Leicester Diabetes Centre

Committed to Growing International Research, Education & Innovation

University Hospitals of Leicester NHS

NHS Trust

University of Leicester

PCDE
primary care diabetes europe

Categorisation of risk phenotypes in type 2 diabetes from the primary care perspective

Kamlesh Khunti
University of Leicester, UK

University Hospitals of Leicester NHS
NHS Trust

UNIVERSITY OF LEICESTER

Leicester Diabetes Centre

© Leicester Diabetes Centre at University Hospitals of Leicester NHS Trust, 2018.
Not to be reproduced in whole or in part without the permission of the copyright owner.

Presenter Disclosure

- **Consultant**: Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi and Servier.

- **Research Support**: AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novartis, Janssen, Novo Nordisk, Roche and Sanofi

- **Speaker's Bureau**: AstraZeneca, Berlin-Chemie AG / Menarini Group, Boehringer Ingelheim, Janssen, Lilly, MSD, Napp, Novartis, Novo Nordisk, Roche and Sanofi

Outline

- Categorisation of risks and Personalised Medicine
- Pragmatic methods to categorise risk
- Evidence based guidelines
- Summary

Outline

- Categorisation of risks and Personalised Medicine
- Pragmatic methods to categorise risk
- Evidence based guidelines
- Summary

Precision Medicine in Type 2 diabetes : Using Individualized Prediction Models to optimise Selection of Treatment

A precision medicine approach based on treatment response would aim to improve on this by identifying predictors of differential drug response for people based on their characteristics and then using this information to select optimal treatment.

Currently not mature enough for implementation in routine clinical practice

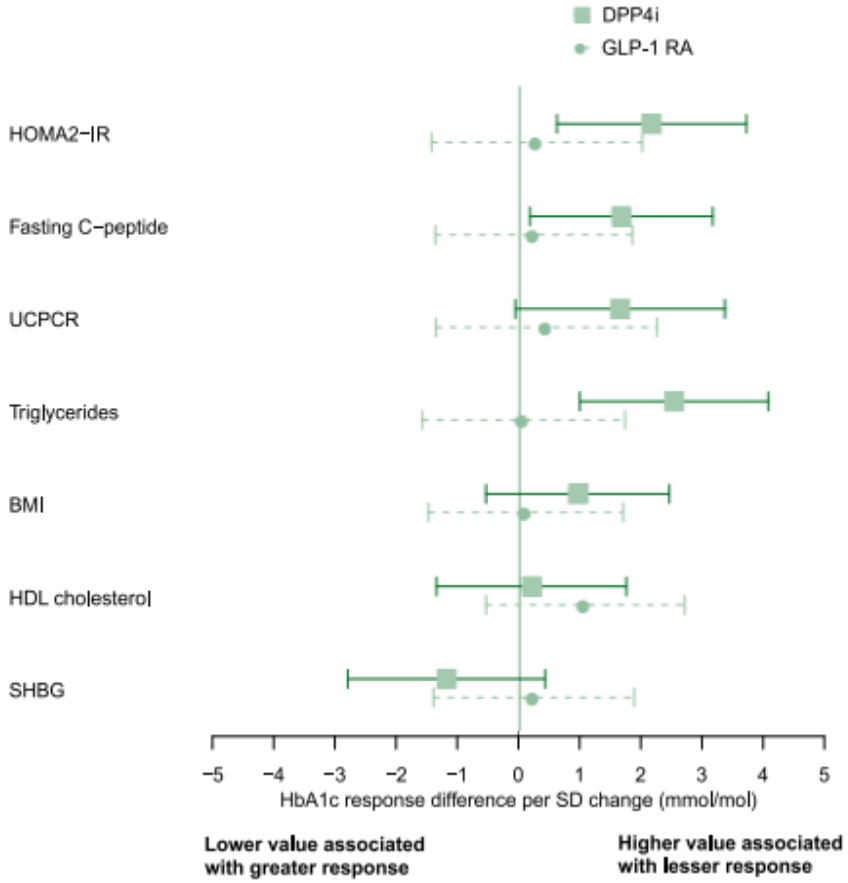
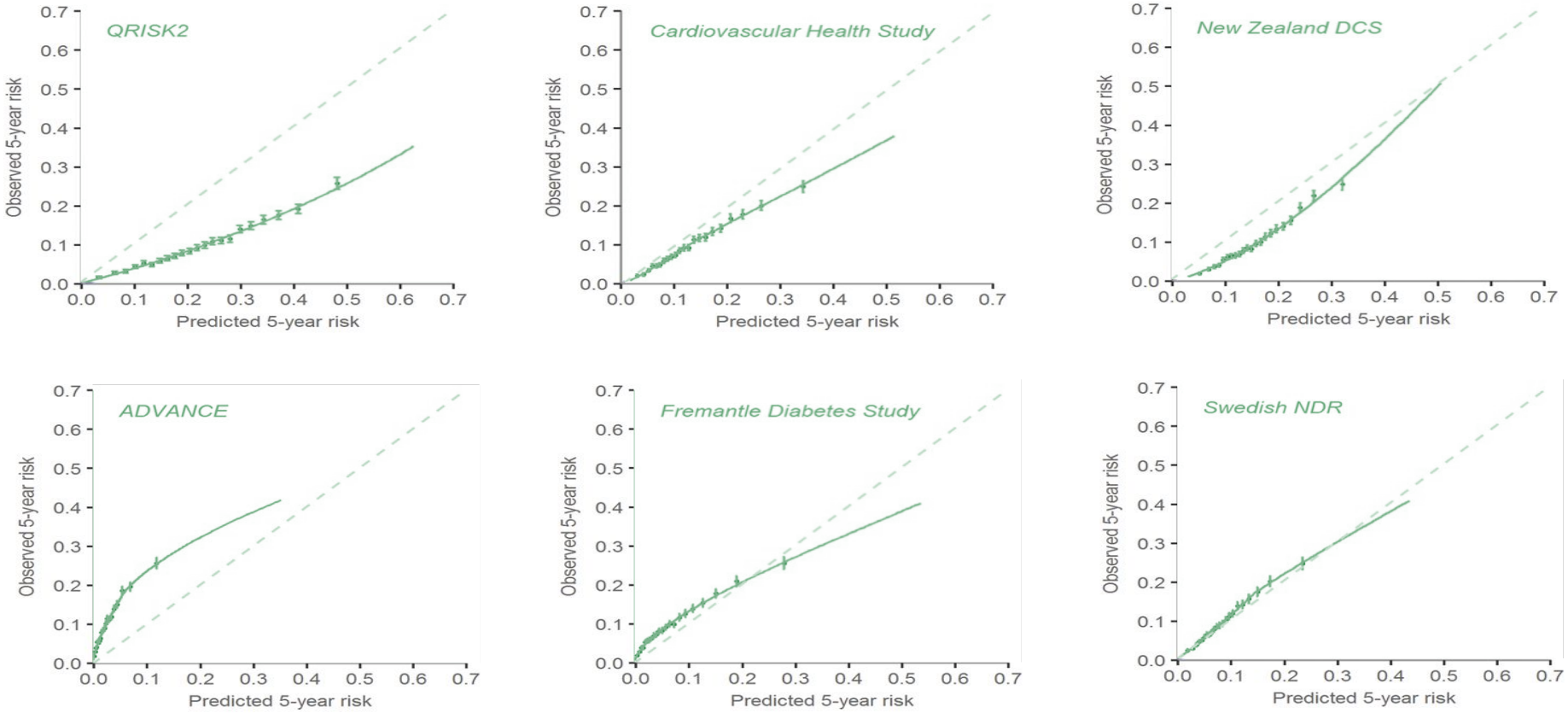


Figure 1:Associations between markers of insulin resistance and HbA1c response with DPP-4i and GLP-1RA treatment in the PRIBA study (n 5 593), in participants not on insulin cotreatment. Estimates denote the mean HbA1c change (mmol/mol) at 6 months (baseline HbA1c minus 6-month HbA1c) per 1-SD higher baseline value of each marker. Associations were tested in a series of independent linear regression models adjusted for baseline HbA1c and cotreatment change. Error bars denote 95% CI. Adapted from Dennis et al. (23). HOMA2-IR, HOMA of insulin resistance; SHBG, sex hormone binding globulin; UCPCR, urine C-peptide creatinine ratio.

Dennis JM. Diabetes Care 2020[Published online 25th August 2020].

Performance of Cardiovascular Disease Risk Scores in People Diagnosed With Type 2 Diabetes: External Validation Using Data From the National Scottish Diabetes Register



None of the risk scores performed well among people with newly diagnosed T2DM

Using these risk scores to predict 5-year CVD risk in this population may not be appropriate

Figure 1—Calibration plots for observed versus predicted 5-year risk of CVD as estimated using QRISK2, ADVANCE, CHS, Fremantle Diabetes Study, NZ DCS, and Swedish NDR risk scores in people diagnosed with type 2 diabetes between 2004 and 2016 in Scotland. Gray dashed line reflects perfect agreement between observed and predicted risk.

Read SH et al. Diabetes Care 2018;41:2010-2018.

Prognostic tools for cardiovascular disease in patients with type 2 diabetes: A systematic review and meta-analysis of C-statistics

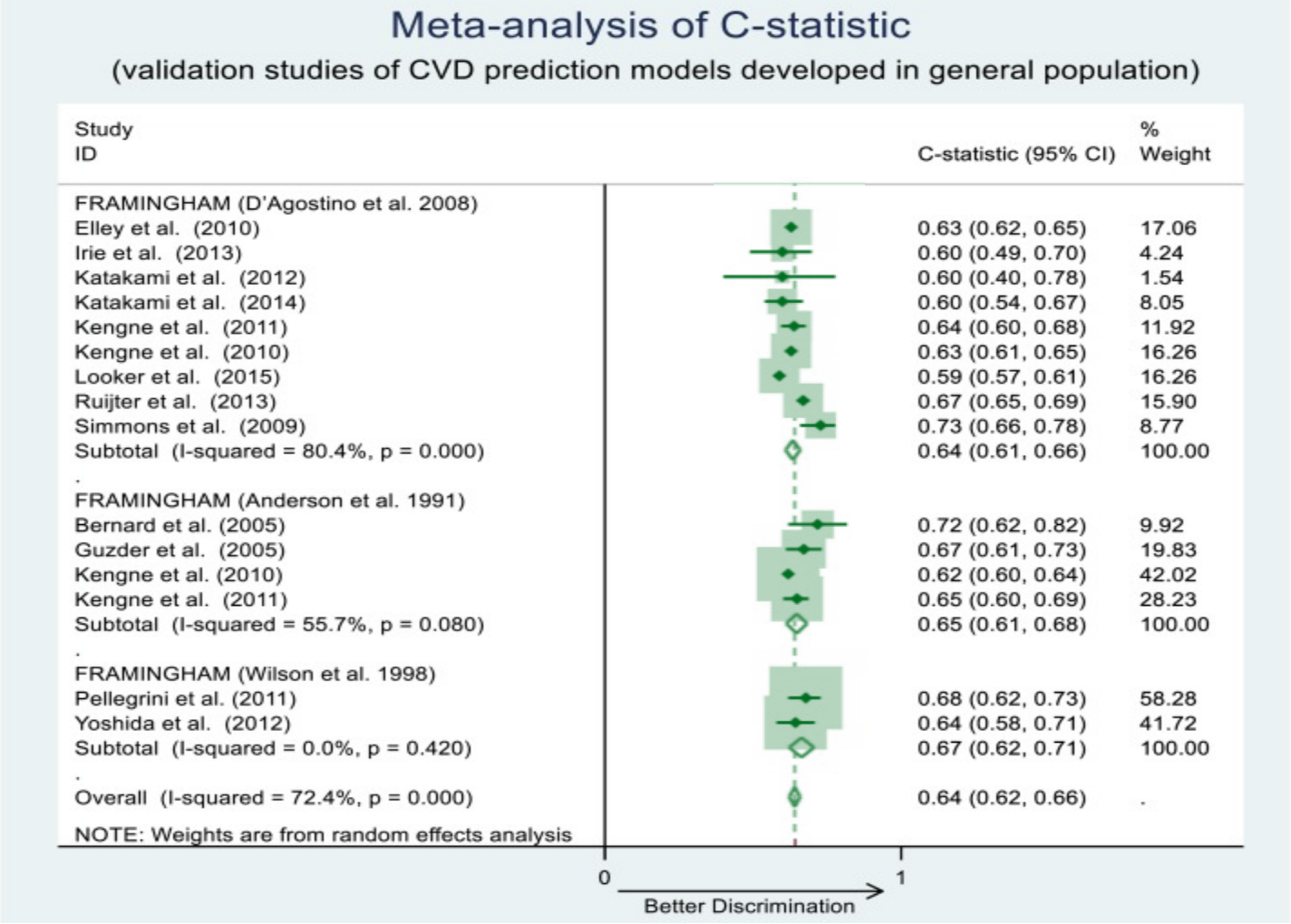


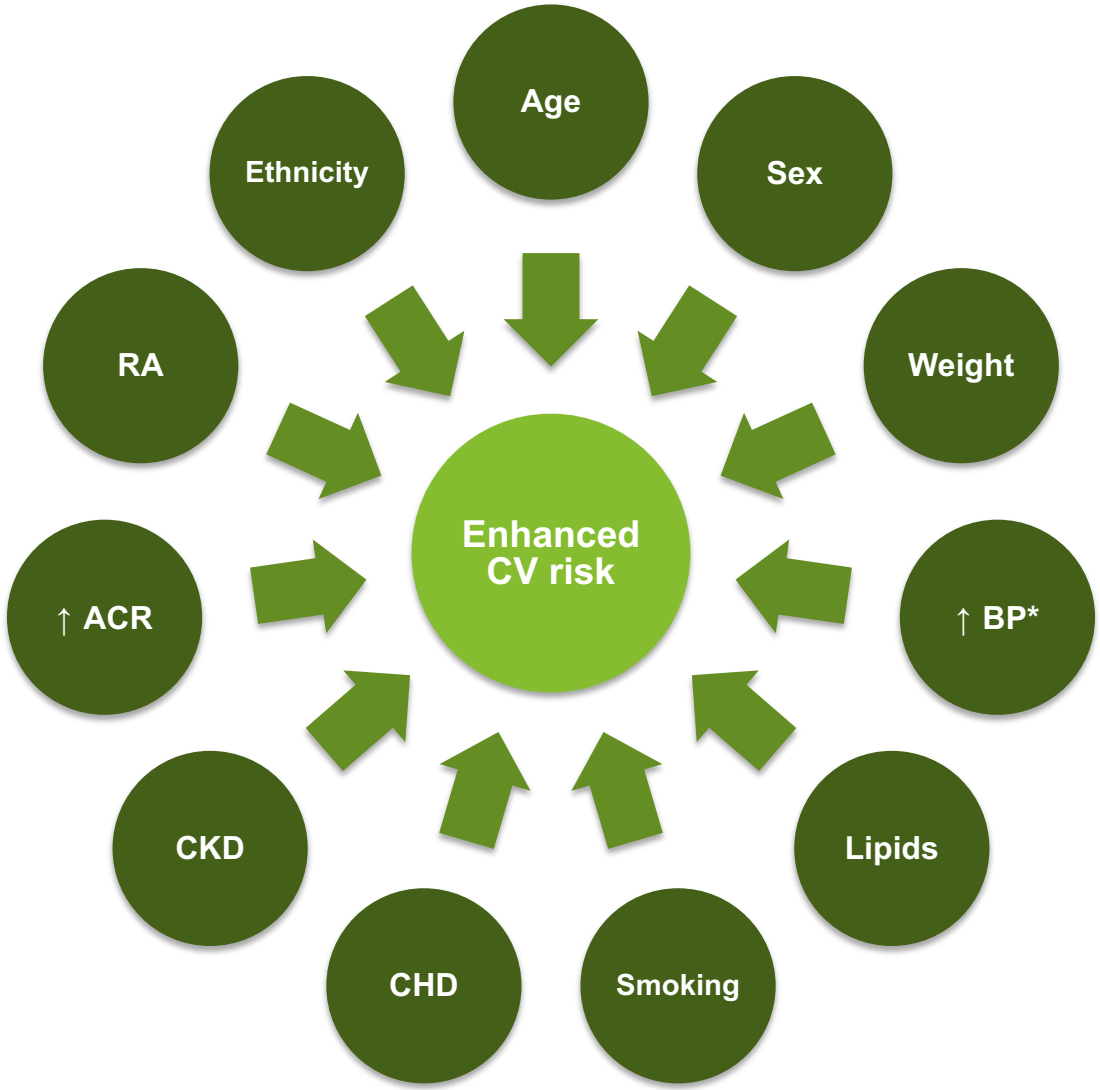
Fig. 3. Forest plot of C-statistics, with 95% confidence intervals (CIs), of CVD prediction models developed in diabetes population that are externally validated in two or more independent cohorts. Validation studies are stratified and identified by the name of the first author of the derivation study, with each external validation study identified below by the validation study's first author name.

Chowdhury M et al. Diabetes complications 2019;33(1):98-111

Outline

- Categorisation of risks and Personalised Medicine
- Pragmatic methods to categorise risk
- Evidence based guidelines
- Summary

CV risk enhancers in diabetes[1–4]

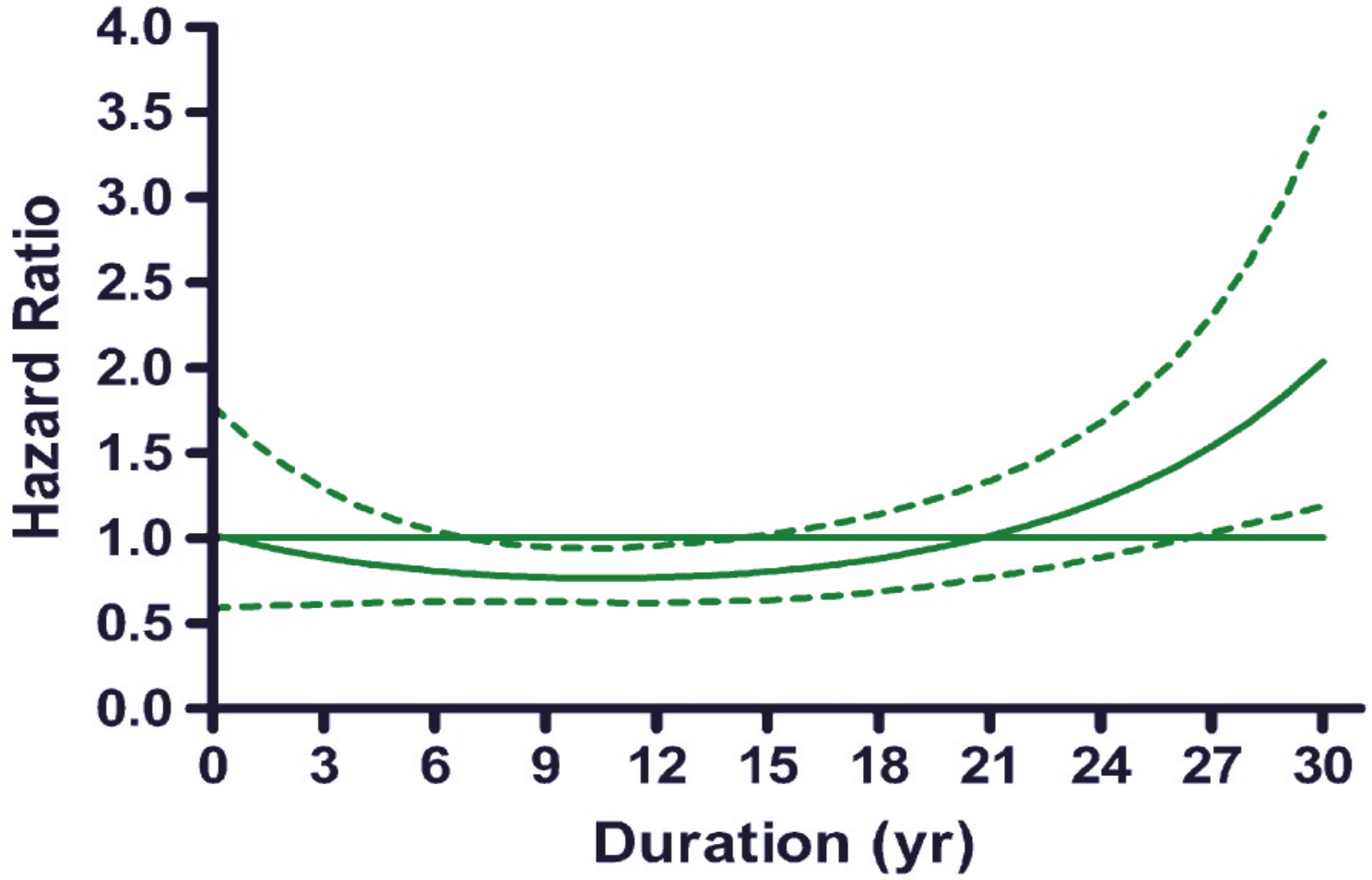


ACR, albumin-creatinine ratio;
BP, blood pressure;
CHD, coronary heart disease;
RA, rheumatoid arthritis

*BP includes pre-eclampsia

1. Arnett DK et al. *J Am Coll Cardiol.* 2019. pii: S0735-1097(19)33876-8. 2. Cosentino F et al. *Eur Heart J.* 2019;00:1–69.
3. American Diabetes Association. *Diabetes Care.* 2019;42:S1–204. 4. Bertoluci MC & Rocha VZ. *Diabetol Metab Syndr.* 2017;9:25.

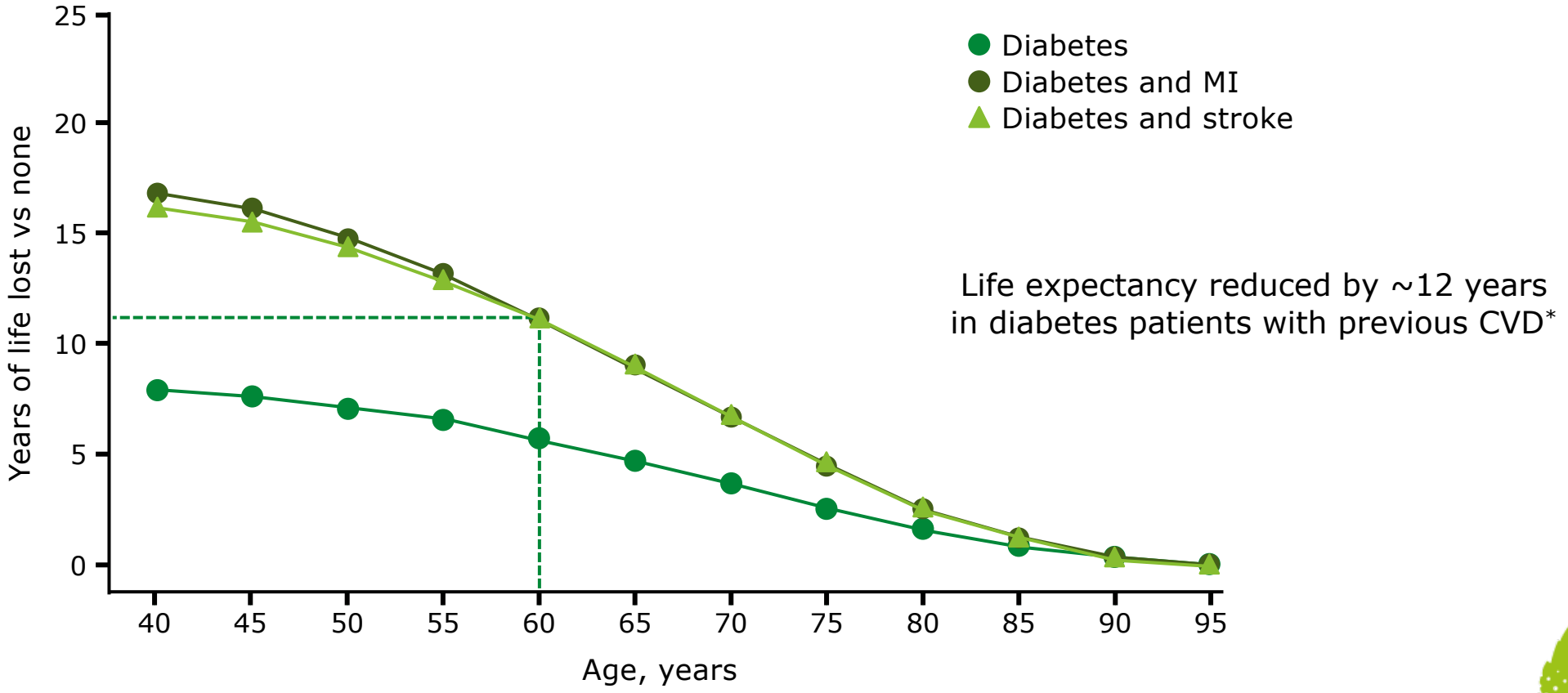
Duration of diabetes and CVD risk in VADT



Duckworth WC, et al. J Diabetes Complications 2011;25:355-361.

Age and multimorbidity

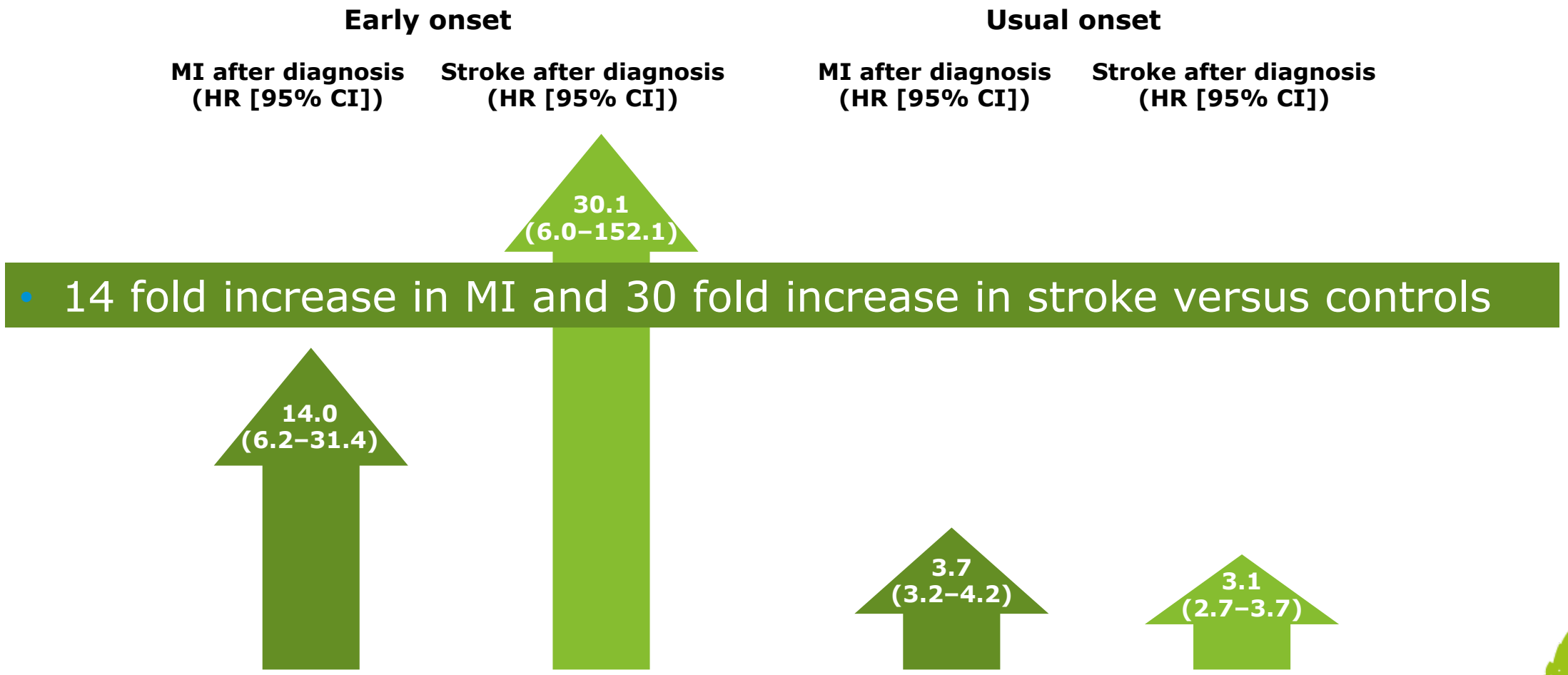
Modelling of years of life lost by disease status of participants at baseline compared with those free of diabetes, stroke and MI



Life expectancy reduced by ~12 years in diabetes patients with previous CVD*

*Male, 60 years of age with history of MI or stroke
CVD, cardiovascular disease; MI, myocardial infarction
The Emerging Risk Factors Collaboration. JAMA 2015;314:52–60

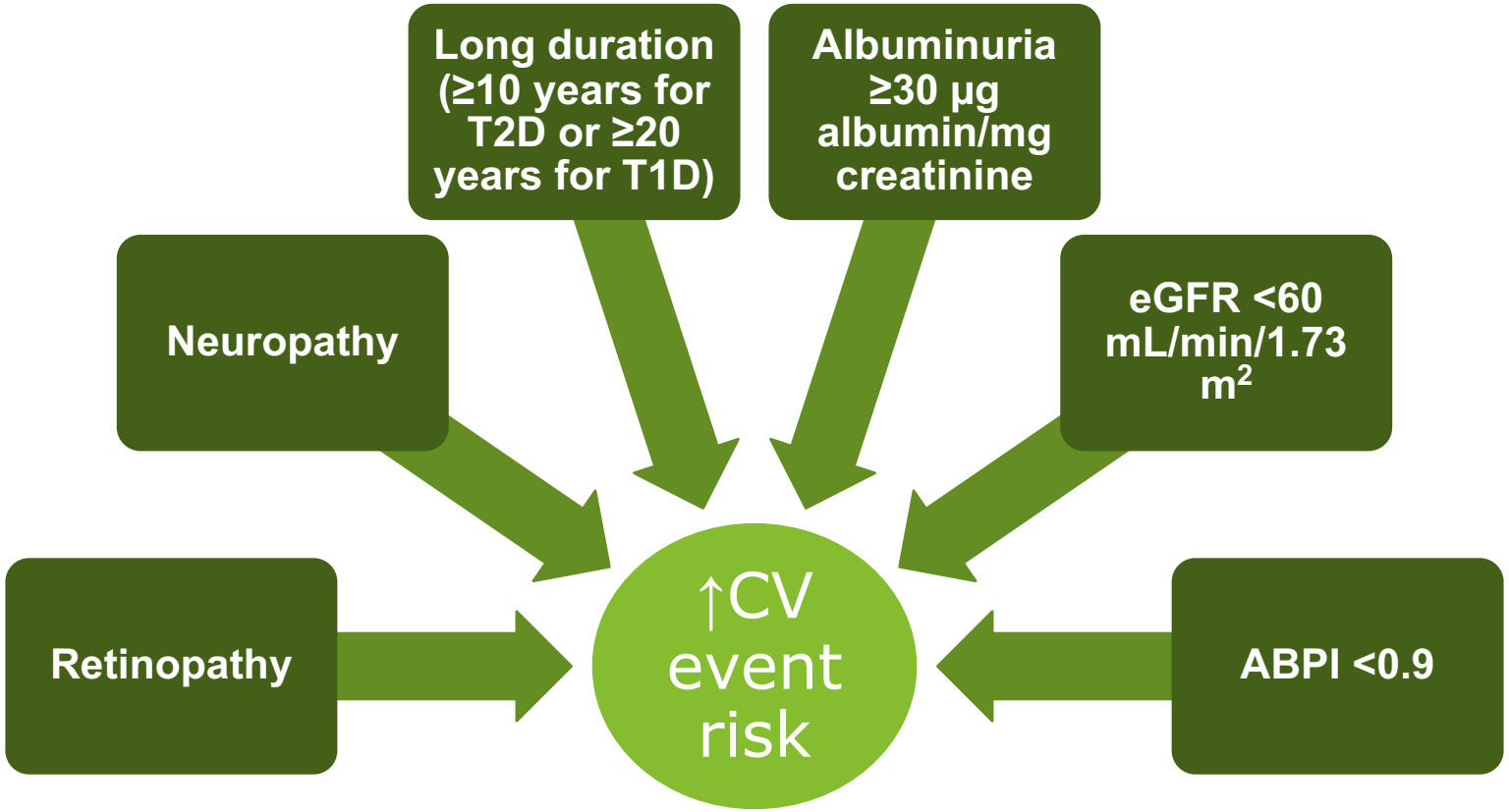
‘Early onset’ T2D has worse outcomes than ‘usual onset’*



*Mean follow-up 3.9 years

Hillier TA & Pedula KL. *Diabetes Care.* 2003;26:2999–3005.

Presence of microvascular disease increases risk of a CV event

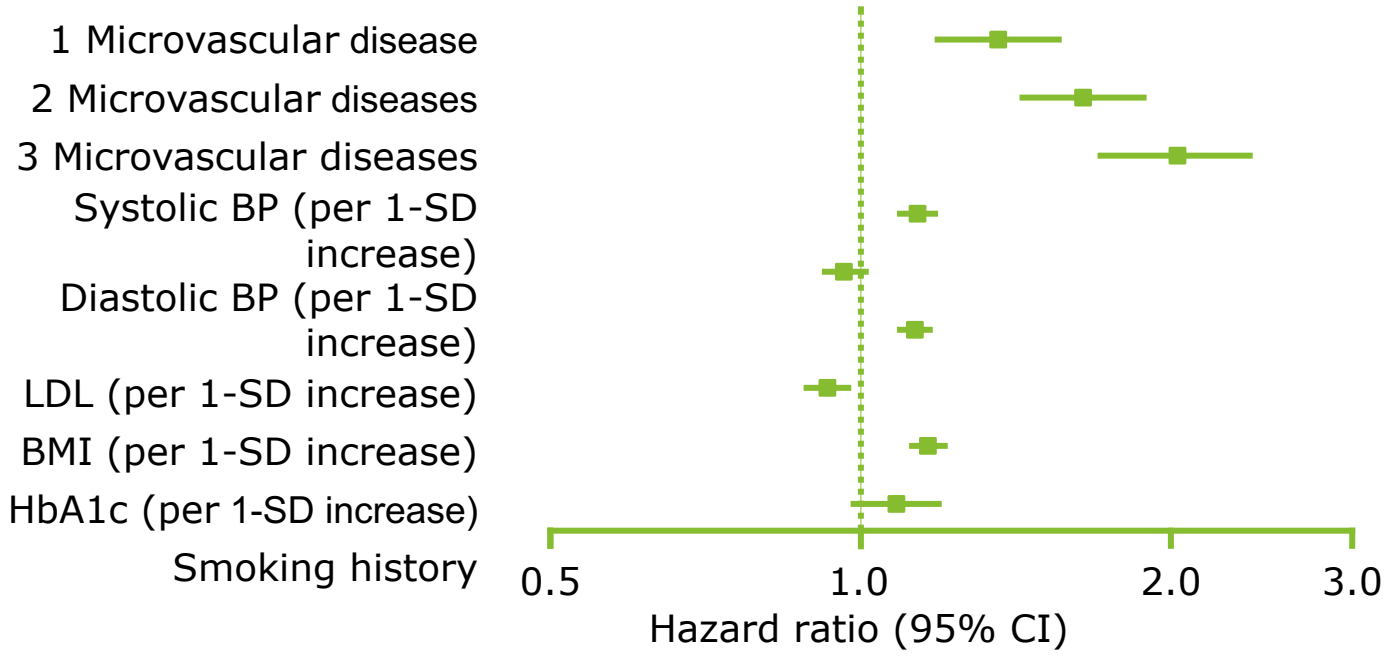


ABI: ankle-brachial pressure index; eGFR: estimated glomerular filtration rate

Arnett DK et al. *J Am Coll Cardiol* 2019. pii: S0735-1097(19)33876-8.

Presence of microvascular disease increases CVD risk in people with T2D

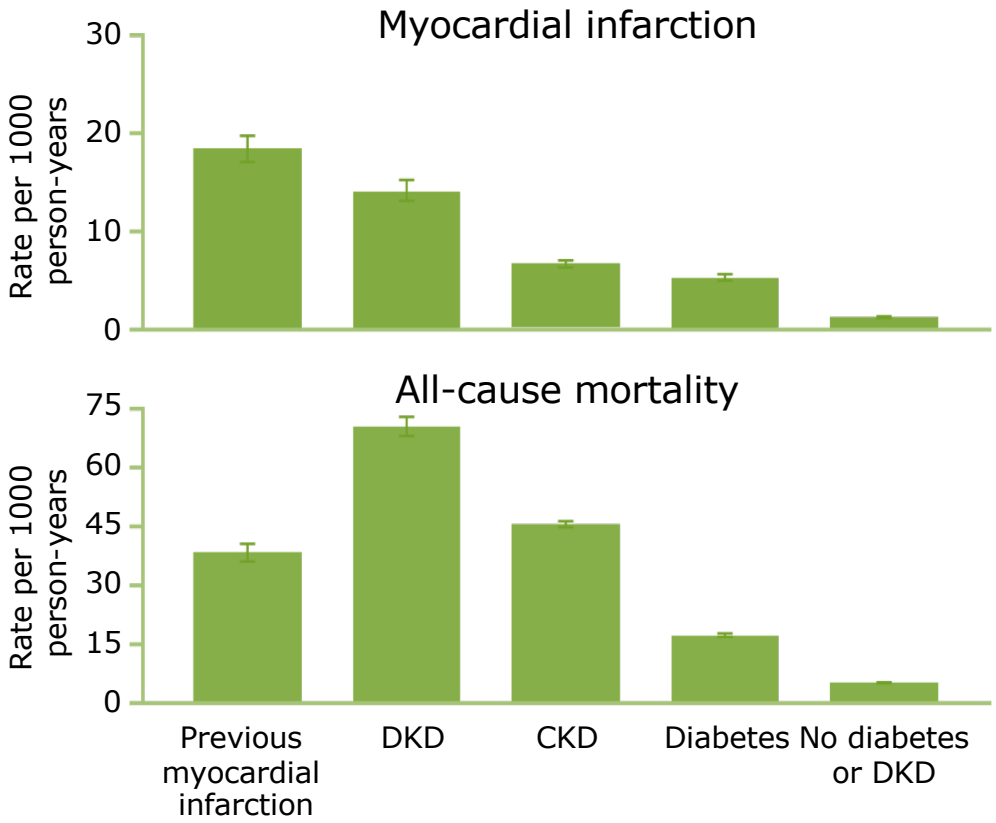
- Data from 49,027 people with T2D
- Multiple manifestations of microvascular disease (retinopathy, nephropathy, peripheral neuropathy) are additive for CVD risk



*1 SD of each established risk factor is: BP 13.5/8.4 mmHg; LDL 0.9 mmol/l; BMI 6.3 kg/m^2; HbA1c 1.3%.

Brownrigg JR et al. *Lancet Diabetes Endocrinol.* 2016;4:588–597.

DKD conveys a risk of myocardial infarction and mortality[1]



Population-based cohort study
N = 1 268 029
Median follow-up: 48 months

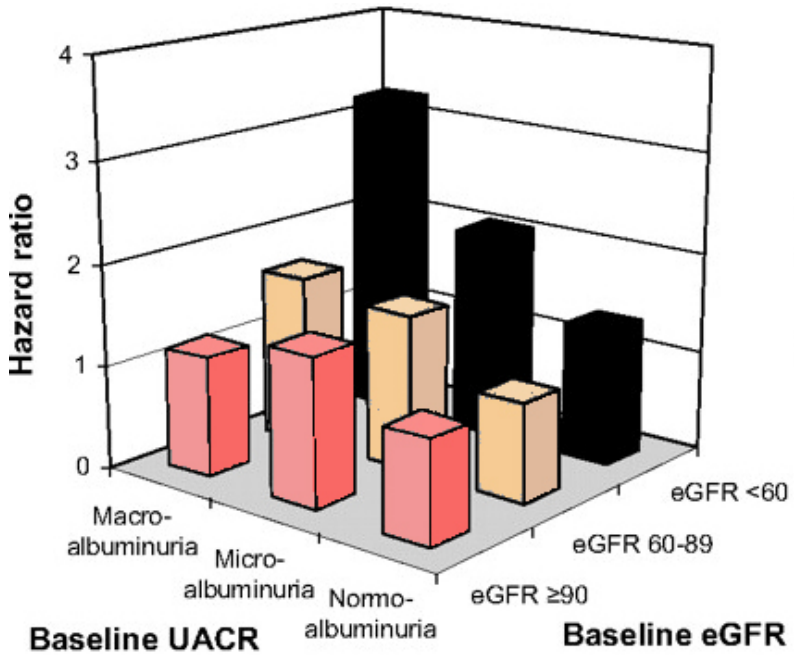
Baseline CKD defined as eGFR of 15–59.9 mL/min/1.73 m^2

CKD, chronic kidney disease; DKD, diabetic kidney disease; eGFR, estimated glomerular filtration rate; MI, myocardial infarction

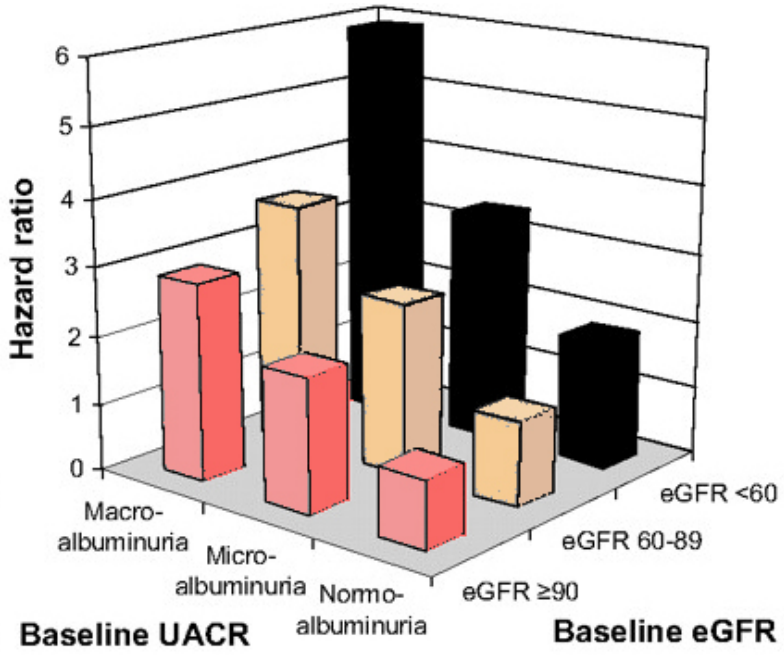
1. Tonelli M et al. Lancet 2012;380:807–14

Impact of baseline albuminuria and eGFR status on CV and renal events

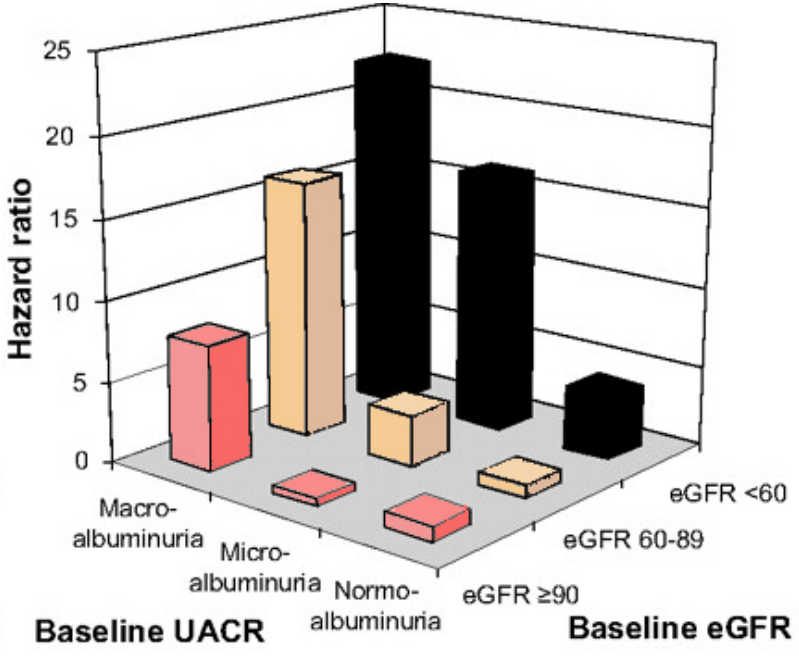
CV Events



CV Death



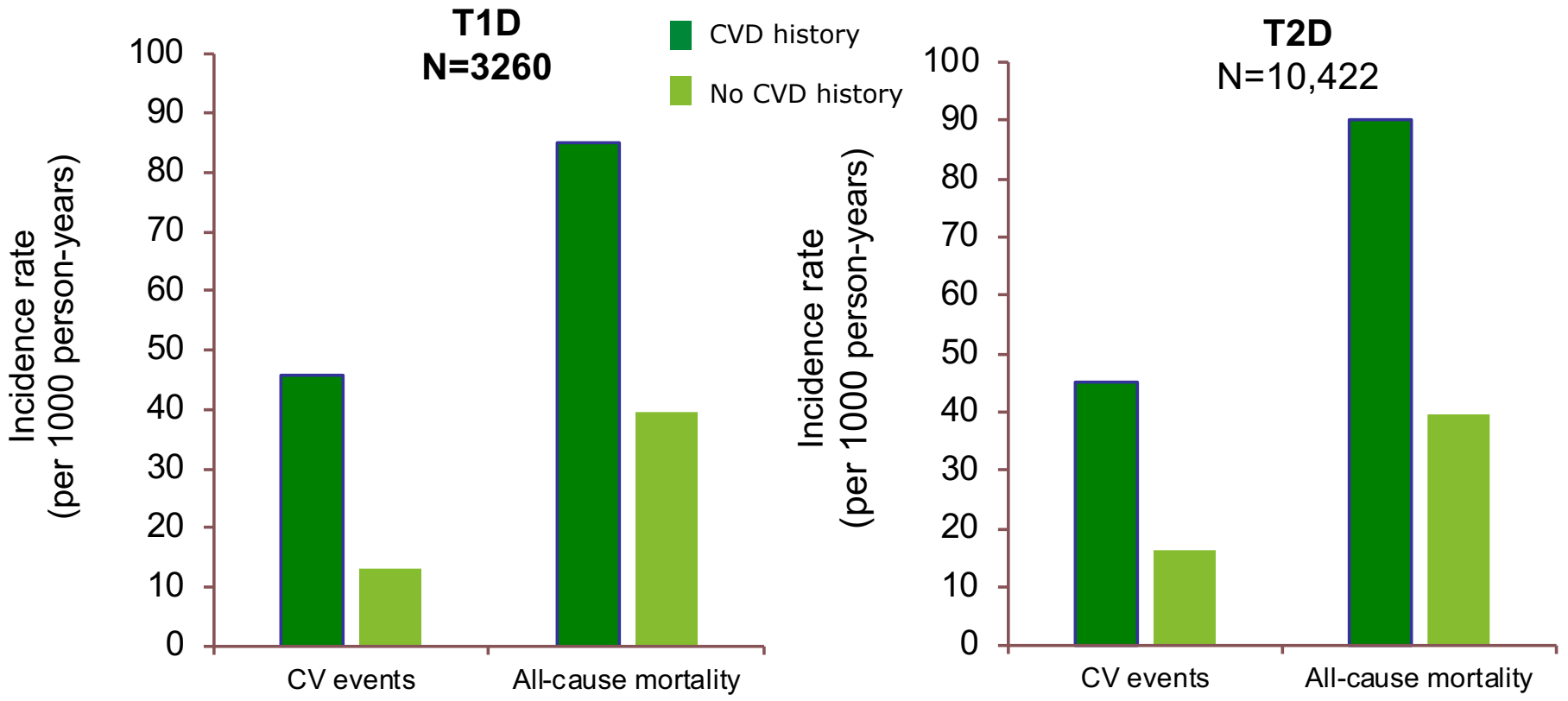
Renal Events



The estimates were adjusted for baseline covariates, including age, gender, duration of diabetes, systolic blood pressure, history of currently treated hypertension, history of macrovascular disease, A1C, LDL cholesterol, HDL cholesterol, log-transformed triglycerides, body mass index, electrocardiogram abnormalities, current smoking, and current drinking. CV, cardiovascular; eGFR, estimated glomerular filtration rate.

Ninomiya T et al. J Am Soc Nephrol. 2009;20(8):1813-21.

Importance of avoiding hypoglycaemia



Data are unadjusted incidence rates. CV, cardiovascular; CVD, cardiovascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes.

Khunti K et al. Diabetes Care. 2015;38:316–22.

Nonlinear association of BMI with all-cause and cardiovascular mortality in type 2 diabetes mellitus: a systematic review and meta-analysis of 414,587 participants in prospective studies

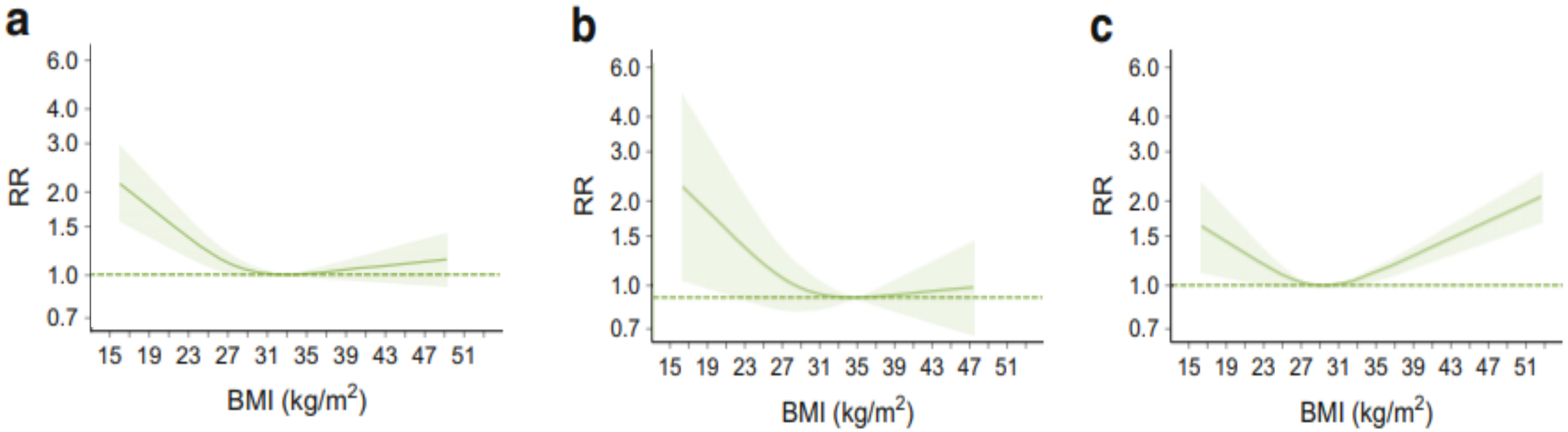
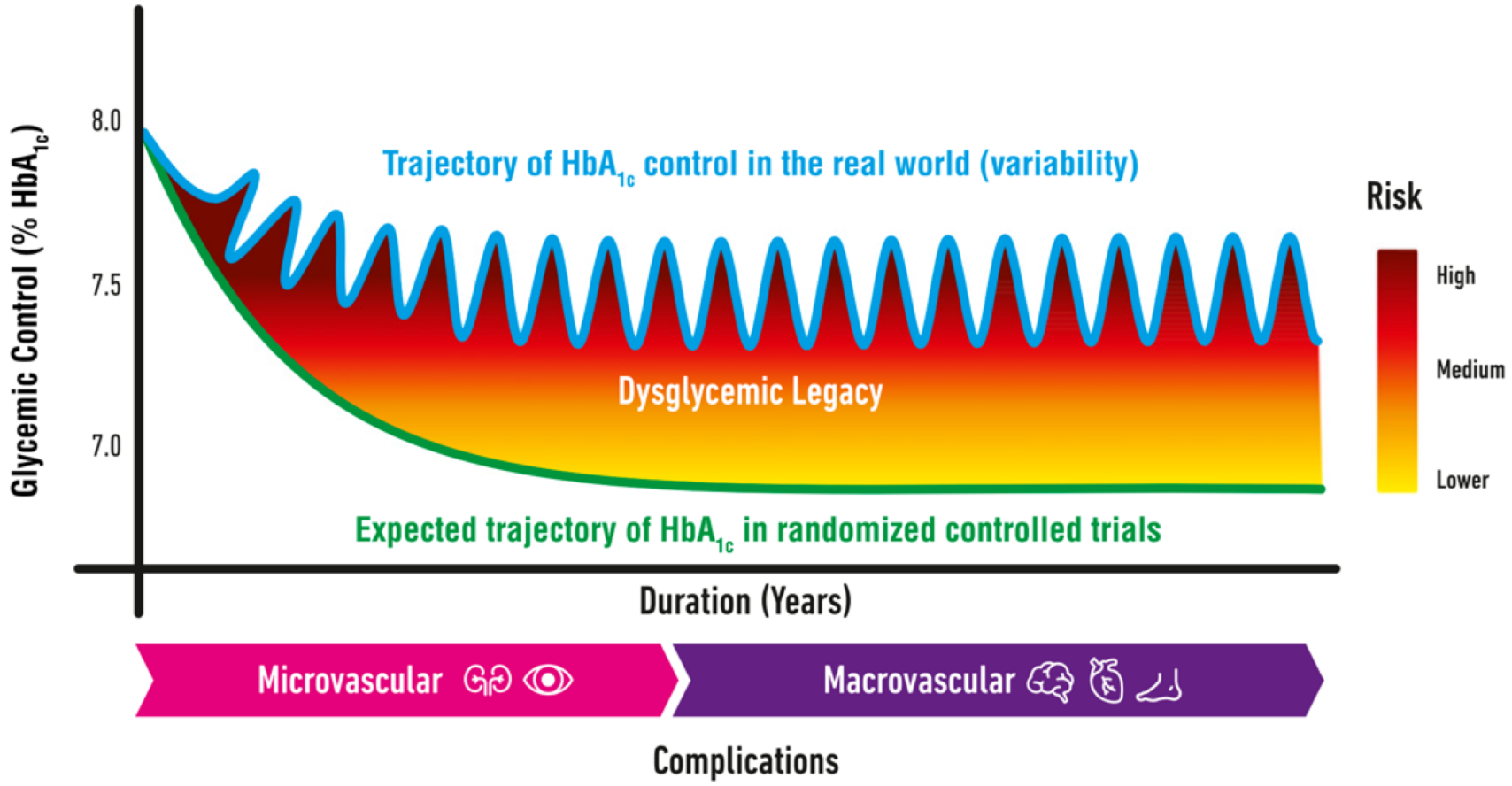


Fig. 2 Relationship between BMI and all-cause mortality for (a) both sexes, (b) men and (c) women. Grey shading indicates 95% CI

Zaccardi F et al. Diabetologia 2017;60(2):240-248

Avoid inertia and glycaemic variability and improve adherence



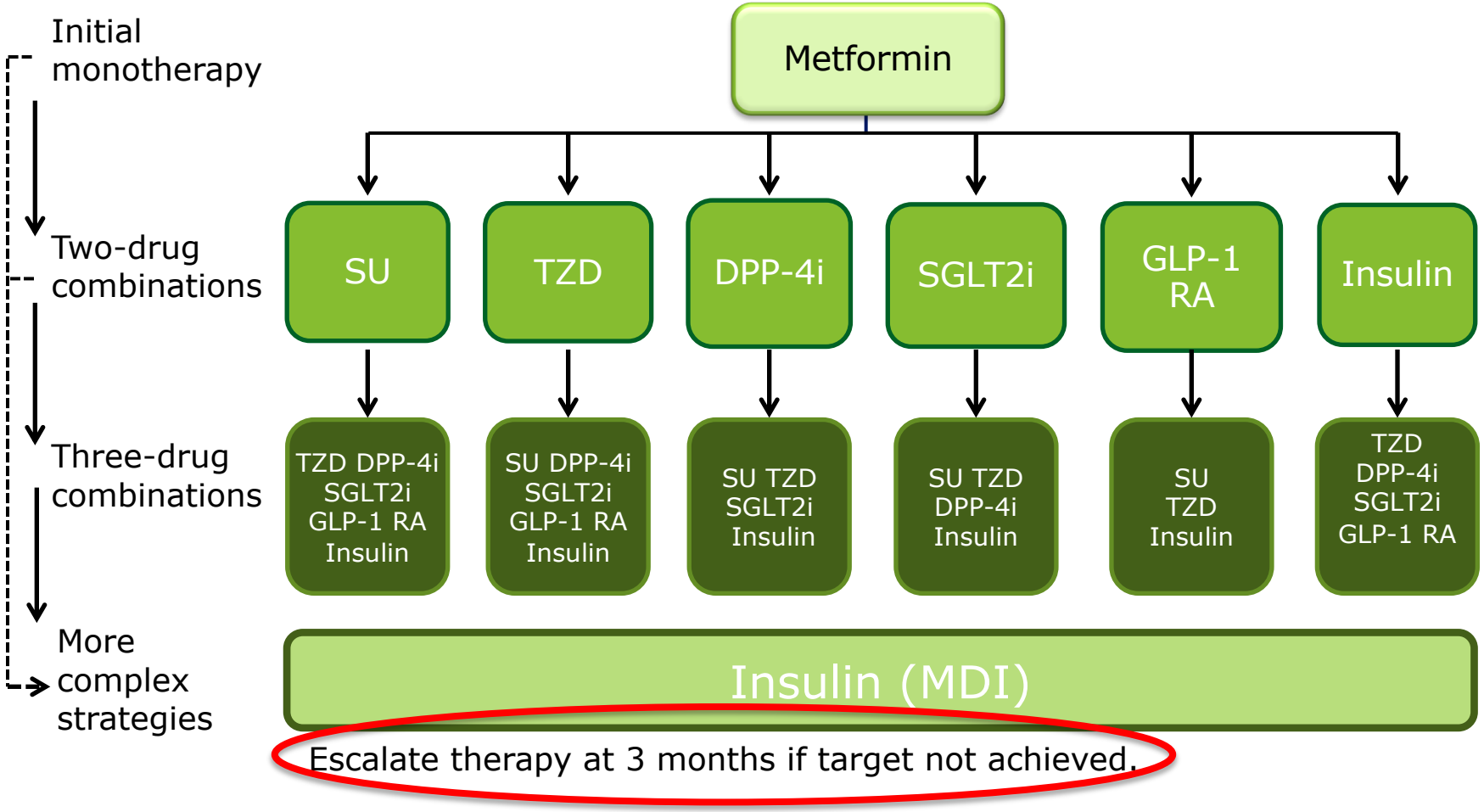
Khunti K, Seidu S. Diabetes Care 2019; 42: 349-351

Outline

- Categorisation of risks and Personalised Medicine
- Pragmatic methods to categorise risk
- Evidence based guidelines
- Summary

ADA/EASD: position statement for managing hyperglycaemia

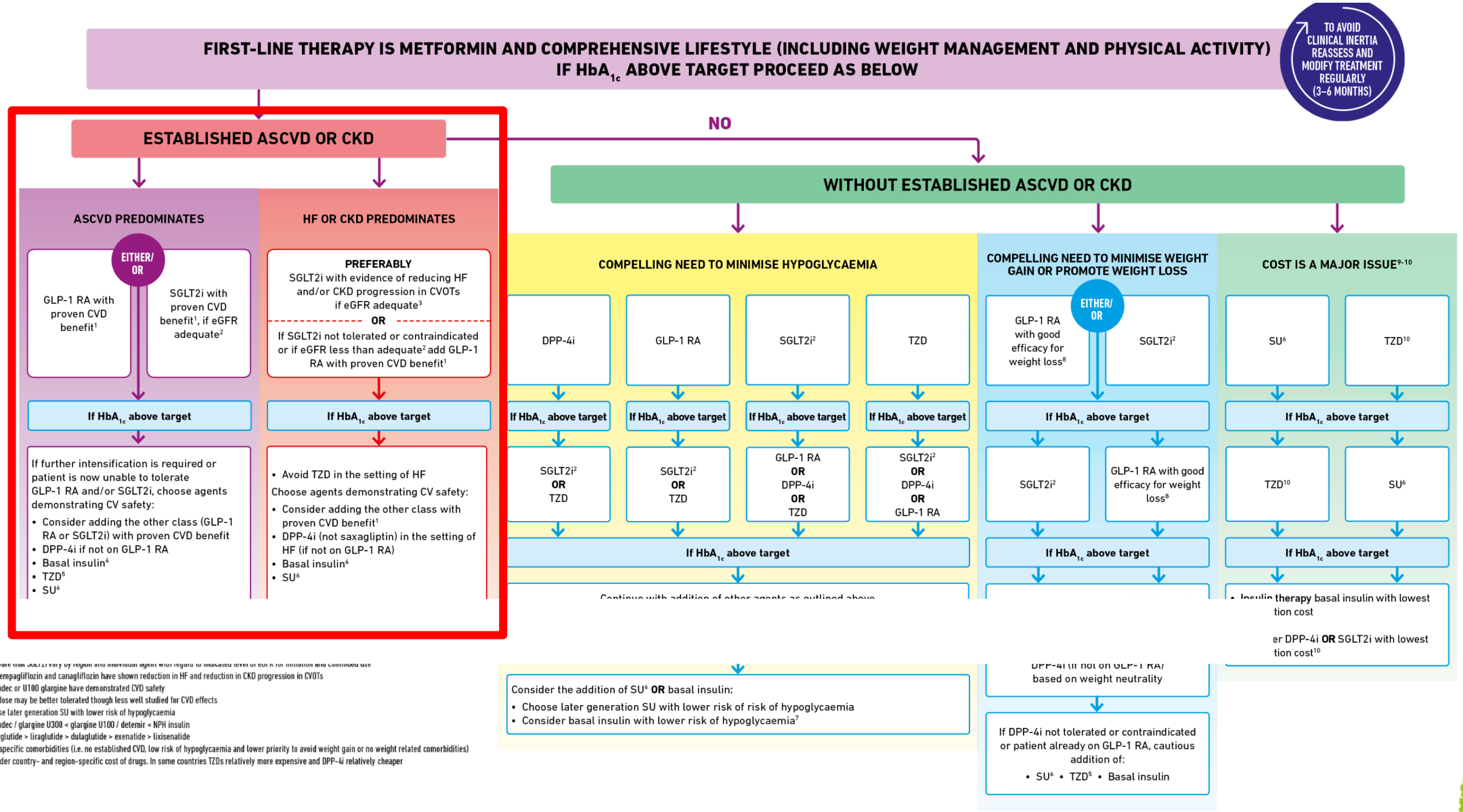
Healthy eating, weight control, increased physical activity



DPP-4i, dipeptidyl peptidase-4 inhibitor; SGLT2i, sodium-glucose cotransporter 2 inhibitor; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MDI, multiple daily injection; SU, sulfonylurea; TZD, thiazolidinedione.

Inzucchi SE, et al. Diabetes Care. 2015;38:140-9. Inzucchi SE, et al. Diabetes Care 2016;39(Suppl. 1):S1–S2.

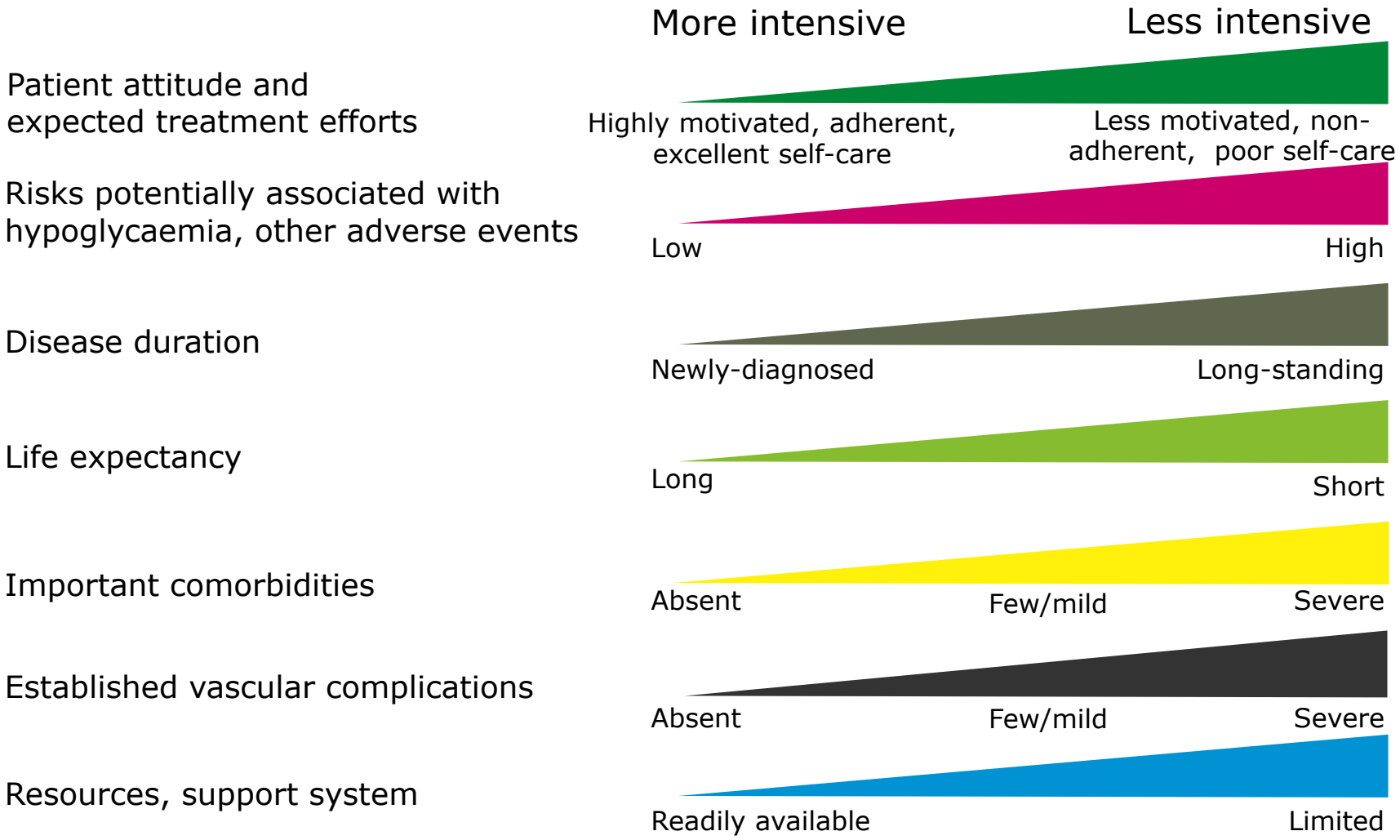
Glucose-lowering medication in type 2 diabetes: overall approach



1.
2. Be aware that SGLT2i vary by region and individual agent with regard to indicated level of eGFR for initiation and continued use
3. Both empagliflozin and canagliflozin have shown reduction in HF and reduction in CKD progression in CVOTs
4. Degludec or U100 glargine have demonstrated CVD safety
5. Low dose may be better tolerated though less well studied for CVD effects
6. Choose later generation SU with lower risk of hypoglycaemia
7. Degludec / glargine U300 < glargine U100 / detemir < NPH insulin
8. Semaglutide > liraglutide > dulaglutide > exenatide > lixisenatide
9. If no specific comorbidities (i.e. no established CVD, low risk of hypoglycaemia and lower priority to avoid weight gain or no weight related comorbidities)
10. Consider country- and region-specific cost of drugs. In some countries TZDs relatively more expensive and DPP-4i relatively cheaper

Davies MJ et al. Diabetes Care 2018. Sep; dci180033. https://doi.org/10.2337/dci18-0033;

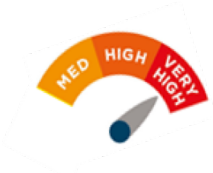
Individualisation of targets



Inzucchi SE, et al. Diabetologia 2012;55:1577-1596.

CV risk categories in patients with diabetes in the new 2019 ESC guidelines

The 2019 ESC guidelines[1a] build upon the SCORE risk from the 2016 European Guidelines on CVD prevention in clinical practice[2] to stratify CV risk in patients with diabetes and pre-diabetes



Very high risk

Patients with DM and established CVD
or other target organ damage[b]
or three or more major risk factors[c]
or early onset T1D of long duration (>20 years)

High risk

Patients with DM duration ≥10 years without target organ damage plus any other additional risk factor

Moderate risk

Young patients (T1D aged <35 years or T2D aged <50 years) with DM duration <10 years, without other risk factors

[a]Modified from the 2016 European guidelines on cardiovascular disease prevention in clinical practice[2]
[b]Proteinuria, renal impairment defined as eGFR ≥30 mL/min/1.73 m^2, left ventricular hypertrophy or retinopathy
[c]Age, hypertension, dyslipidaemia, smoking, obesity
ESC, European Society of Cardiology; SCORE, Systematic Coronary Risk Estimation

1. Cosentino F et al. *Eur Heart J.* 2019;00:1–69.
2. Piepoli MF et al. *Eur Heart J.* 2016;37:2315–2381

Outline

- Categorisation of risks and Personalised Medicine
- Pragmatic methods to categorise risk
- Evidence based guidelines
- Summary

Summary

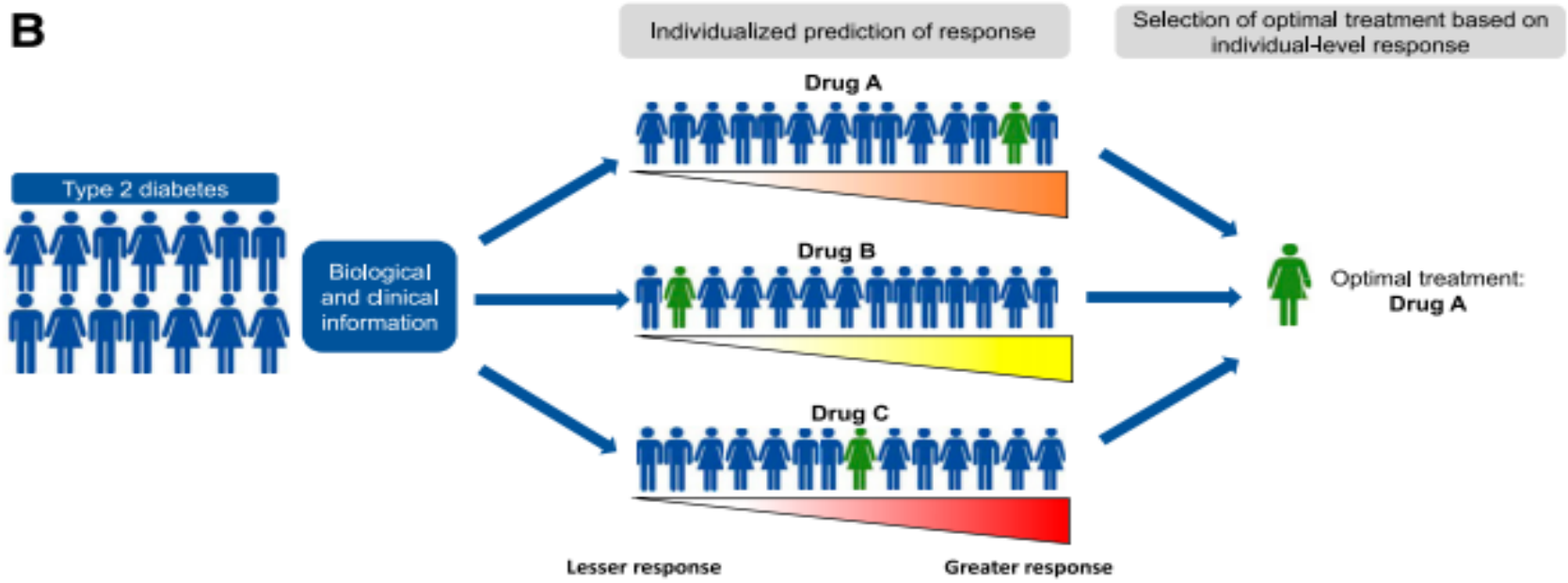
- T2DM Progressive disease
- Early risk factor control associated with longer term benefits
- A number of pragmatic risk factors can be used to categorise risk
- We await further research in precision medicine
- Key issue is INDIVIDUALISING therapies

Advantages

- Simple to communicate.
- Can assess risk of multiple outcomes based on subgroup assignment.
- Classification could take place at one time point only, e.g. around diagnosis (important if nonroutine testing is required).
- May enhance understanding of the pathophysiological basis for type 2 diabetes

Disadvantages

- People within a subtype may be very different but are assumed to have the same outcome.
- Cannot be assumed to represent true pathophysiological subtypes—highly dependent on features used to classify them.
- Subtypes are not discrete, but overlap in phenotypic characteristics.
- Subtypes not stable—unless defined solely by genetics, a person can shift from one subgroup to another over time.



Advantages

- Optimal prediction of outcome, as predictions based on precise individual level characteristics.[39]
- Predictions specific to a person's characteristics at the point in time an optimal treatment strategy is being considered.

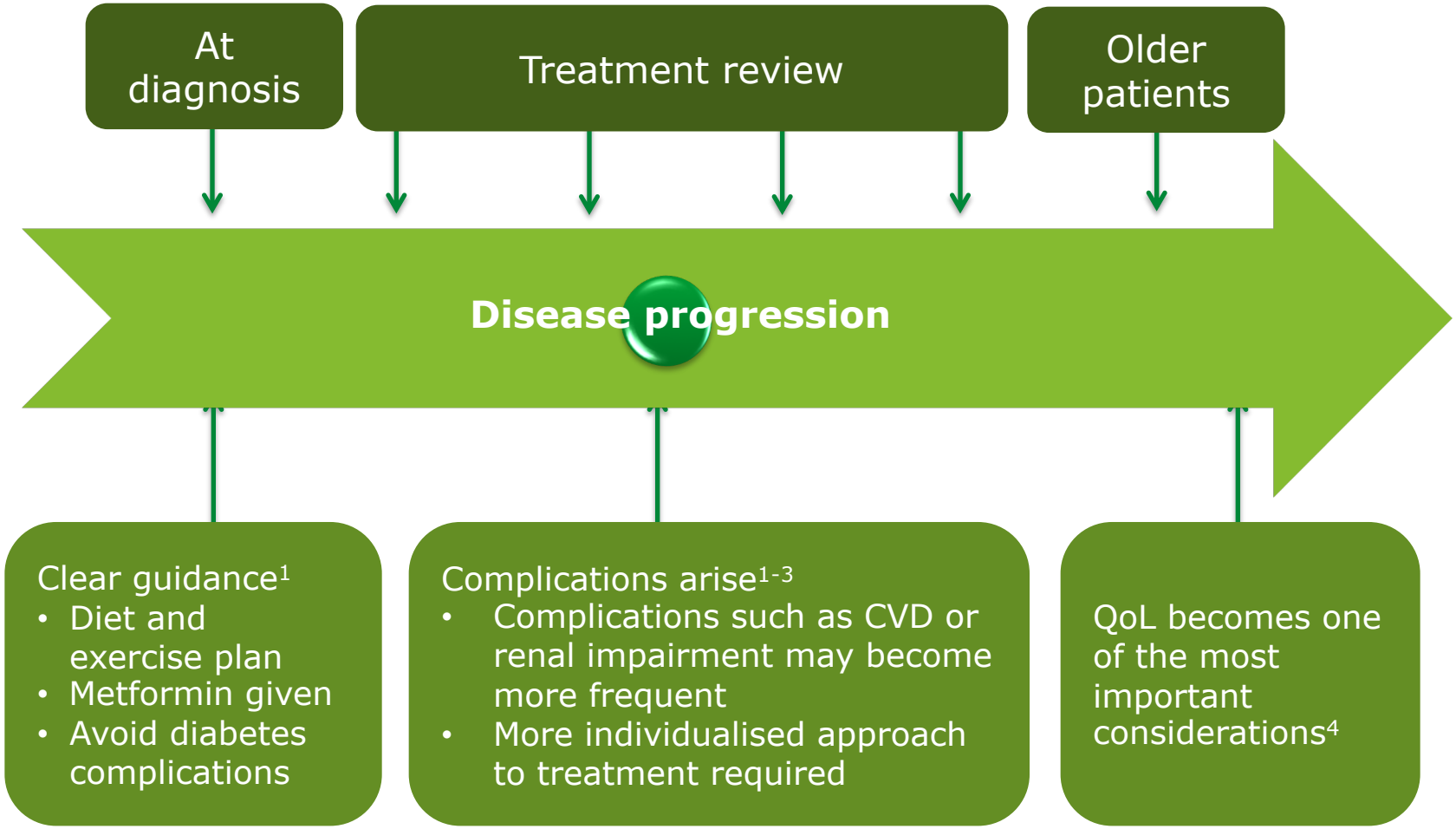
Disadvantages

- Complexity—specific models required for different outcomes, e.g., risk of complications.
- Challenging to weigh up models for different outcomes and communicate these.
- Input data for prediction required at different time points.

Fig2 ; Individualized prediction compared with classification into subtypes: advantages and disadvantages of two strategies to apply a precision medicine approach in type 2 diabetes. A) Classification into subtypes. B) Individualized prediction.

Dennis JM. Diabetes Care 2020[Published online 25th August 2020].

Management of T2D Becomes More Complex Over Time



1,2. Adapted from National Institute for Health and Clinical Excellence. Clinical Guideline 87. Type 2 diabetes – newer agents (a partial update of CG66): quick reference guide. NICE clinical guideline 66: Type 2 Diabetes Management. Available at: http://www.nice.org.uk/nicemedia/pdf/CG66NICEGuideline.pdf (accessed November 2012).
3. Go AS, et al. N Engl J Med. 2004;351:1296–1305; 4. Morley JE. Diabet Med. 1998;15 (Suppl. 4): S41–6.

PCDE
primary care diabetes europe

Thank you

www.leicesterdiabetescentre.org.uk

www.facebook.com/LeicesterDiabetesCentre

@kamleshkhunti

@LDC_Tweets