No change in major clinical microvascular events, but significant reduction in ESRD (p = 0.007)[5]

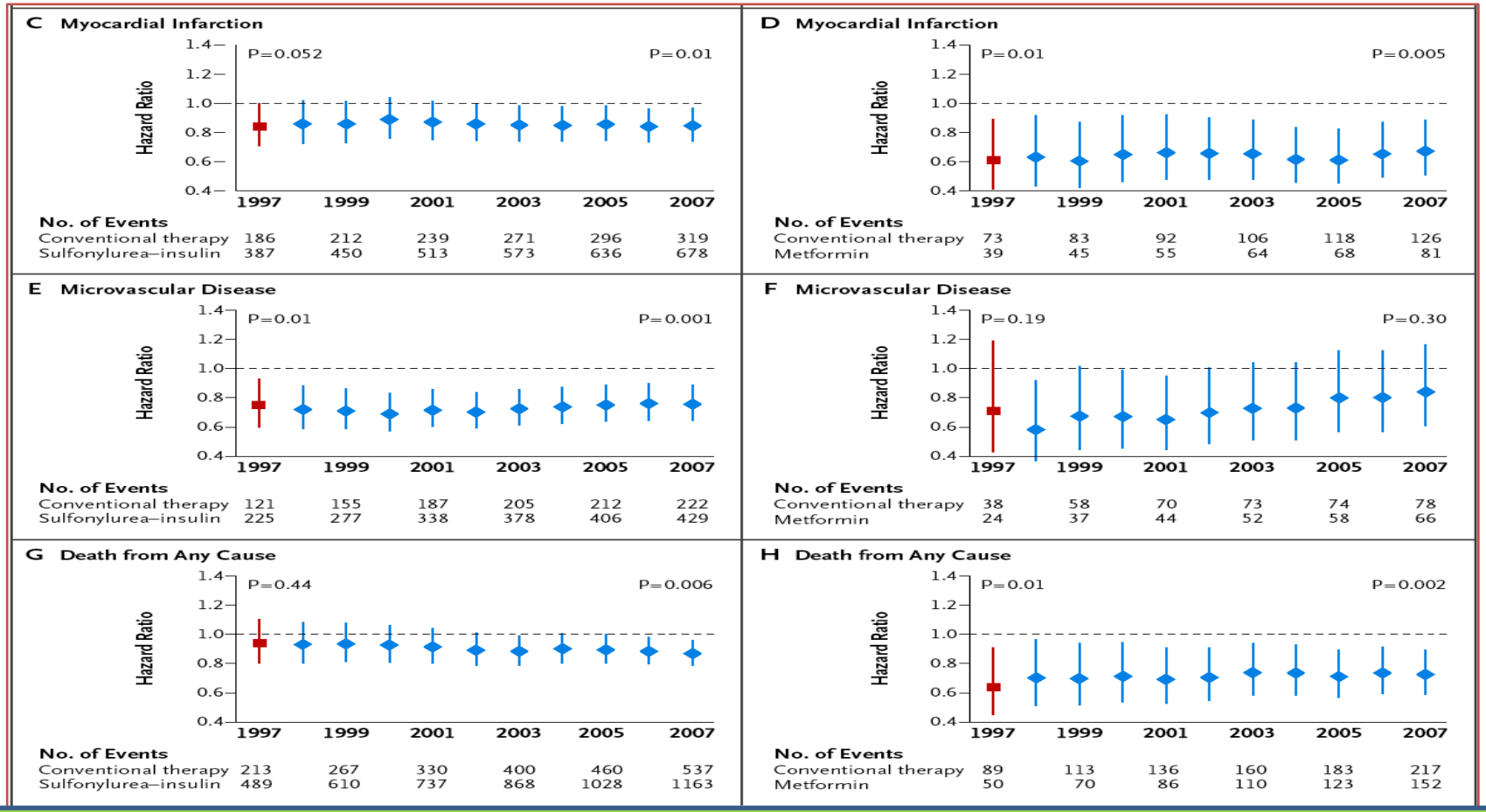
Long-term follow-up[1,6,7]

Adapted from Bergenstal et al. 2010

1. Bergenstal et al. Am J Med 2010;123:374.e9–18. 2. UKPDS 33. Lancet 1998;352:837–53. 3. Duckworth et al. N Engl J Med 2009;360:129–39. 4. Gerstein et al. N Engl J Med 2008;358:2545–59. 5. Patel et al. N Engl J Med 2008; 358:2560–72. 6. Hayward et al. N Engl J Med 2015;372:2197–206. 7. Zoungas et al. N Engl J Med 2014;371:1392–406.

UKPDS – welcome to the legacy effect[1]

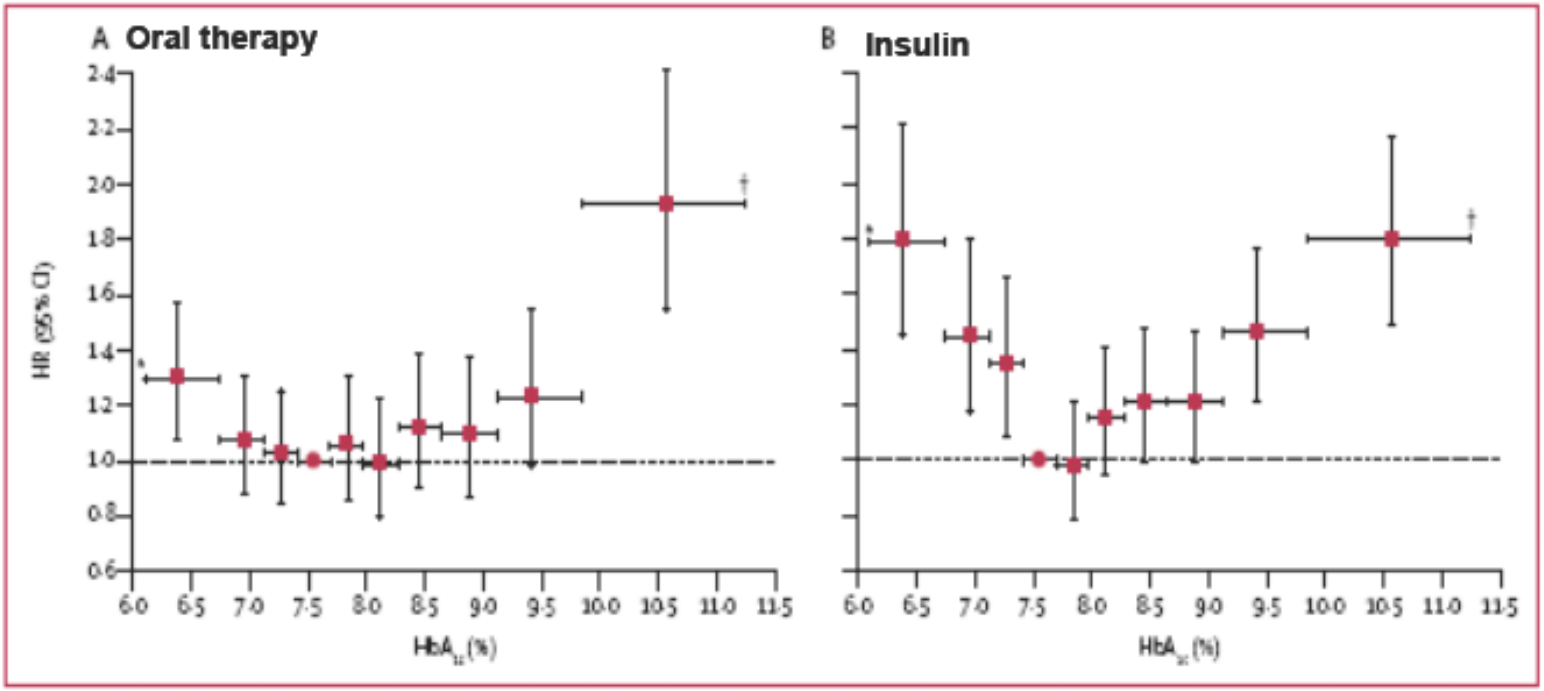
Insulin / SU | **Metformin**



1. Adapted from Holman et al.NEJM, 2008

What does NICE have to say about individualised care?

Relationship Between Glycated Haemoglobin and Mortality in 47,970 Patients



Currie C et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010: 375 (9713): 481-89

Treat the patient not the number

1.1 Individualised care

- Adopt an individualised approach to diabetes care that is tailored to your patient's needs and circumstances:
- Personal preferences
- Risks of polypharmacy
- Co-morbidities (especially if multi-morbidity)
- Impact of life expectancy on potential benefit

Older adults with type 2 diabetes

- Older people are more likely to have co-existing conditions and to be on a greater number of medicines. Their ability to benefit from risk-reduction interventions in the longer term may also be reduced.
- Particular consideration should be given to their broader health and social care needs

Diet and lifestyle

- Integrate dietary advice with a personalised diabetes management plan, including other aspects of lifestyle modification, such as increasing physical activity and losing weight. **[2009] [1.3.4]**
- Structured education for patients and/or carers at diagnosis, reinforced annually

Antiplatelet therapy

- 1.5.1 Do not offer antiplatelet therapy (aspirin or clopidogrel) for adults with type 2 diabetes without cardiovascular disease. **[new 2015]**

Blood pressure targets

- Below 140/80 or
- Below 130/80 if kidney, eye or cerebrovascular damage
- Repeat within 1 month if above 150/90
- Repeat within 2 months if above 140/80 (or 130/80if kidney, eye or cerebrovascular damage)
- 1st line ACE-I or
- ACE-I + diuretic/CCB if Afro-Caribbean or
- CCB if chance of pregnancy

Blood glucose

- Involve adults with type 2 diabetes in decisions about their individual HbA1c target.
- Encourage them to achieve the target and maintain it unless any resulting adverse effects (including hypoglycaemia), or their efforts to achieve their target, impair their quality of life. **[new 2015]**

What's gone wrong?

- Offer lifestyle advice and drug treatment to support adults with type 2 diabetes to achieve and maintain their HbA1c target **[new 2015]**
- When HbA1c rises, look at drug changes in the context of
- Diet
- Lifestyle
- **Drug adherence**

Measuring HbA1c

- In adults with type 2 diabetes, measure HbA1c levels at:
- 3–6-monthly intervals (tailored to individual needs), until the HbA1c is stable on unchanging therapy
- 6-monthly intervals once the HbA1c level and blood glucose lowering therapy are stable. **[2015]**

Targets

- If controlled with diet and lifestyle +/- a single drug that is **not associated with hypoglycaemia,** aim for HbA1c target of 48mmol/mol (6.5%)

Targets (2)

- If HbA1c on one or two drugs rises to above 58mmol/mol (7.5%)

- Intensify drug treatment **and**
- Agree a target and aim for an HbA1c level of 53 mmol/mol (7.0%). **[new 2015] [1.6.8]**

When is a target not a target?

- 1.6.9 Consider relaxing the target HbA1c level on a case-by-case basis, particularly if **older or frail**, for adults with type 2 diabetes with:
- □ Low chance of longer-term risk-reduction benefits, eg people with a reduced **life expectancy**
- □ High risk of the **consequences of hypoglycaemia** from tight control, eg:
- **risk of falling**
- **impaired awareness of hypoglycaemia**
- people who **drive or operate machinery as part of their job**
- □ for whom intensive management would not be appropriate eg significant **comorbidities**. **[new 2015]**

Self monitoring of glucose

- Consider DVLA regs **[new 2015]**
- Do not routinely offer self-monitoring of blood glucose levels for adults with type 2 diabetes unless:
- The person is on insulin **or**
- There is evidence of hypoglycaemic episodes **or**
- The person is on oral medication that may increase their risk of hypoglycaemia while driving or operating machinery **or**
- The person is pregnant, or is planning to become pregnant **[new 2015] [1.6.13]**

If the person is symptomatically hyperglycaemic, consider insulin or an SU. Review treatment when blood glucose control has been achieved.

ADULT WITH TYPE 2 DIABETES WHO CAN TAKE METFORMIN

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:

- Offer standard–release metformin
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%)

If standard-release metformin is not tolerated, consider a trial of modified–release metformin

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):

- Consider dual therapy with:
  - metformin and a DPP-4i
  - metformin and pioglitazone[a]
  - metformin and an SU
  - *metformin and an SGLT-2i*[b]
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):

- Consider:
  - triple therapy with:
    - metformin, a DPP-4i and an SU
    - metformin, pioglitazone[a] and an SU
    - *metformin, pioglitazone[a] or an SU, and an SGLT-2i*[b]
  - insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

If triple therapy is not effective, not tolerated or contraindicated, consider combination therapy with metformin, an SU and a GLP-1 mimetic[c] for adults with type 2 diabetes who:

- have a BMI of 35 kg/m^2 or higher (adjust accordingly for people from black, Asian and other minority ethnic groups) **and** specific psychological or other medical problems associated with obesity **or**
- have a BMI lower than 35 kg/m^2, **and** for whom insulin therapy would have significant occupational implications, **or** weight loss would benefit other significant obesity-related comorbidities

METFORMIN CONTRAINDICATED OR NOT TOLERATED

If HbA1c rises to 48 mmol/mol (6.5%) on lifestyle interventions:

- Consider one of the following[d]:
  - a DPP-4i, pioglitazone[a] or an SU
- Support the person to aim for an HbA1c level of 48 mmol/mol (6.5%) for people on a DPP-4i or pioglitazone or 53 mmol/mol (7.0%) for people on an SU

FIRST INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):

- Consider dual therapy[e] with:
  - a DPP-4i and pioglitazone[a]
  - a DPP-4i and an SU
  - pioglitazone[a] and an SU
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

SECOND INTENSIFICATION
If HbA1c rises to 58 mmol/mol (7.5%):

- Consider insulin-based treatment
- Support the person to aim for an HbA1c level of 53 mmol/mol (7.0%)

In English please?

- **1st line** – metformin standard release
- If standard release not tolerated, consider MR Metformin

- In adults with type 2 diabetes, if metformin is contraindicated or not tolerated, consider initial drug treatment with:

 a dipeptidyl peptidase-4 (DPP-4) inhibitor **or**

 pioglitazone **or**

  a sulfonylurea. **[new 2015]**

Aim for 48mmol/mol if on DPP-4i or pioglitazone, 53mmol/mol if on SU

Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Available a

In English please?

- **2nd line**
- Consider dual therapy with:
- metformin and **pioglitazone**
- metformin and an **SU**
- metformin and a **DPP-4i**
- *metformin and an SGLT-2i* (Treatment with combinations of medicines including sodium–glucose 8 cotransporter 2 (**SGLT-2**) inhibitors may be appropriate for some people with type 2 diabetes; see the NICE guidance..)

National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Available at

In English please?

- **triple therapy** with:
- metformin, a DPP-4i and an SU
- metformin, pioglitazone and an SU
- metformin, pioglitazone or an SU, and an SGLT-2i
- (see NICE TAG. All three licensed for dual, only cana/empa currently for triple. All three are also recommended as options in combination with insulin.
- Watch out for DKA with SGLT-2is – test for ketones in patients with symptoms, even if glucose normal

National Institute for Health and Care Excellence. Type 2 diabetes in adults: management. Available at

LET'S MAKE IT PERSONAL WHERE HYPOGLYCAEMIA IS CONCERNED

National Institute for Health and Care Excellence. Type 2 diabetes in adults: NICE guideline DRAFT (January 2015). Available at http://www.nice.org.uk/guidance/gid-cgwave0612/resources/type-2-diabetes-draft-guideline-nice2 last accessed 13th August 2015


SOTP

Hypoglycaemia – the risk factors

- Living alone
- Working at heights
- Operating heavy machinery
- Older people[1,2]
- Driving

- CKD[1]
- Long duration diabetes[1]
- Irregular eating habits[3]
- Exercise[3]
- Have lower HbA1c [4]
- Periods of fasting eg Ramadam
- Prior hypoglycemia [5,6,6a]
- Hypoglycemia unawareness [7]
- Alcohol[8]

1) Henderson JN et al. *Diabet Med.* 2003;20:1016–1021.
2) Matyka K et al. *Diabetes Care.* 1997;20(2):135–141
3) Miller CD et al. *Arch Intern Med*. 2001;161:1653–1659.
4) Wright et al. *J Diabetes Complications*. 2006;20:395–401;
5) Chico A et al. *Diabetes Care.* 2003;26(4):1153–1157.
6) Canadian Diabetes Association Clinical Practice Guidelines Expert Committee. *Can J Diabetes*. 2008;32(suppl 1):S62–S64.
6a) California Healthcare Foundation. *J Am Ger Soc.* 2003;51(5, suppl):S265–S280
7) Amiel SA et al. *Diabet Med*. 2008;25(3):245–254.
8) Salti L Diabetes Care 2004

Just how big a problem is hypoglycaemia with SUs?

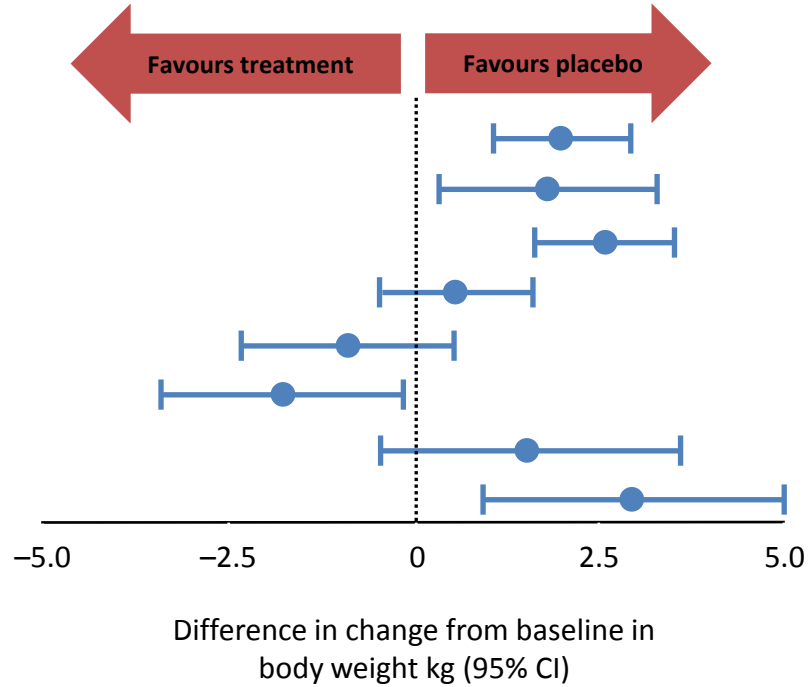
- In a 2014 survey of drivers taking SUs
- Within the previous 12 months
- 14% had 1-2 severe hypos
- 27% had 3 or more severe hypos
- 17% had 1-2 mild hypos
- 60% had 3 or more mild hypos

Parkes A et al. **The forgotten risk of driving with hypoglycaemia in type 2 diabetes . Transport Research Laboratory, 2014**

As if driving wasn't tough enough already….

And if you ask a patient if they'd rather take a drug that made them put on weight?

Treatment	MTC estimate (95% CrI)
Sulphonylureas	2.01 (1.09, 2.94)
Meglitinides	1.80 (0.35, 3.29)
Thiazolidinediones	2.59 (1.66, 3.51)
DPP-4 inhibitors	0.57 (–0.45, 1.60)
Alpha-glucosidase inhibitors	–0.92 (–2.35, 0.51)
GLP-1 analogues	–1.79 (–3.43, –0.14)
Basal insulin	1.56 (–0.46, 3.63)
Biphasic insulin	2.96 (0.96, 5.00)



Mixed-treatment comparison (MTC) results showing the effect of adding second-line agents versus placebo in adults taking metformin on change from baseline in bodyweight (kg). MTC analysis based on 30 randomised controlled trials (n=15,265). Most trials were 6–12 months long. Overall, meta-regression and sensitivity analyses yielded minimal differences from the reference case.

CrI=credible interval; DPP-4=dipeptidyl peptidase-4; GLP-1=glucagon-like peptide-1.

McIntosh B et al (2011) *Open Med* **5**: e35-48

Are we intensifying treatment to reduce complications?

In a retrospective cohort study of 81,573 UK patients in general practice

How long do we take	in real life to intensify Rx?	(median times in years)
	From 1 oral agent (years)	From 2 oral agents (years)
HbA_{1c} ≥7.0% (≥53mmol/mol)	2.9	> 7.2*
HbA_{1c} ≥7.5% (≥58mmol/mol)	1.9	> 7.2*
HbA_{1c} ≥8.0% (≥64mmol/mol)	1.6	> 6.9

*7.2 years was the maximum follow up

Khunti K, Wolden M, Larsen Thorsted et al. Diabetes Care 2013 ; 36 (11): 3411-3417

Are we intensifying treatment to reduce complications?

In a retrospective cohort study of 81,573 UK patients in general practice

And the mean HbA1c at which	treatment was intensified?
Add second agent	8.7% (72mmol/mol)
Add third agent	9.1% (76mmol/mol)
Intensify if on 3 agents	9.7% (83mmol/mol)

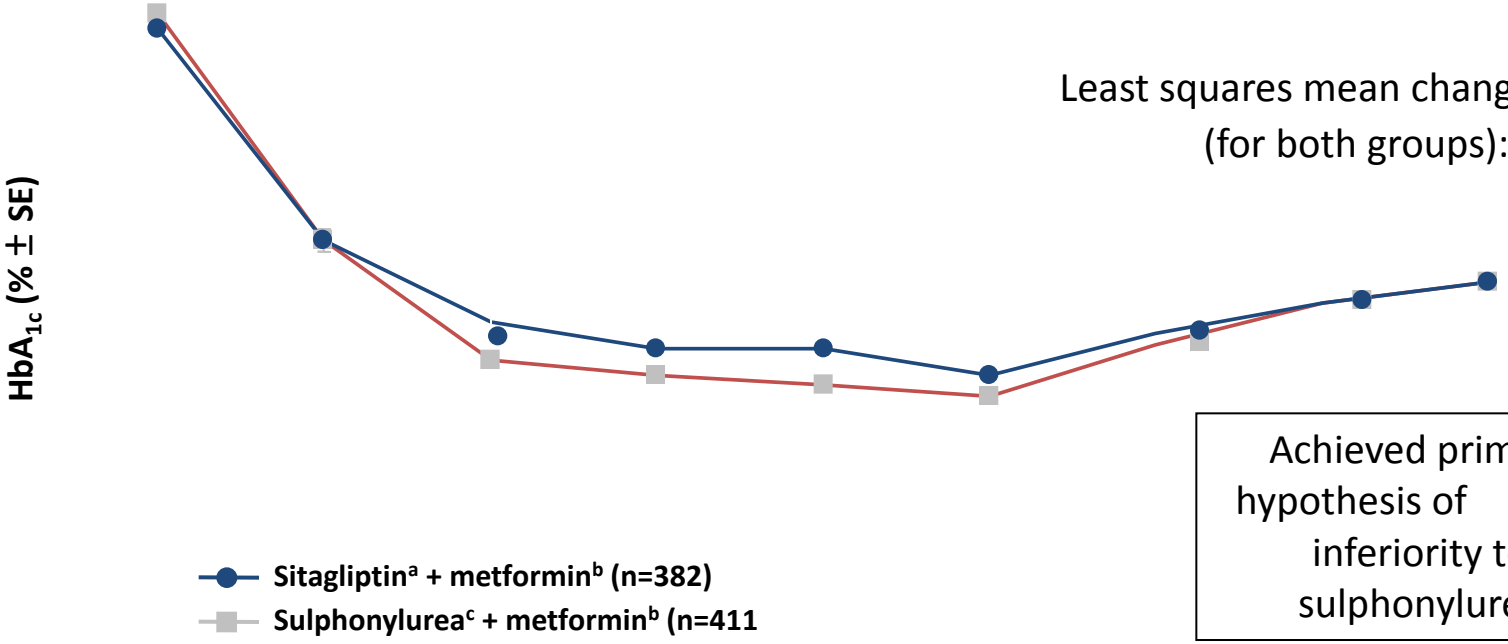
Khunti K, Wolden M, Larsen Thorsted et al. Diabetes Care 2013 ; 36 (11): 3411-3417

WE WANT DRUGS WITH EFFICACY, TOLERABILITY, SAFETY, NO WEIGHT GAIN AND VERY LOW RISK OF HYPOS

A truly harmonious combination?


http://pp.funpic.hu

Sitagliptin with metformin showed comparable efficacy to sulphonylurea with metformin[32]



Achieved primary hypothesis of non-inferiority to sulphonylurea

Per protocol population [a]Sitagliptin 100 mg o.d.; [b]Metformin ≥1,500 mg/day; [c]Glipizide (5 mg/day to 20 mg/day)

32. Nauck et al. *Diab Obes Metab* 2007;9:194-205.

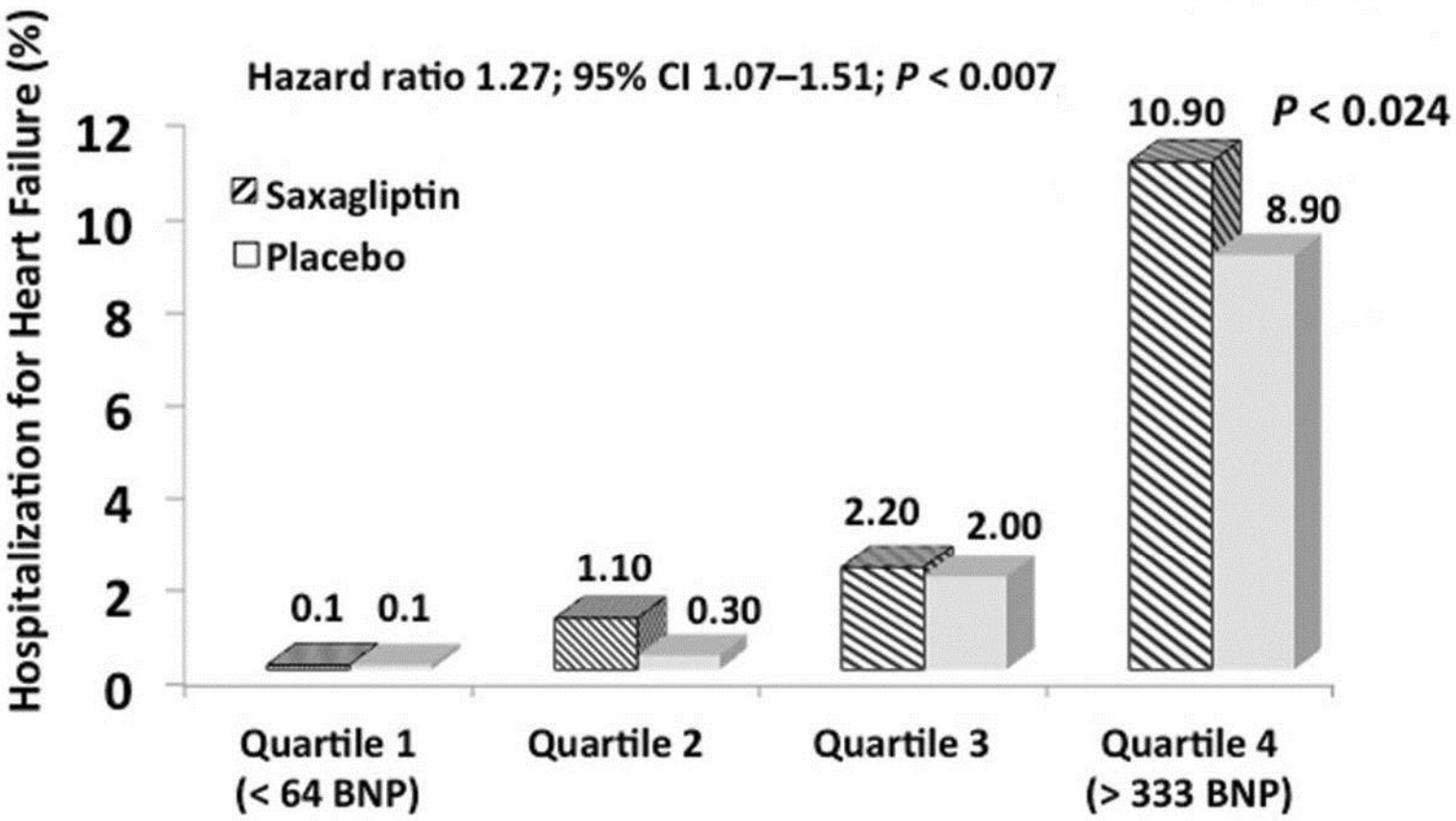
And to complete the picture – some Retro Data and meta-analysis

- Decreased risk of all-cause mortality (adjusted hazard ratio 1.357 {1.076-1.710, p=0.01}) with DPP-4i +metformin combination therapy compared with SU +metformin (Currie C, abstract 200 EASD 2013)

- In a large meta analysis, (n = 1,325,446) SU use was associated with a significantly increased risk of CV death (relative risk 1.27, 95% CI 1.18–1.34) (Phung, Diabet. Med. 30, 1160–1171 2013)

So much for the SUs – are the Gliptins safe?

Possible off-target effect of increased HF hospitalizations from saxagliptin in SAVOR trial.

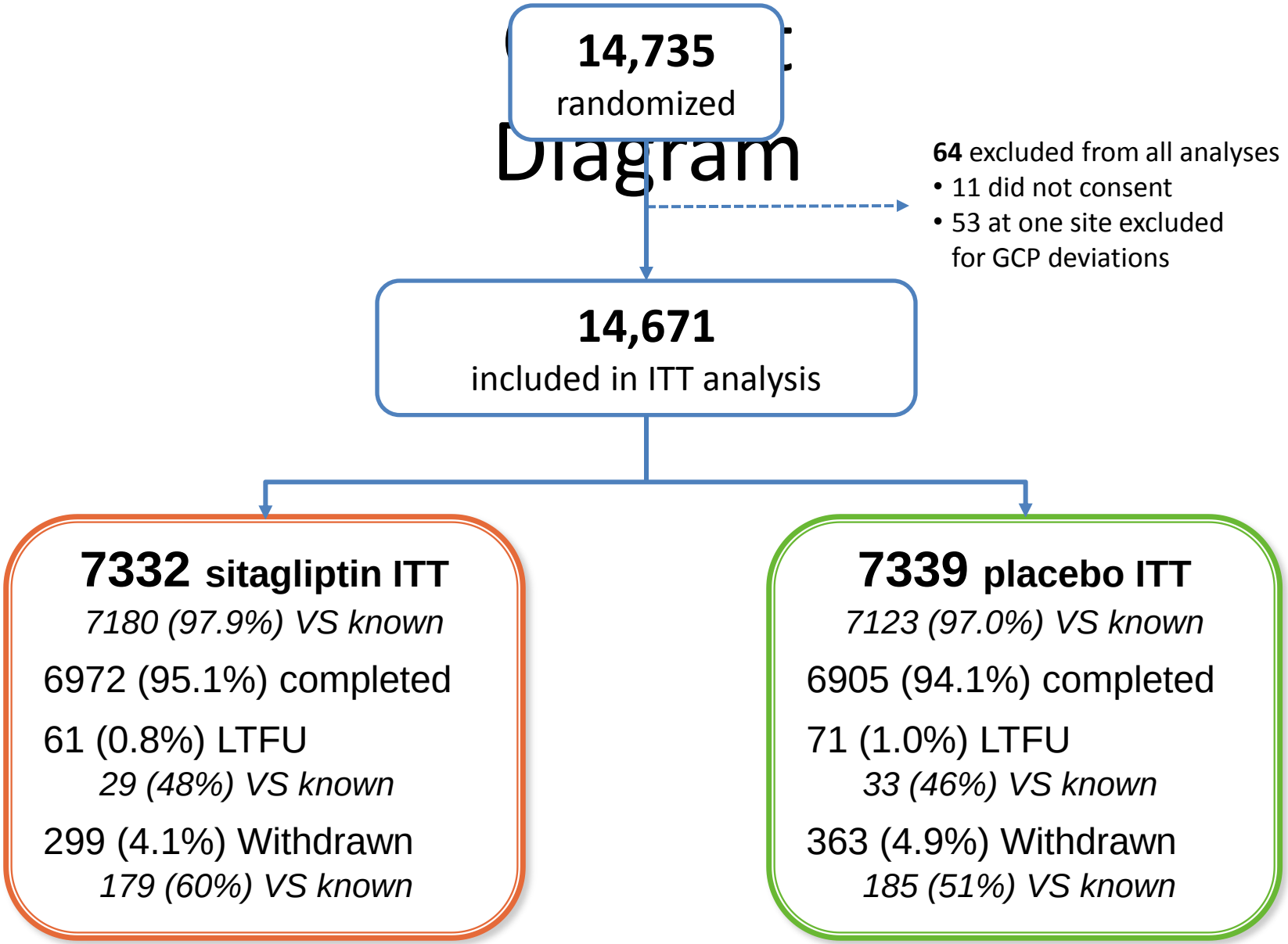


Vani P. Sanon et al. Clin Diabetes 2014;32:121-126

American Diabetes Association.

Primary Results

8th June 2015



ITT = intention-to-treat; LTFU = lost to follow-up;
VS = vital status, GCP = Good Clinical Practice

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Primary Composite Cardiovascular Outcome

Time to first occurrence of:

- Cardiovascular-related death
- Nonfatal myocardial infarction
- Nonfatal stroke
- Hospitalization for unstable angina

A Clinical Endpoints Committee, blinded to therapy allocation, reviewed all potential CVD endpoints independently.

55

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Secondary Cardiovascular Outcomes

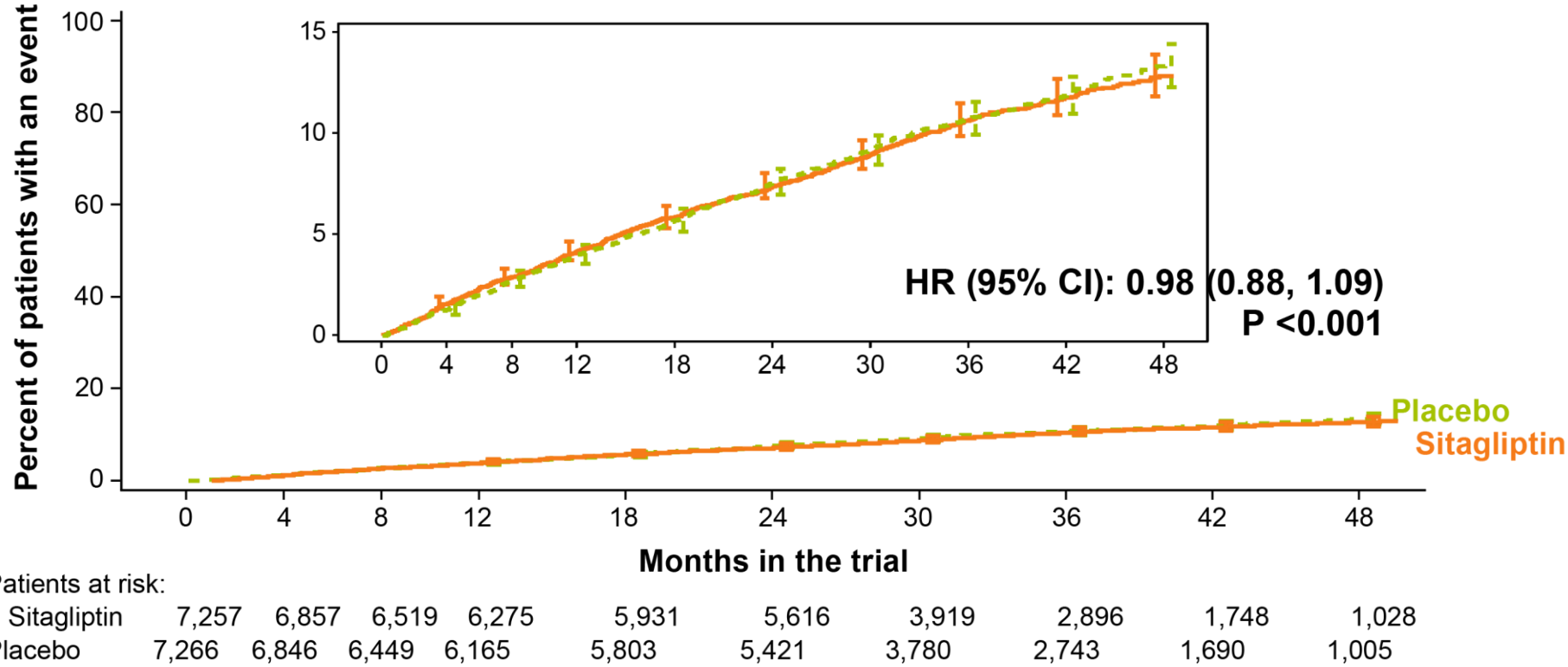
Time to —

- Secondary composite CV outcome (nonfatal MI, nonfatal stroke, or CV-related death)
- First confirmed component event in the primary outcome (Cardiovascular-related death, nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina)
- First fatal or nonfatal MI
- First fatal or nonfatal stroke
- All-cause mortality
- Hospitalization for heart failure
- Hospitalization for heart failure or CV-related death

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Primary Composite Cardiovascular Outcome*

PP Analysis for Non-inferiority



Patients at risk:

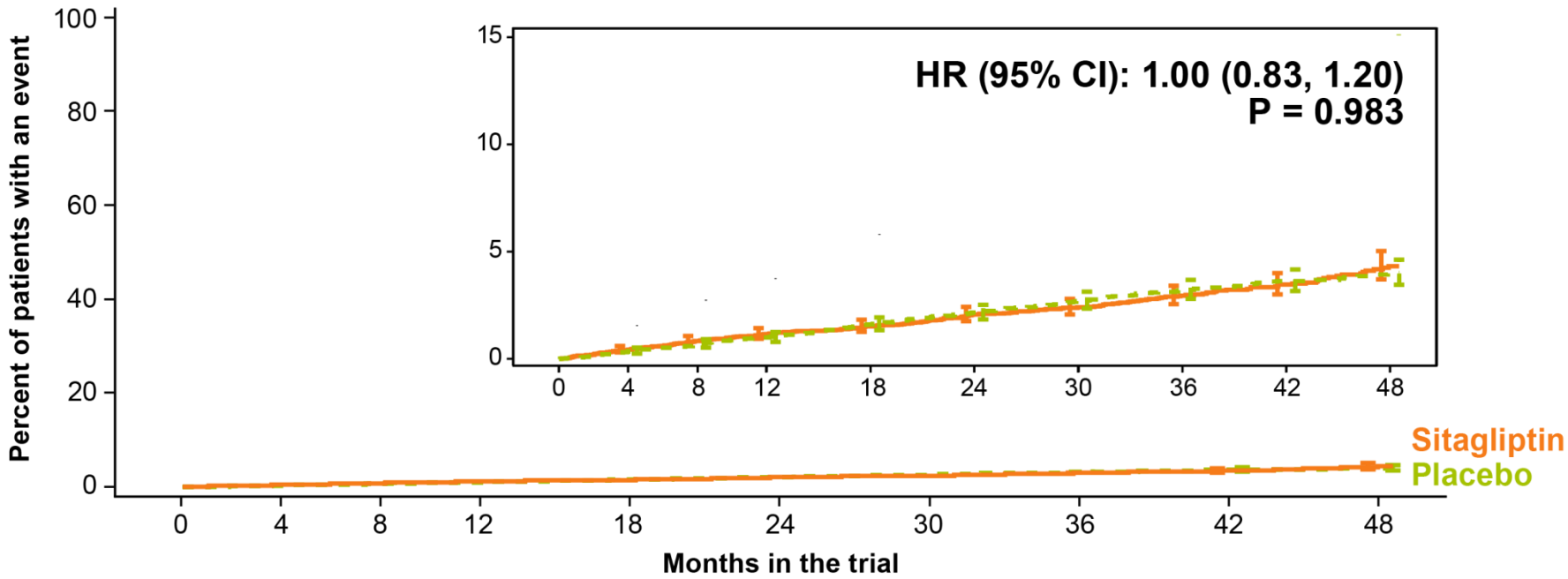
Sitagliptin	7,257	6,857	6,519	6,275	5,931	5,616	3,919	2,896	1,748	1,028
Placebo	7,266	6,846	6,449	6,165	5,803	5,421	3,780	2,743	1,690	1,005

** CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Hospitalization for Heart Failure*

ITT Analysis



Patients at risk:

Sitagliptin	7,332	7,189	7,036	6,917	6,780	6,619	4,728	3,515	2,175	1,324
Placebo	7,339	7,204	7,025	6,903	6,712	6,549	4,599	3,443	2,131	1,315

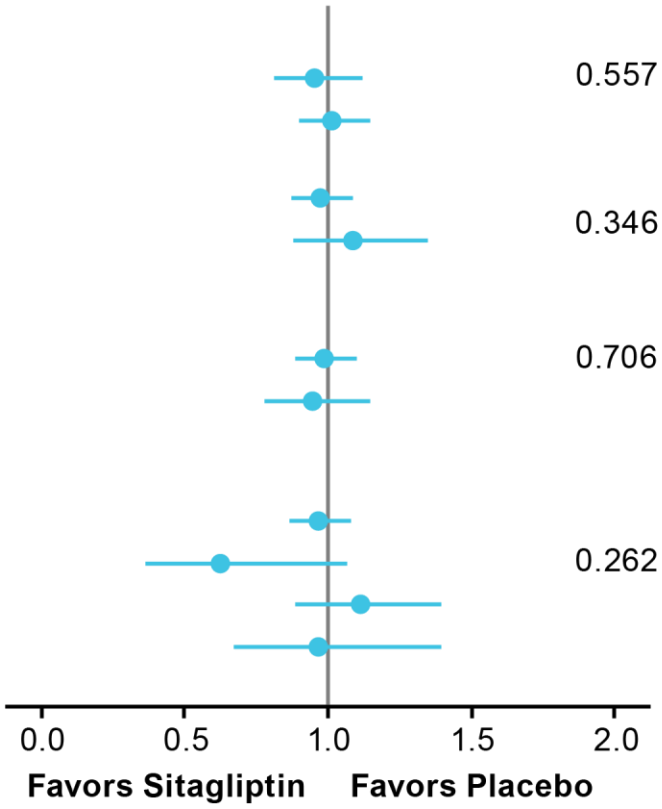
** Adjusted for history of heart failure at baseline*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Primary Composite Cardiovascular Outcome

Prespecified Subgroup Analyses (1)*

Subject Group	n / N	Hazard Ratio	95% CI	Interaction P-Value
Age				
<65 years	593 / 6,616	0.95	0.81, 1.12	0.557
≥65 years	1,026 / 7,735	1.01	0.90, 1.15	
<75 years	1,281 / 12,347	0.97	0.87, 1.08	0.346
≥75 years	338 / 2,004	1.09	0.88, 1.35	
Sex				
Male	1,272 / 10,374	0.99	0.88, 1.10	0.706
Female	418 / 4,297	0.95	0.78, 1.15	
Race				
White	1,214 / 9,957	0.97	0.87, 1.08	
Black	58 / 447	0.62	0.36, 1.07	0.262
Asian	302 / 3,265	1.11	0.89, 1.40	
Other	116 / 1,002	0.97	0.67, 1.40	



** ITT Population*

Green JB et al. NEJM 2015; DOI: 10.1056/NEJMoa1501352

Remember, there ARE even worse jobs than trying to hit QOF targets