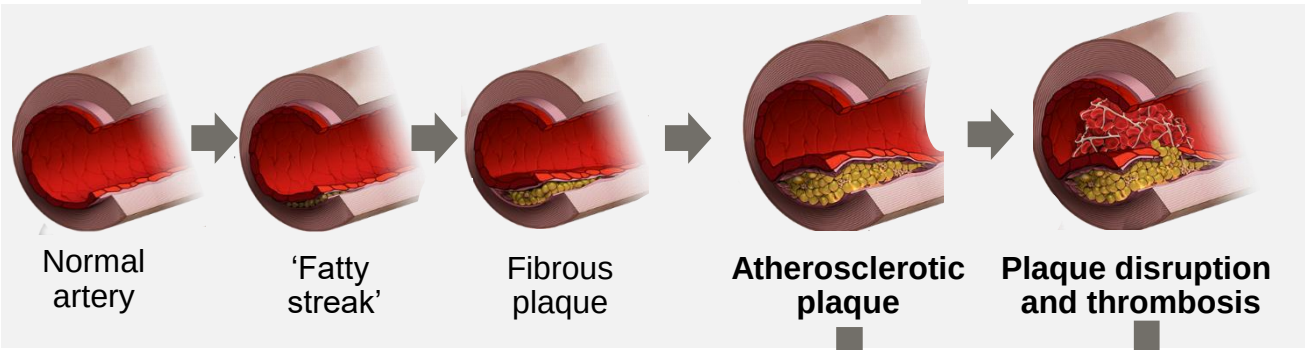
GLP-1 RA在PAD相關之運用

臺大醫院心臟內科

李任光醫師

Atherosclerosis Is a Progressive Disease Leading to Atherothrombosis and Ischaemia



Flow-limiting stenosis
Symptoms with exercise, e.g. stable angina and intermittent claudication

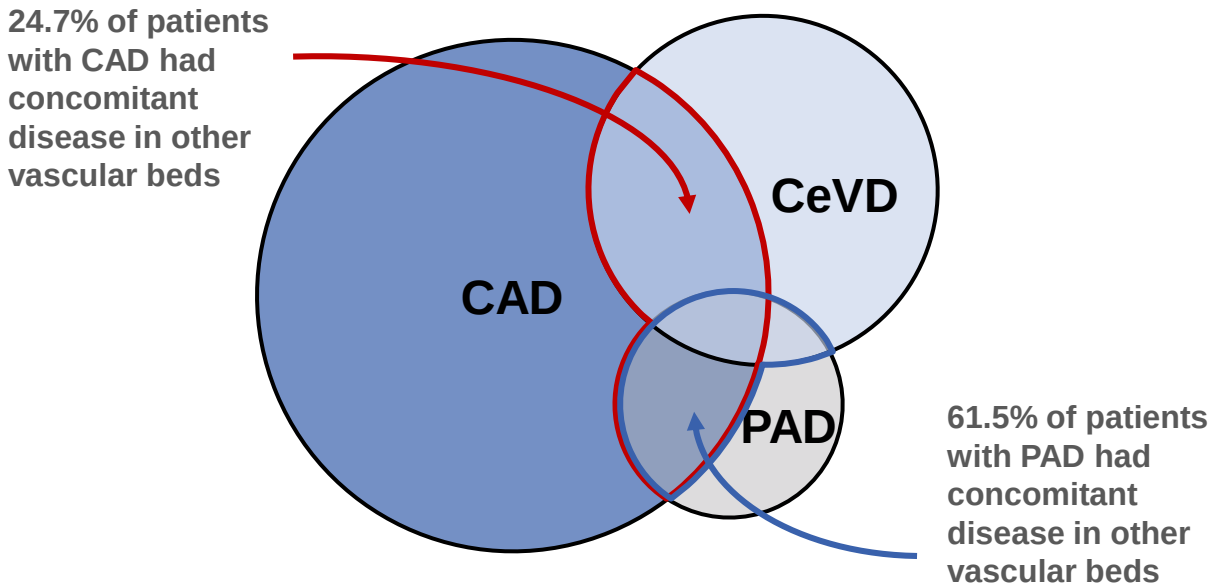
Atherothrombosis

- **MI**
- **Stroke**
- **CV death**
- **Limb ischaemia**

1. Insull W Jr, *Am J Med* 2009;122(1 Suppl):S3–S14; 2. Bradberry JC *et al*, *J Am Pharm Assoc* 2004;44:S37–S45

Atherosclerosis Is a Polyvascular Disease

REACH: More than 3 in 5 patients with PAD have atherothrombotic disease also in other arterial territories



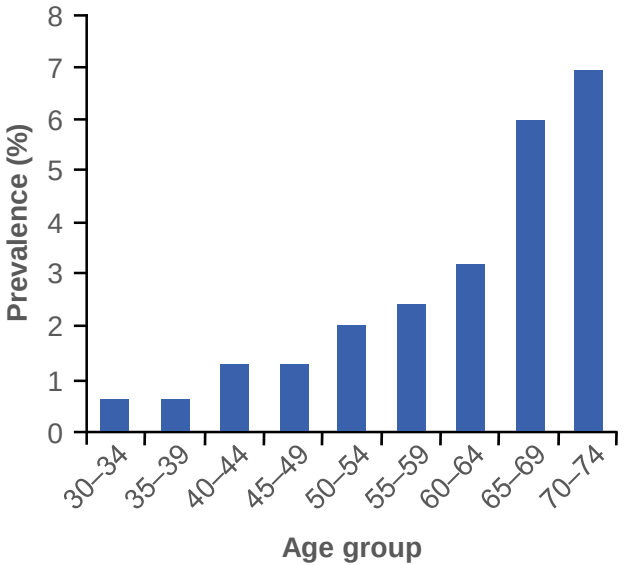
Percentages are calculated from the total population included in the REACH registry. N=67,888

Bhatt DL *et al*, *JAMA* 2006;295:180–189

Peripheral Arterial Disease

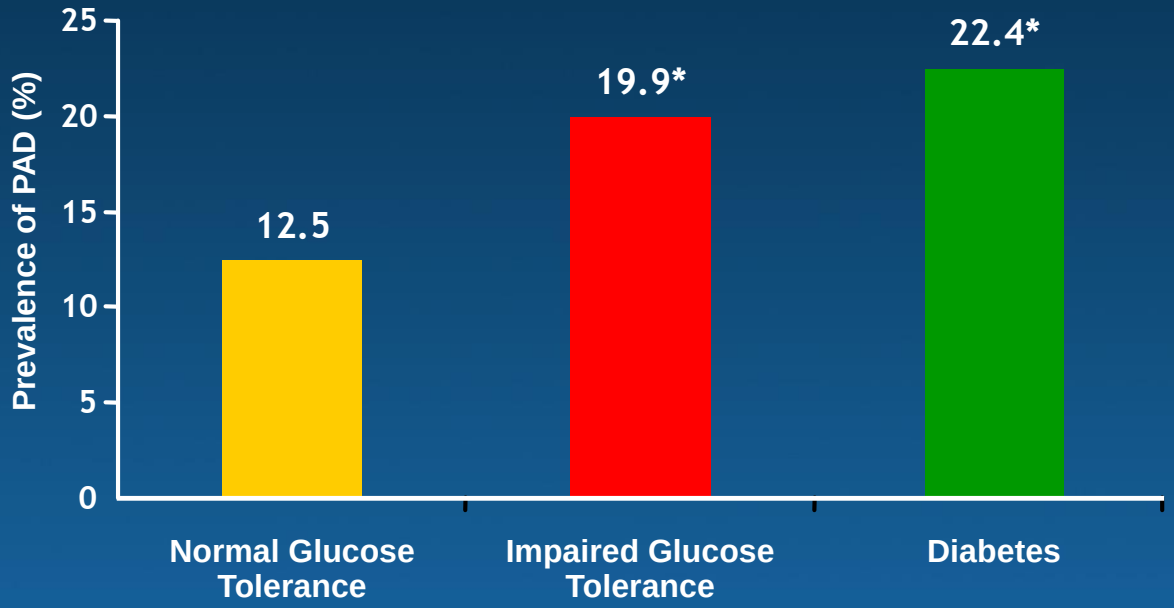
- *'Non-coronary arterial syndromes caused by altered structure and function of arteries supplying the brain, visceral organs, and the limbs'*[1]
- Epidemiological studies have focused on lower extremity PAD:
  - Prevalence of asymptomatic lower limb PAD estimated at up to 10%, rising to 20% among those aged >70 years[2]
  - Prevalence of symptomatic lower limb PAD rises from <3% in those aged <60 years to ~7% in those aged 70–74 years[2]

Weighted mean prevalence of symptomatic lower limb PAD derived from large population-based studies[2]



1. Hirsch AT *et al*, *Circulation* 2006;113:e463–e654; 2. Norgren L *et al*, *Eur J Vasc Endovasc Surg* 2007;33(Suppl 1):S1–S75

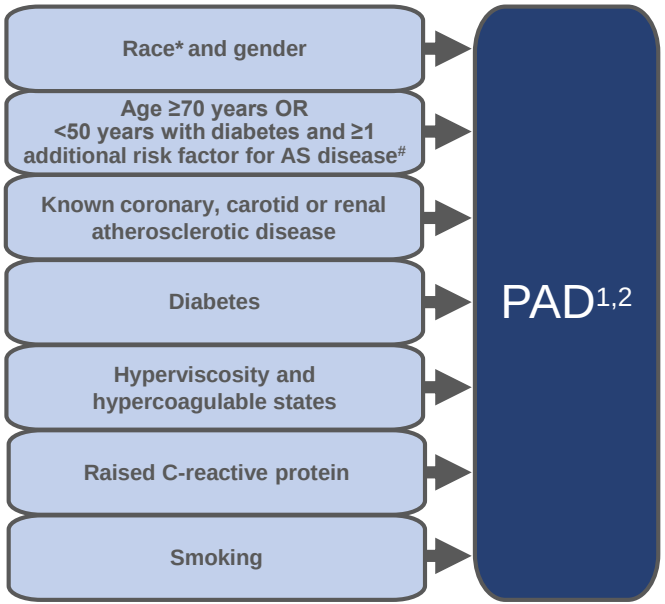
Diabetes Increases the Risk of PAD



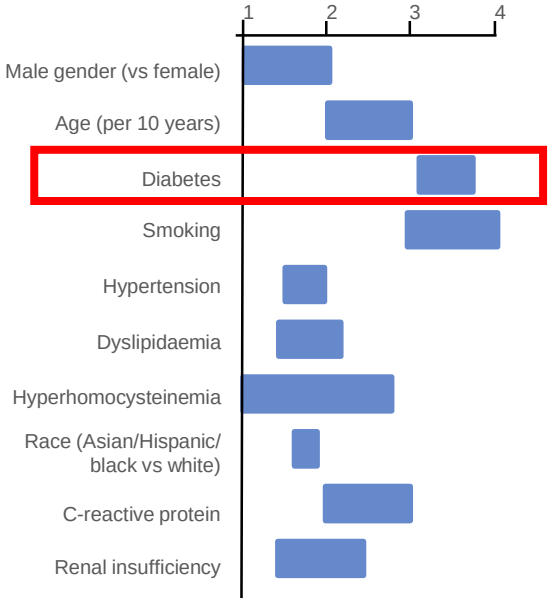
Impaired glucose tolerance was defined as oral glucose tolerance test value ≥140 mg/dL but <200 mg/dL.
*$P \leq .05$ vs. normal glucose tolerance.
Reprinted with permission from Lee AJ, et al. *Br J Haematol.* 1999;105:648-654. www.blackwell-synergy.com

Peripheral Arterial Disease: Risk Factors

Factors associated with increased risk of PAD; overlap exists with known risk factors for CV disease[1,2]

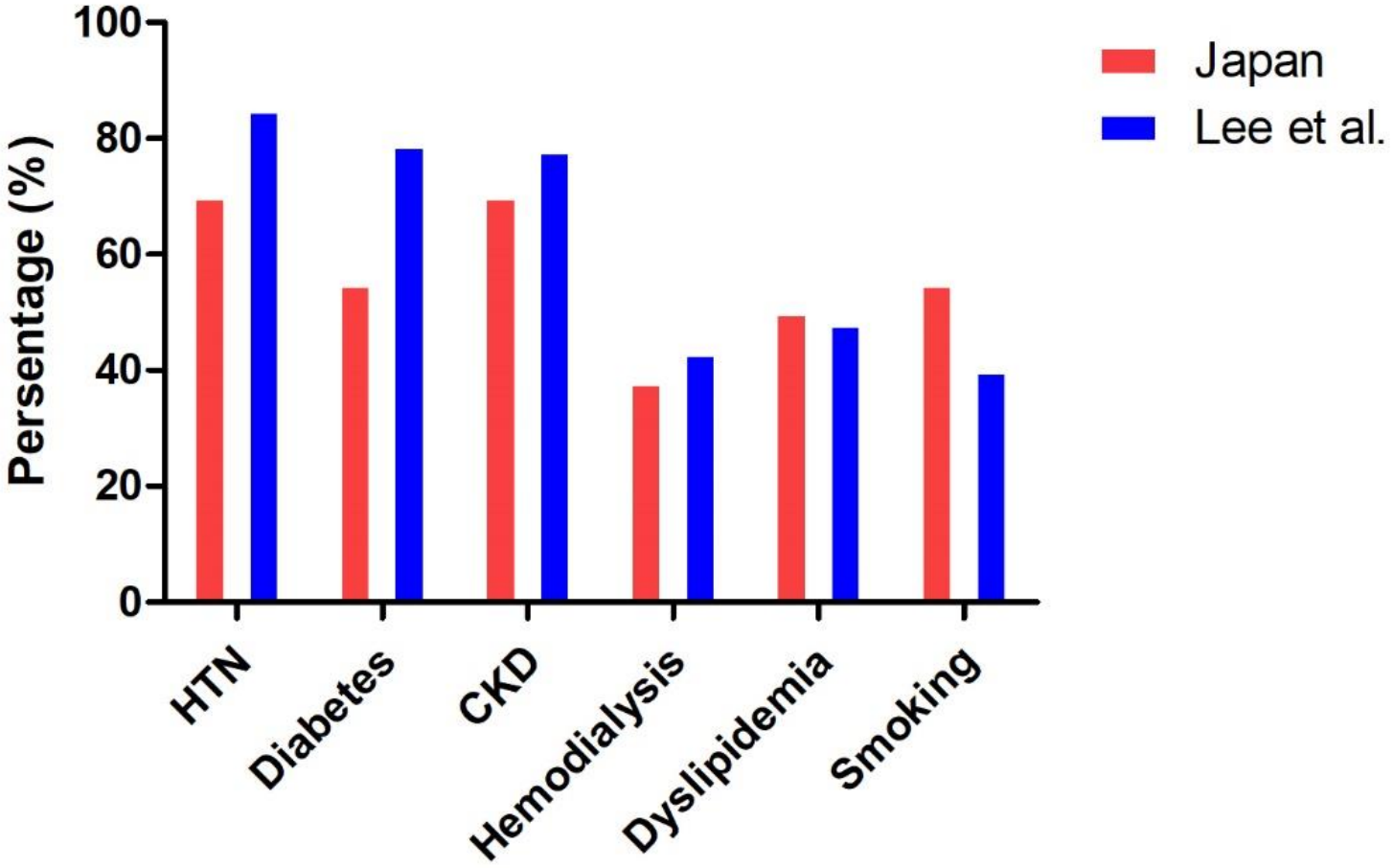


Approximate ORs for risk factors for symptomatic PAD[2]



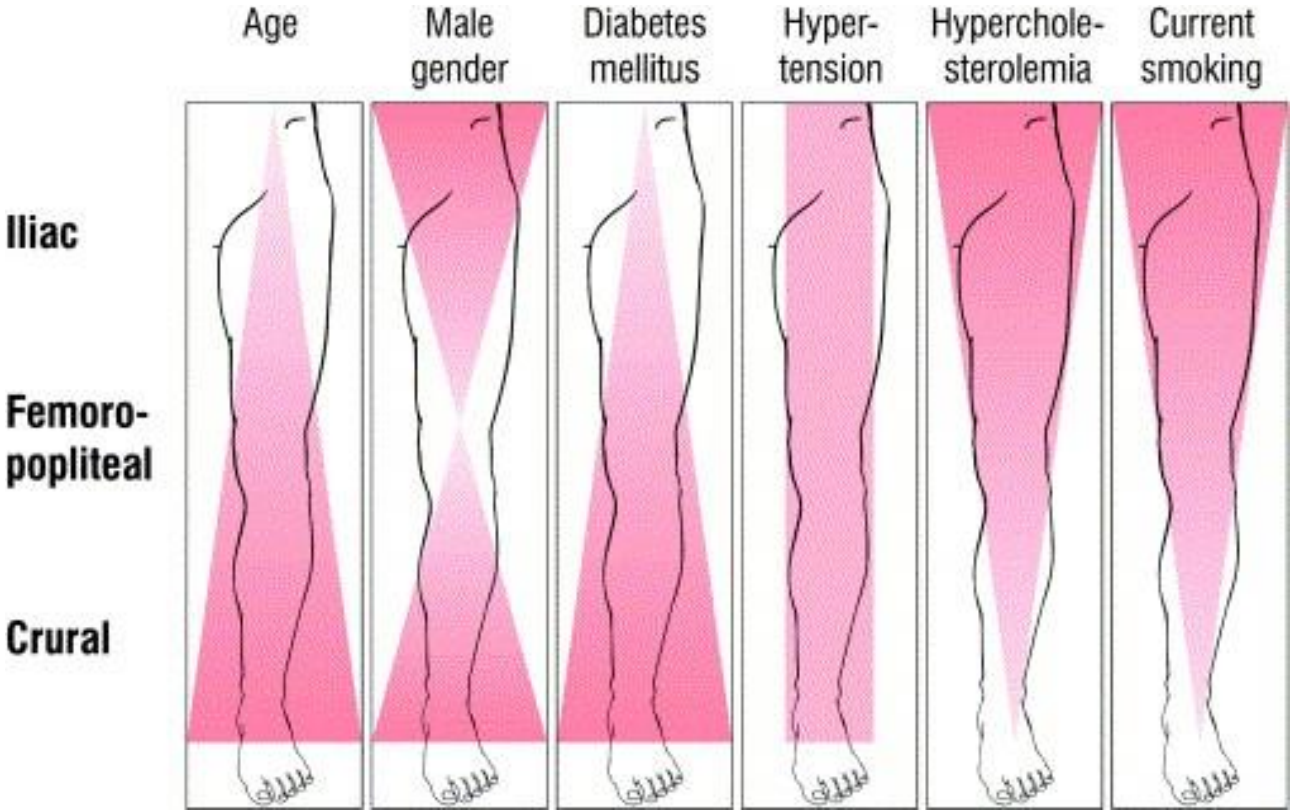
*More common in non-Hispanic black (7.8%) than white populations (4.4%), and slightly more common among males than females;
#smoking, hypertension, dyslipidaemia, hyperhomocysteinaemia

1. Hirsch AT *et al*, *Circulation* 2006;113:e463–e654; 2. Norgren L *et al*, *Eur J Vasc Endovasc Surg* 2007;33(Suppl 1):S1–S75



Eur J Vasc Endovasc Surg. 58 (2019) pp. 56-65

Association of risk factors with the level of atherosclerotic target lesions

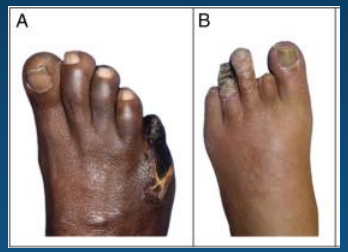


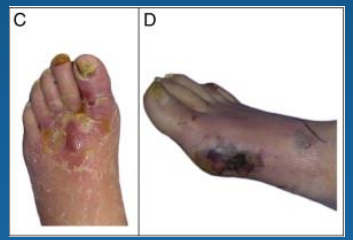
EJVES Vol 31,1 2006

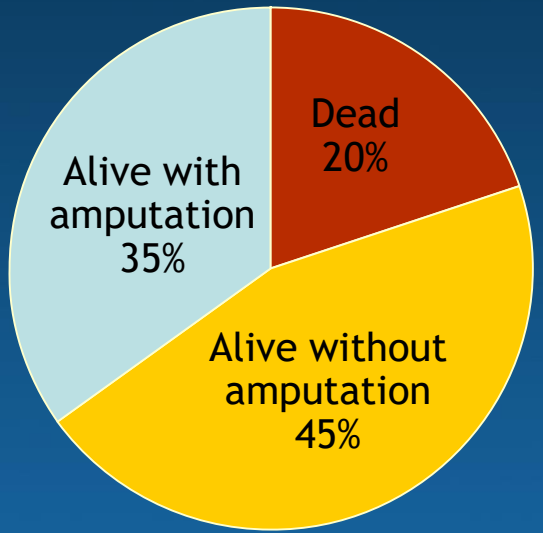
Critical Limb Ischemia (CLI)

Fate of Patients With CLI After Initial Treatment

Summary of 6-month outcomes from 19 studies



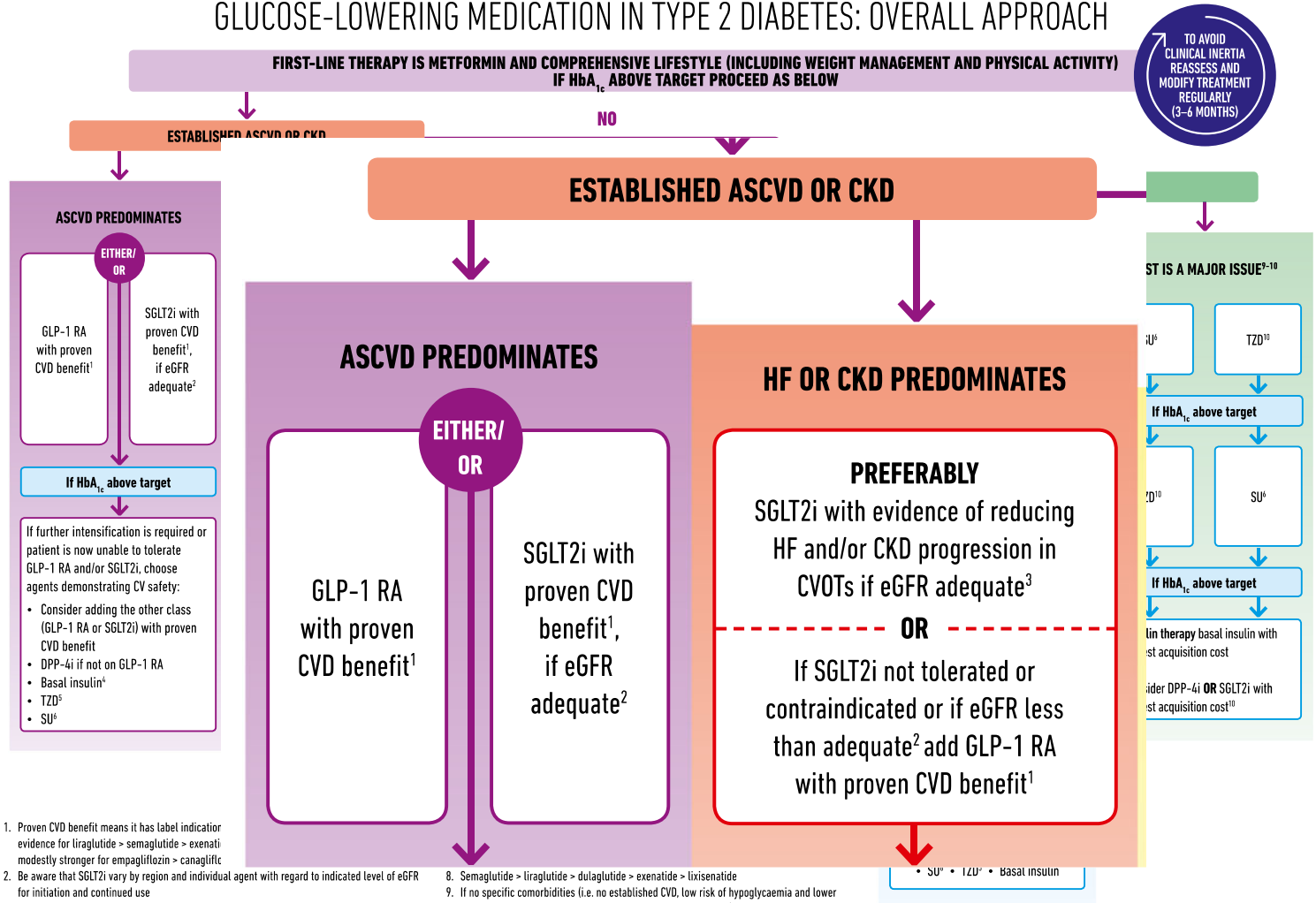




Critical limb ischemia is defined as ischemic rest pain, nonhealing wounds, or gangrene.

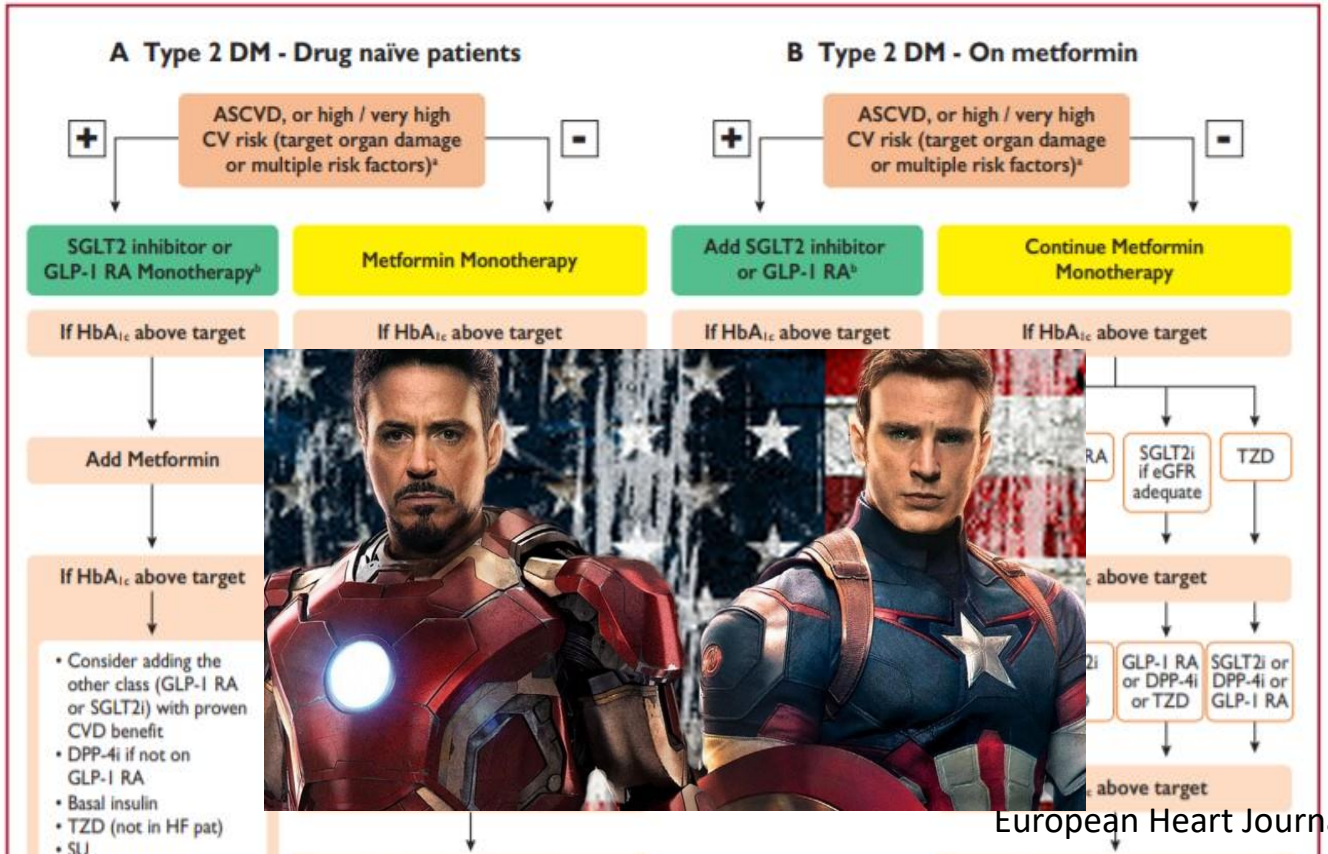
Dormandy JA, Rutherford RB. *J Vasc Surg*. 2000;31:S1-S296.

GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indicatior evidence for liraglutide > semaglutide > exenati modestly stronger for empagliflozin > canagliflc
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
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

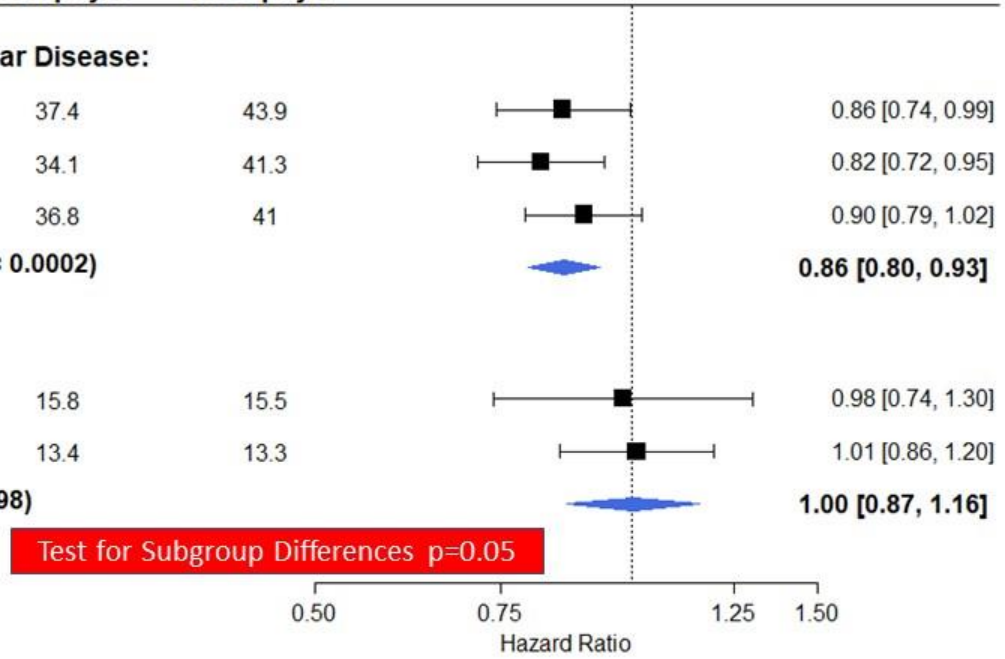
2019 ESC/EASD Guidelines on DM & CVD



European Heart Journal (2019) 00, 169

Meta-Analysis of CVOTs: MACE by Presence of ASCVD

MACE	Treatment Events per 1000 pt-yrs	Placebo Events per 1000 pt-yrs	HR [95% CI]
Atherosclerotic Cardiovascular Disease:			
EMPA-REG OUTCOME	37.4	43.9	0.86 [0.74, 0.99]
CANVAS Program	34.1	41.3	0.82 [0.72, 0.95]
DECLARE-TIMI 58	36.8	41	0.90 [0.79, 1.02]
FE Model for ASCVD (P-value = 0.0002)			**0.86 [0.80, 0.93]**
Multiple Risk Factor:			
CANVAS Program	15.8	15.5	0.98 [0.74, 1.30]
DECLARE-TIMI 58	13.4	13.3	1.01 [0.86, 1.20]
FE Model for MRF (P-value = 0.98)			**1.00 [0.87, 1.16]**



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HARVARD MEDICAL SCHOOL TEACHING HOSPITAL

Zelniker TA, Wiviott SD...Sabatine MA, Lancet 2018

ORIGINAL ARTICLE

Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes

Bruce Neal, M.B., Ch.B., Ph.D., Vlado Perkovic, M.B., B.S., Ph.D., Kenneth W. Mahaffey, M.D., Dick de Zeeuw, M.D., Ph.D., Greg Fulcher, M.D., Ngozi Erondu, M.D., Ph.D., Wayne Shaw, D.S.L., Gordon Law, Ph.D., Mehul Desai, M.D., and David R. Matthews, D.Phil., B.M., B.Ch., for the CANVAS Program Collaborative Group*

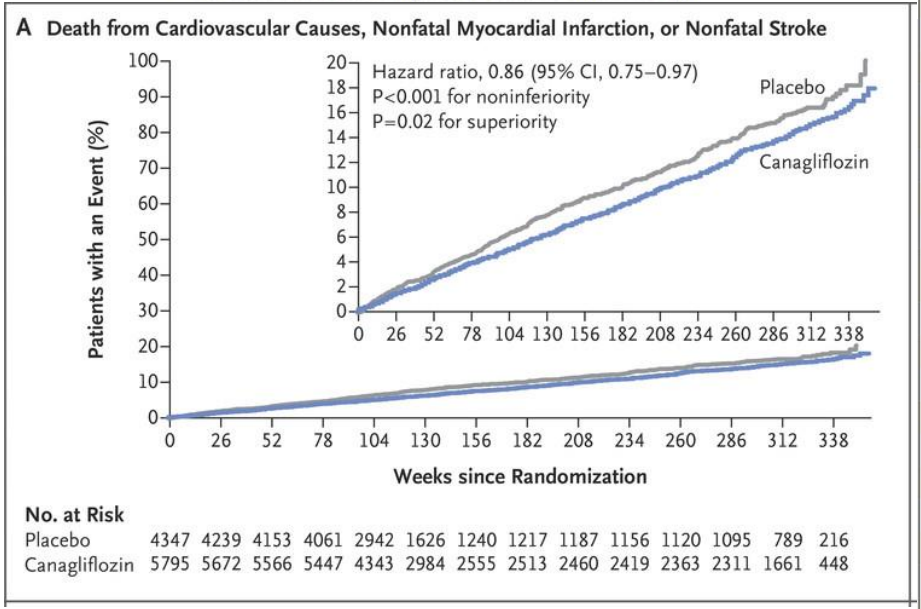


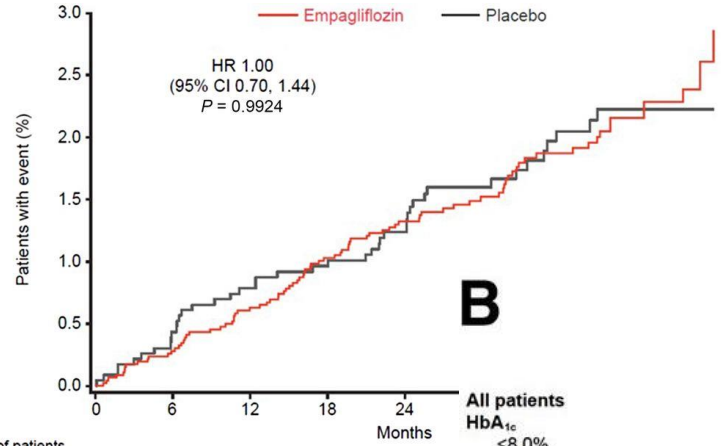
Table 2. Adverse Events.*

Event	Canagliflozin	Placebo	P Value†
	event rate per 1000 patient-yr		
All serious adverse events	104.3	120.0	0.04
Adverse events leading to discontinuation	35.5	32.8	0.07
Serious and nonserious adverse events of interest recorded in the CANVAS Program			
Acute pancreatitis (adjudicated)	0.5	0.4	0.63
Cancer			
Renal cell	0.6	0.2	0.17
Bladder	1.0	1.1	0.74
Breast	3.1	2.6	0.65
Photosensitivity	1.0	0.3	0.07
Diabetic ketoacidosis (adjudicated)	0.6	0.3	0.14
Amputation	6.3	3.4	<0.001
Fracture (adjudicated)‡			
All	15.4	11.9	0.02
Low-trauma	11.6	9.2	0.06
Venous thromboembolic events	1.7	1.7	0.63
Infection of male genitalia§	34.9	10.8	<0.001
Serious and nonserious adverse events of interest collected in CANVAS alone¶			
Osmotic diuresis	34.5	13.3	<0.001
Volume depletion	26.0	18.5	0.009
Hypoglycemia	50.0	46.4	0.20
Acute kidney injury	3.0	4.1	0.33
Hyperkalemia	6.9	4.4	0.10
Urinary tract infection	40.0	37.0	0.38
Mycotic genital infection in women	68.8	17.5	<0.001
Severe hypersensitivity or cutaneous reaction	8.5	6.1	0.17
Hepatic injury	7.4	9.1	0.35
Renal-related (including acute kidney injury)	19.7	17.4	0.32

Neal B et al. N Engl J Med 2017;377:644-657.

Empagliflozin and Assessment of Lower-Limb Amputations in the EMPA-REG OUTCOME Trial

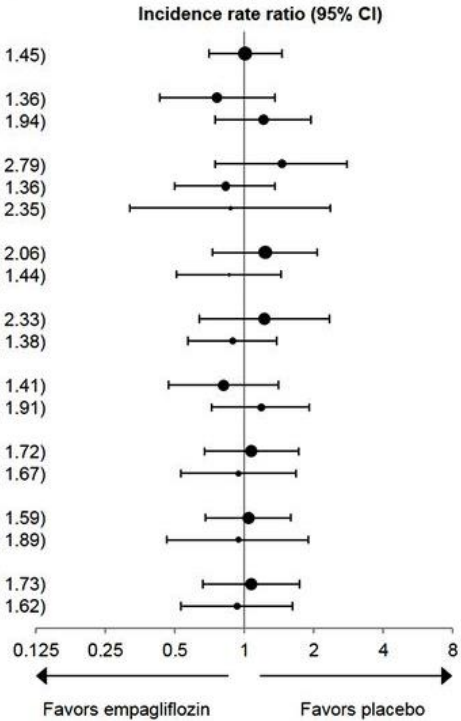
A



No. of patients					
Empagliflozin	4,687	4,616	4,526	4,428	3,987
Placebo	2,333	2,283	2,238	2,185	1,947

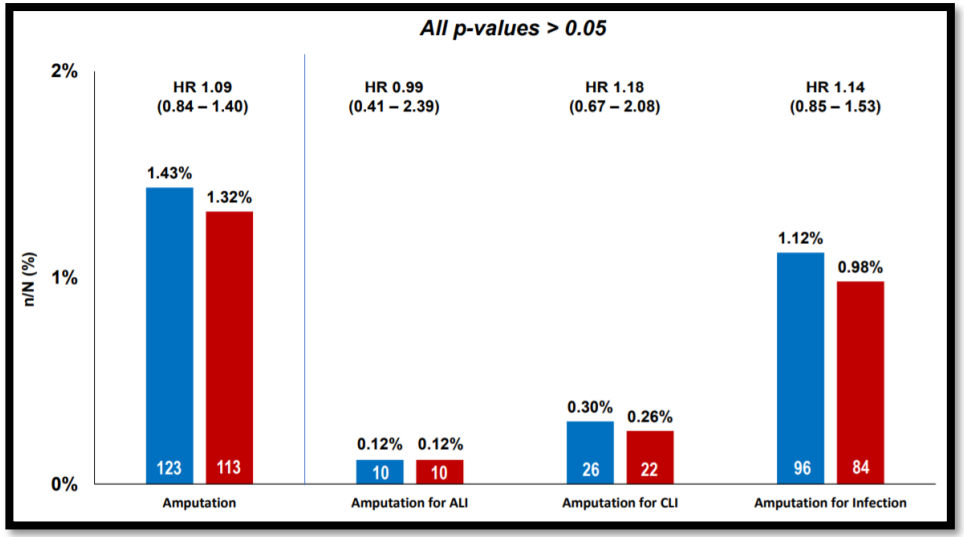
B

	Empagliflozin		Placebo		Incidence rate ratio (95% CI)
	n with event/N (%)	*Incidence rate/ 1,000 patient-yrs*	*n with event/N (%)*	*Incidence rate/ 1,000 patient-yrs*	
All patients	88/4,687 (1.9)	6.5	43/2,333 (1.8)	6.5	1.01 (0.70, 1.45)
HbA_{1c}					
<8.0%	30/2,339 (1.3)	4.5	19/1,156 (1.6)	5.8	0.76 (0.43, 1.36)
≥8.0%	58/2,346 (2.5)	8.6	24/1,177 (2.0)	7.1	1.21 (0.75, 1.94)
Smoking status					
Never smoked	35/1,925 (1.8)	6.3	12/957 (1.3)	4.4	1.45 (0.75, 2.79)
Ex-smoker	42/2,135 (2.0)	6.8	25/1,074 (2.3)	8.2	0.83 (0.50, 1.36)
Smoker	11/627 (1.8)	6.3	6/302 (2.0)	7.3	0.87 (0.32, 2.35)
History of diabetic foot					
No	50/4,424 (1.1)	3.9	20/2,188 (0.9)	3.2	1.23 (0.73, 2.06)
Yes	38/263 (14.4)	57.1	23/145 (15.9)	66.6	0.86 (0.51, 1.44)
History of peripheral artery occlusive disease					
No	32/3,669 (0.9)	3.0	13/1,841 (0.7)	2.4	1.22 (0.64, 2.33)
Yes	56/1,018 (5.5)	20.3	30/492 (6.1)	22.9	0.89 (0.57, 1.38)
History of diabetic neuropathy					
No	33/3,217 (1.0)	3.5	20/1,606 (1.2)	4.3	0.81 (0.47, 1.41)
Yes	55/1,470 (3.7)	13.6	23/727 (3.2)	11.6	1.18 (0.72, 1.91)
History of diabetic retinopathy					
No	55/3,664 (1.5)	5.2	25/1,810 (1.4)	4.8	1.07 (0.67, 1.72)
Yes	33/1,023 (3.2)	11.7	18/523 (3.4)	12.4	0.94 (0.53, 1.67)
History of diabetic nephropathy					
No	66/3,783 (1.7)	6.0	31/1,866 (1.7)	5.8	1.04 (0.68, 1.59)
Yes	22/904 (2.4)	8.7	12/467 (2.6)	9.3	0.94 (0.46, 1.89)
eGFR, mL/min/1.73 m²					
≥60	52/3,473 (1.5)	5.2	24/1,726 (1.4)	4.9	1.07 (0.66, 1.73)
<60	36/1,212 (3.0)	10.4	19/607 (3.1)	11.2	0.93 (0.53, 1.62)

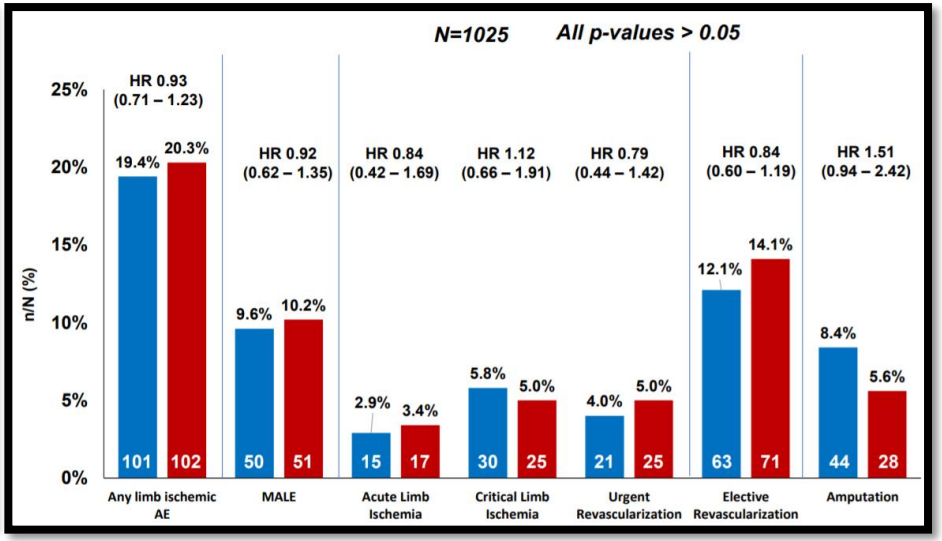


Diabetes Care 2017 Nov; dc171551.

Dapagliflozin and Outcomes in Patients with Peripheral Artery Disease: Insights from DECLARE-TIMI 58



All patients



PAD patients

DAPA Placebo

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, Kyungah Im, Erica L Goodrich, Marc P Bonaca, Ofri Mosenzon, Eri T Kato, Avivit Cahn, Remo H M Furtado, Deepak L Bhatt, Lawrence A Leiter, Darren K McGuire, John P H Wilding, Marc S Sabatine

Summary

Background The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.

Methods We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes. We searched PubMed and Embase for trials published up to Sept 24, 2018. Data search and extraction were completed with a standardised data form and any discrepancies were resolved by consensus. Efficacy outcomes included major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of renal function.

Findings We included data from three identified trials and 34 322 patients (60·2% with established atherosclerotic cardiovascular disease), with 3342 major adverse cardiovascular events, 2028 cardiovascular deaths or hospitalisation sfor heart failure events, and 766 renal composite outcomes. SGLT2i reduced major adverse cardiovascular events by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014), with benefit only seen in patients with atherosclerotic cardiovascular disease (0·86 [0·80–0·93]) and not in those without (1·00 [0·87–1·16], p for interaction=0·0501). SGLT2i reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (0·77 [0·71–0·84], p<0·0001), with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. SGLT2i reduced the risk of progression of renal disease by 45% (0·55 [0·48–0·64], p<0·0001), with a similar benefit in those with and without atherosclerotic cardiovascular disease. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in hospitalisations for heart failure (p for interaction=0·0073) and lesser reductions in progression of renal disease (p for interaction=0·0258) in patients with more severe kidney disease at baseline.

Interpretation SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that seem confined to patients with established atherosclerotic cardiovascular disease. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.

Lancet 2019; 393: 31–39

Published Online
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See Comment page 3

This online publication has been corrected. The corrected version first appeared at thelancet.com on January 3, 2019

TIMI Study Group, Cardiovascular Division, Brigham and Women's Hospital, Boston, MA, USA (T A Zelinker MD, S D Wiviott MD, K Im PhD, E L Goodrich MS, M P Bonaca MD, R H M Furtado MD, Prof D L Bhatt MD, Prof M S Sabatine MD); **The Diabetes Unit, Department of Endocrinology and Metabolism, Hadassah Medical Center, Hebrew University of Jerusalem, The Faculty of Medicine, Jerusalem, Israel** (Prof I Raz MD, O Mosenzon MD, A Cahn MD); **Department of Cardiovascular Medicine, Kyoto University Graduate School of Medicine, Kyoto, Japan** (E T Kato PhD); **Li Ka Shing**

Figure S18: Risk of amputations

Q statistic = 9·56, p=0·0084, I^2= 79·1%

Research

JAMA Internal Medicine | Original Investigation

Association Between Sodium-Glucose Cotransporter 2 Inhibitors and Lower Extremity Amputation Among Patients With Type 2 Diabetes

Hsien-Yen Chang, PhD; Sonal Singh, MD, MPH; Omar Mansour, BA; Sheriza Baksh, MPH; G. Caleb Alexander, MD, MS

CONCLUSIONS AND RELEVANCE Use of SGLT-2 inhibitors may be associated with increased risk of amputation compared with some oral treatments for type 2 diabetes. Further observational studies are needed with extended follow-up and larger sample sizes.

39869 new users/28036 canagliflozin/8647 dapagliflozin/3186 empagliflozin

JAMA Intern Med. 2018;178(9):1190-1198

RESEARCH

OPEN ACCESS

Check for updates

Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study

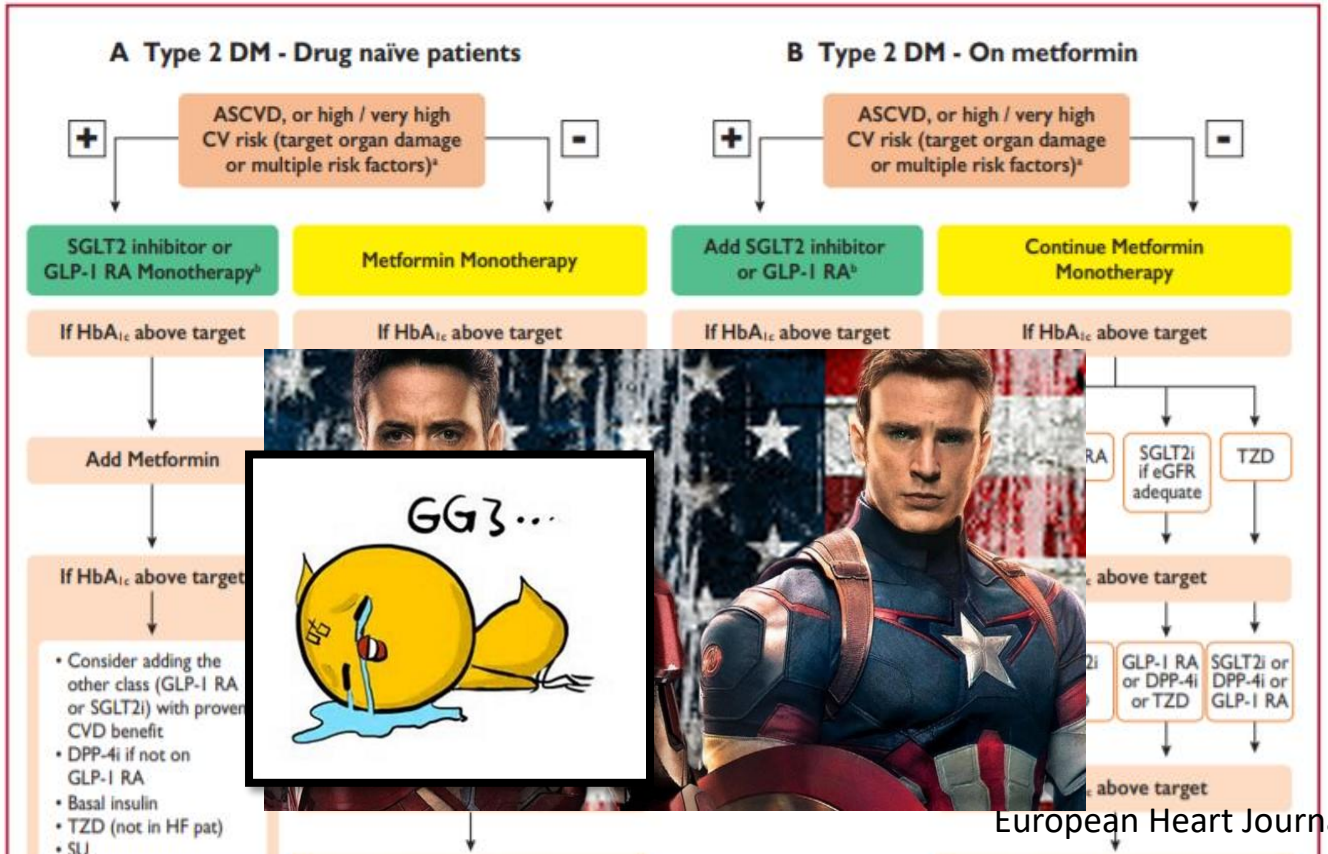
Peter Ueda,[1] Henrik Svanström,[1,2] Mads Melbye,[2,3,4] Björn Eliasson,[5] Ann-Marie Svensson,[6] Stefan Franzén,[6] Soffia Gudbjörnsdottir,[5,6] Kristian Hveem,[7,8] Christian Jonasson,[7,8] Björn Pasternak[1,2]

Conclusions In this analysis of nationwide registers from two countries, use of SGLT2 inhibitors, as compared with GLP1 receptor agonists, was associated with an increased risk of lower limb amputation and diabetic ketoacidosis, but not with other serious adverse events of current concern.

17213 new users/ canagliflozin, 1%/ dapagliflozin, 61%/ empagliflozin, 38%

BMJ 2018;363:k4365

2019 ESC/EASD Guidelines on DM & CVD



European Heart Journal (2019) 00, 169

The impact of liraglutide on diabetes-related foot ulceration and associated complications in patients with type 2 diabetes at high risk for cardiovascular events: results from the LEADER trial

Ketan Dhatariya, Stephen C Bain, John B Buse, Richard Simpson, Lise Tarnow, Margit Staum Kaltoft, Michael Stellfeld, Karen Tornøe, Richard E Pratley, the LEADER Publication Committee on behalf of the LEADER Trial Investigators

Dhatariya *et al. Diabetes Care* 2018;41:2229–35

Background

- DFUs are a common complication in people with diabetes, estimated to affect between 9.1 million and 26.1 million people worldwide[1]
- Long-term outcomes for patients with DFUs are poor,[1] particularly the 5-year mortality rate of 44%,[2] which may be as high as 70% when patients have a related amputation[3]
- Currently, the standard of care for DFUs consists of wound care, pressure offloading, and, when necessary, antibiotics, vascular reconstruction or surgical debridement; however, there is a high risk that DFUs will recur[1]
- While good glycaemic control reduces the risk of complications in people with diabetes,[4] little is known about the effect of glucose-lowering drugs on DFU and its outcomes

We conducted a *post hoc* analysis to assess the impact of liraglutide on the incidence of DFUs and their sequelae in people in the LEADER trial

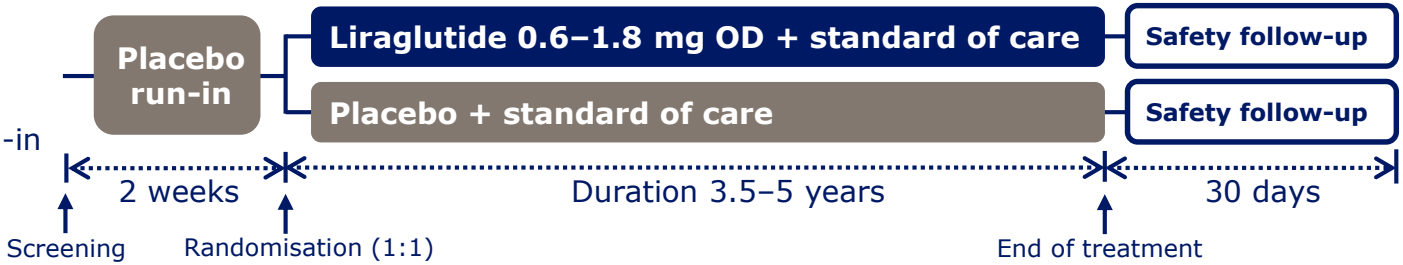
DFU, diabetes-related foot ulcer

1. Armstrong *et al. N Engl J Med* 2017;376:2367–75; 2. Moulik *et al. Diabetes Care* 2003;26:491–4; 3. Lavery *et al. Diabetes Care* 2010;33:2365–9;
4. UKPDS. *Lancet* 1998;352:837–53
Dhatariya *et al. Diabetes Care* 2018;41:2229–35

LEADER: study design

9340 patients

- Double blinded
- 2-week placebo run-in



Key inclusion criteria

- T2D, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/ premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
  or
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1D
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin

CV, cardiovascular; DPP-4i, dipeptide peptidase-4 inhibitor; GLP-1RA, glucagon-like peptide-1 receptor agonist; HbA_{1c}, glycated haemoglobin; OAD, oral antidiabetic drug; OD, once daily; T1D, type 1 diabetes; T2D, type 2 diabetes

Marso *et al*. *N Engl J Med* 2016;375:311–22

Dhatariya *et al. Diabetes Care* 2018;41:2229–35

Collection of DFU data

The definition of a DFU in this *post hoc* analysis was an open foot wound

Data collection:

- Reporting of safety data was required only for events meeting the definition of an SAE or pre-specified MESI
- In the trial, DFU was pre-specified as a MESI
- Information related to DFU events was collected on a designated form
- Identification of DFU events was based on a search using pre-specified MedDRA terms
  - A blinded review of the case narratives was used to establish the nature of the DFU and any associated complications

Patients were classified as having a DFU event if they:

- Reported a new DFU or
- Had a worsening of an existing DFU

Patients not included in the analysis were those who:

- Did not experience a DFU or
- Had a pre-existing, non-worsening DFU

Complications analysed were:

- Amputation
- Infection
- Involvement of underlying structures
- Peripheral revascularisation

DFU, diabetes-related foot ulcer; MedDRA, Medical Dictionary for Regulatory Activities; MESI, medical event of special interest; SAE, serious adverse event

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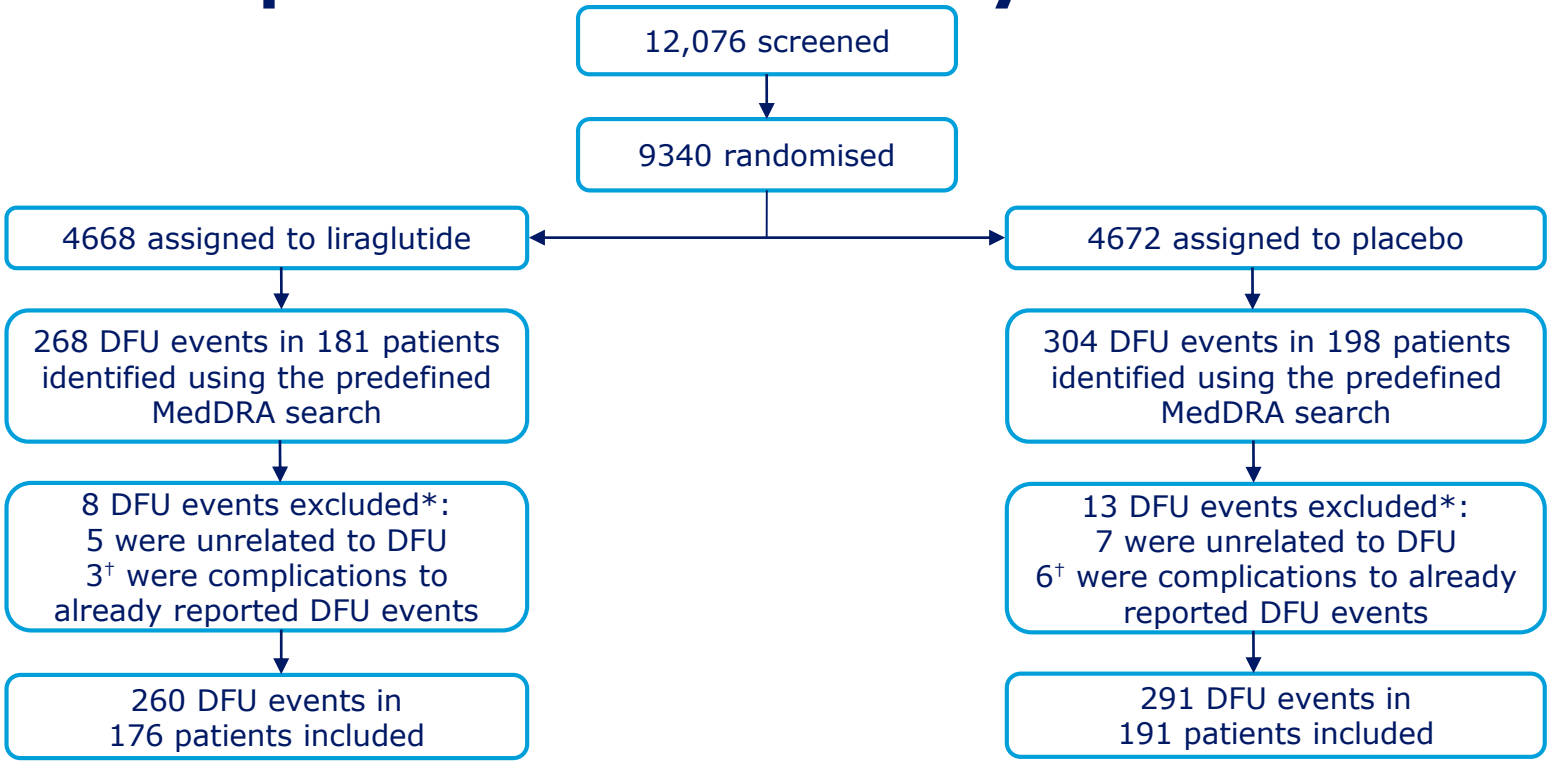
Patient disposition for the analysis of DFU events



Adapted from Figure S1. *Post-blinded review of case narratives. †For these 9 events (3 liraglutide and 6 placebo), information on complications to the DFU events was captured from the narrative review of the already reported events. DFU, diabetes-related foot ulcer; MedDRA, Medical Dictionary for Regulatory Activities

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Baseline characteristics (1/2)

	Patients with DFU events		Patients without DFU events	
	Liraglutide (N=176)	Placebo (N=191)	Liraglutide (N=4492)	Placebo (N=4481)
Age, years	64.7 ± 7.0	64.6 ± 7.8	64.2 ± 7.3	64.4 ± 7.2
Male, n (%)	130 (73.9)	140 (73.3)	2881 (64.1)	2852 (63.6)
Duration of diabetes, years	15.6 ± 7.2	16.4 ± 8.4	12.7 ± 8.0	12.7 ± 8.0
HbA_{1c}, % (mmol/mol)	9.2 ± 1.9 (77 ± 21)	9.1 ± 1.7 (76 ± 18)	8.7 ± 1.5 (72 ± 17)	8.6 ± 1.5 (71 ± 16)
History of DFU, n (%)	71 (40.3)	69 (36.1)	137 (3.0)	127 (2.8)
DFU at baseline	29 (16.5)	26 (13.6)	40 (0.9)	33 (0.7)
Peripheral neuropathy, n (%)	120 (68.2)	127 (66.5)	1454 (32.4)	1452 (32.4)
Nephropathy, n (%)	109 (61.9)	108 (56.5)	1773 (39.5)	1809 (40.4)
Peripheral vascular artery disease, n (%)	48 (27.3)	60 (31.4)	519 (11.6)	540 (12.1)

Adapted from Table S3. Full table in supplementary data (slides 27–9). Values are mean ± standard deviation unless otherwise stated. %, proportion of patients reporting the characteristic of the total treatment group; DFU, diabetes-related foot ulcer; HbA_{1c}, glycated haemoglobin; N, number of patients in the treatment group

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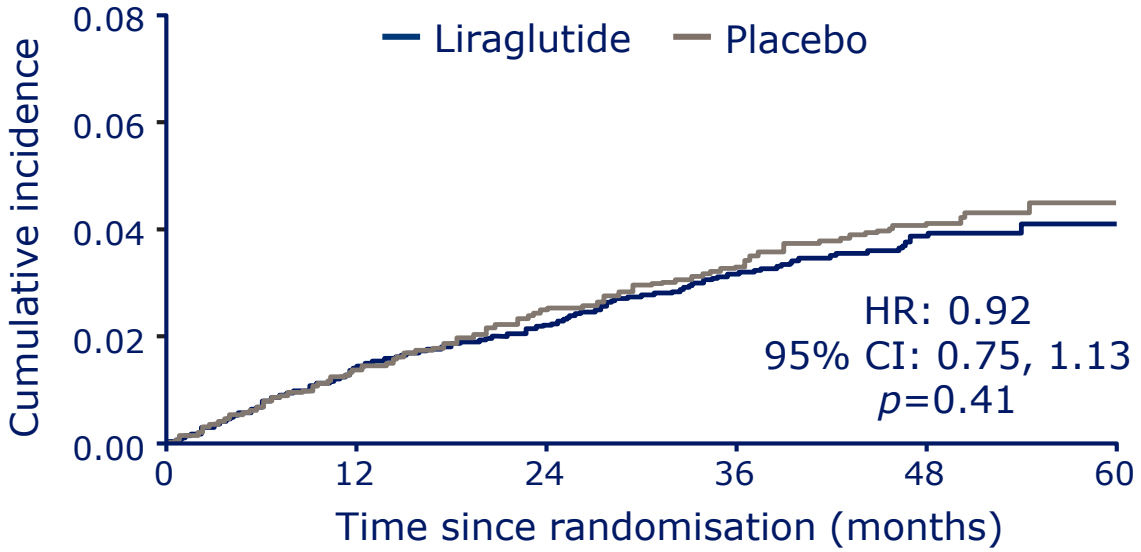
Cumulative incidence plot of time to first DFU event among all patients



Adapted from Figure 1. Aalen-Johansen plot, with death as a competing risk factor. This figure includes data from the first DFU events in 176 liraglutide-treated and 191 placebo-treated patients. CI, confidence interval; DFU, diabetes-related foot ulcer; HR, hazard ratio

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Complications associated with DFU events

	Liraglutide (N=4668)					Placebo (N=4672)					HR (95% CI)	*p*-value
	n	%	% with DFU	E	R	n	%	% with DFU	E	R		
With DFU event(s)	176	3.8	100.0	260	1.46	191	4.1	100.0	291	1.64	0.92 (0.75, 1.13)	0.41
With DFU event(s) + complication of:												
- **Amputation**	44	0.9	25.0	60	0.34	67	1.4	35.1	78	0.44	0.65 (0.45, 0.95)	0.03
Minor*	34	0.7	19.3	45	0.25	46	1.0	24.1	50	0.28	0.74 (0.47, 1.15)	0.17
Major*	11	0.2	6.3	13	0.07	22	0.5	11.5	24	0.14	0.50 (0.24, 1.02)	0.06
Unknown*	1	0.0	0.6	2	0.01	4	0.1	2.1	4	0.02	-	-
- **Infection***	107	2.3	60.8	146	0.82	131	2.8	68.6	162	0.91	0.81 (0.63, 1.05)	0.11
- **Involvement of underlying structures***	64	1.4	36.4	86	0.48	80	1.7	41.9	98	0.55	0.80 (0.57, 1.11)	0.17
- **Peripheral revascularisation**	20	0.4	11.4	24	0.13	23	0.5	12.0	26	0.15	0.87 (0.48, 1.58)	0.64

Adapted from Table 2. *See slide notes for further details. CI, confidence interval; DFU, diabetes-related foot ulcer; E, number of events; HR, hazard ratio; N, number of patients in the treatment group; n, number of patients with an event or complication; R, event rate per 100 patient-years of observation

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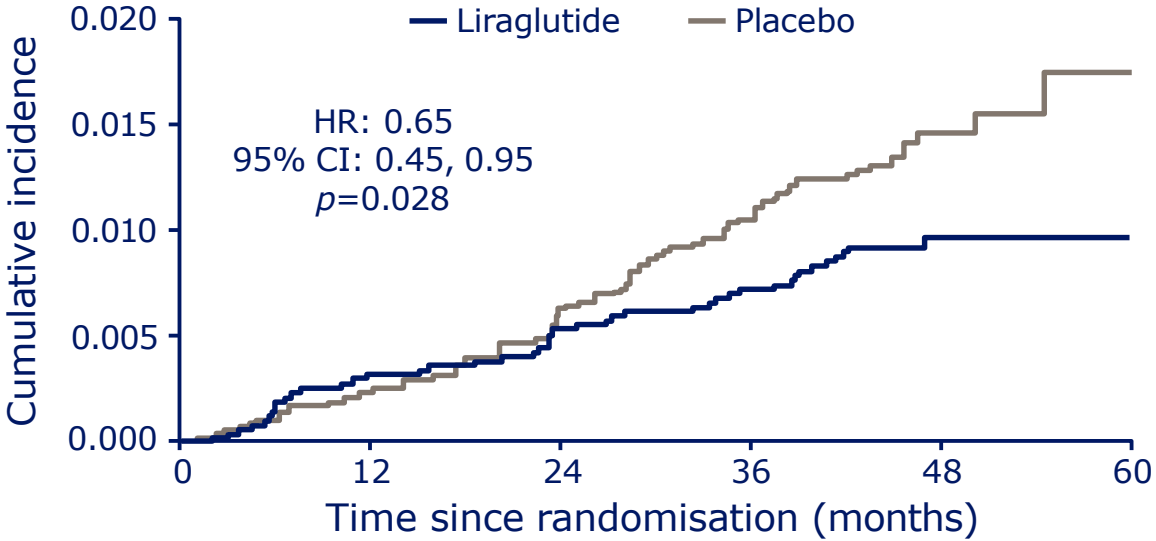
Cumulative incidence plot of time to first DFU-related amputation



Adapted from Figure 2A. This figure includes data from 44 first DFU events in the liraglutide group and 67 first DFU events in the placebo group
CI, confidence interval; DFU, diabetes-related foot ulcer; HR, hazard ratio

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Take home message

- **Lower extremity arterial disease** is prevalent in DM patient
  - CLI, amputation, mortality
- **Controversial results** of SGLT-2 in **clinical trials** & **RWD**
  - Class effect?
  - The reason is unknown
- **Strong evidence** in clinical trial for Liraglutide
  - Waiting for real world data

Thanks for your attention!!