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Diabetes Alliance Integration Program
Diabetes Master class

Micro and Macrovascular complications Diabetes and Pregnancy

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HNE Health

phn
HUNTER NEW ENGLAND AND CENTRAL COAST
An Australian Government Initiative

NSW GOVERNMENT
Health
Hunter New England
Local Health District

Learning Objectives

- Micro and Macrovascular complications and implications for newer agents
- Diabetes and foot disease
- Diabetes and Pregnancy

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Diabetes complications

- Acute
  - Diabetic Ketoacidosis (DKA) [beware euDKA with SGLT2i]
  - Hyperosmolar hyperglycaemia state (HHS)
  - Hypoglycaemia from treatment
  - Immune paresis
- Chronic
  - Microvascular: nephropathy, neuropathy, retinopathy
  - Macrovascular: IHD, PVD and CVD
  - Neuropathy: peripheral, autonomic

Mechanism of development of chronic complications

- glycosylation of proteins
  - Transient
  - Permanent
    - Protein dysfunction
- Inflammatory activation
- Tissue hypoxia
- Excess energy storage (hyperinsulinemia)

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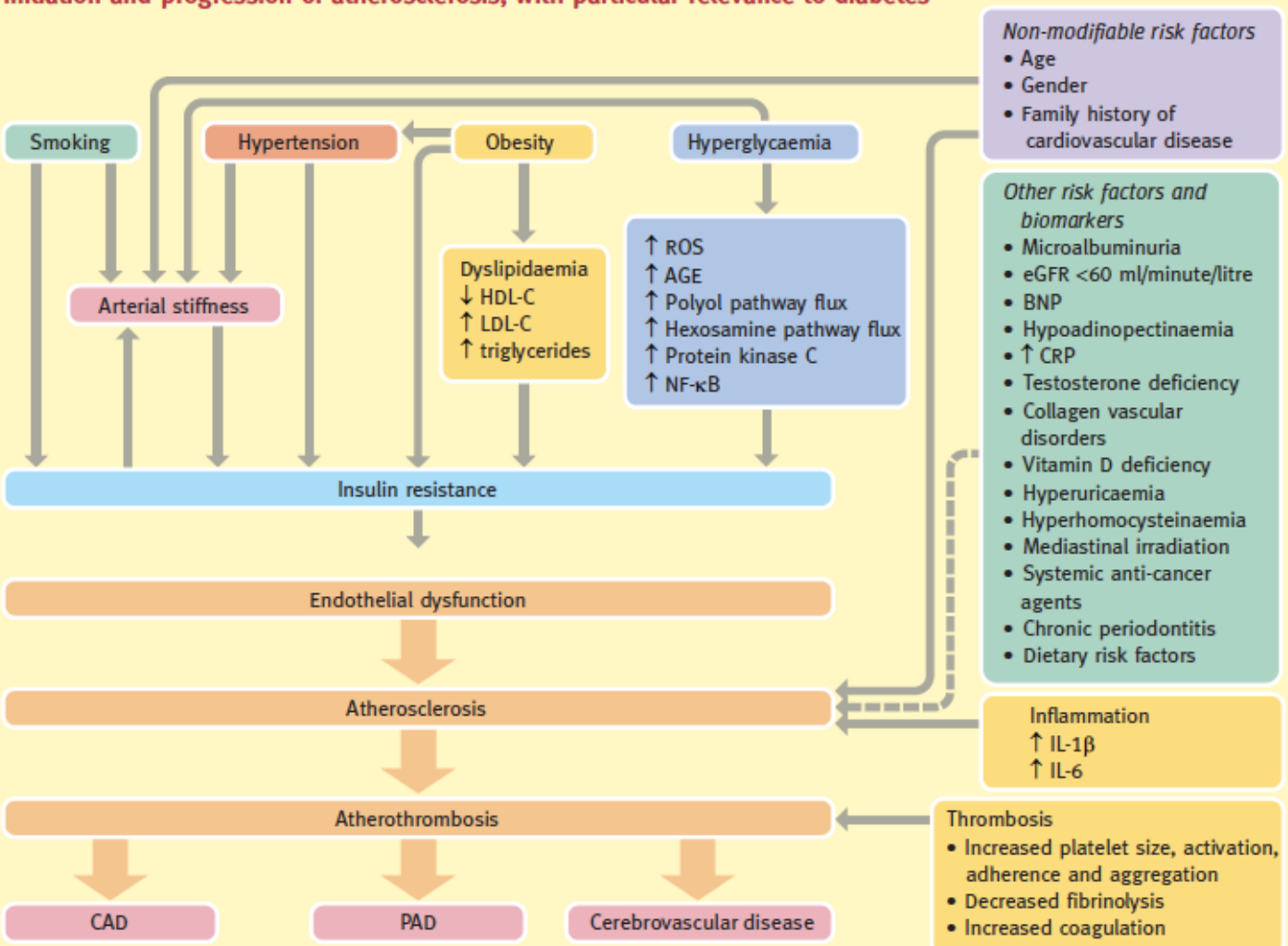
Schematic representation summarizing the current understanding of the interaction between risk factors and the initiation and progression of atherosclerosis, with particular relevance to diabetes



Causality and directionality of relationships are not firmly established for all pathways and intermediate mechanisms shown.
AGE, advanced glycation end-products; BNP, B-type natriuretic peptide; CAD, coronary artery disease; CRP, C-reactive protein; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; IL-1β, interleukin-1β; IL-6, interleukin-6; LDL-C, low-density lipoprotein cholesterol; NF-B, nuclear factor-κB; PAD, peripheral artery disease; ROS, reactive oxygen species.

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S Vella and R Petrie (2014). Medicine 43:1

Pre-existing Diabetes and Pregnancy

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gestation	Week 1	Week 2	Week 3	Week 4	Week 5	week 6
	Zygote spends 3 days in fallopian tube another 3 days in	Implantation in the uterus and establishment of contact	Neural tube formation and closure	Single chamber heart	Cardiac septation	Great vessels Primordial kidney

By the time woman comes with positive pregnancy test – it is too late to avoid major malformation

gestation	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
			Caudal regression	Anencephaly myelocele	hydrocephalus	Spina bifida
				dextrocardia	Conus arteriosus defects	VSD Renal agenesis hypoplasia

OVER SUPPLY OF GLUCOSE AND ABNORMAL METABOLISM

hyperglycaemia

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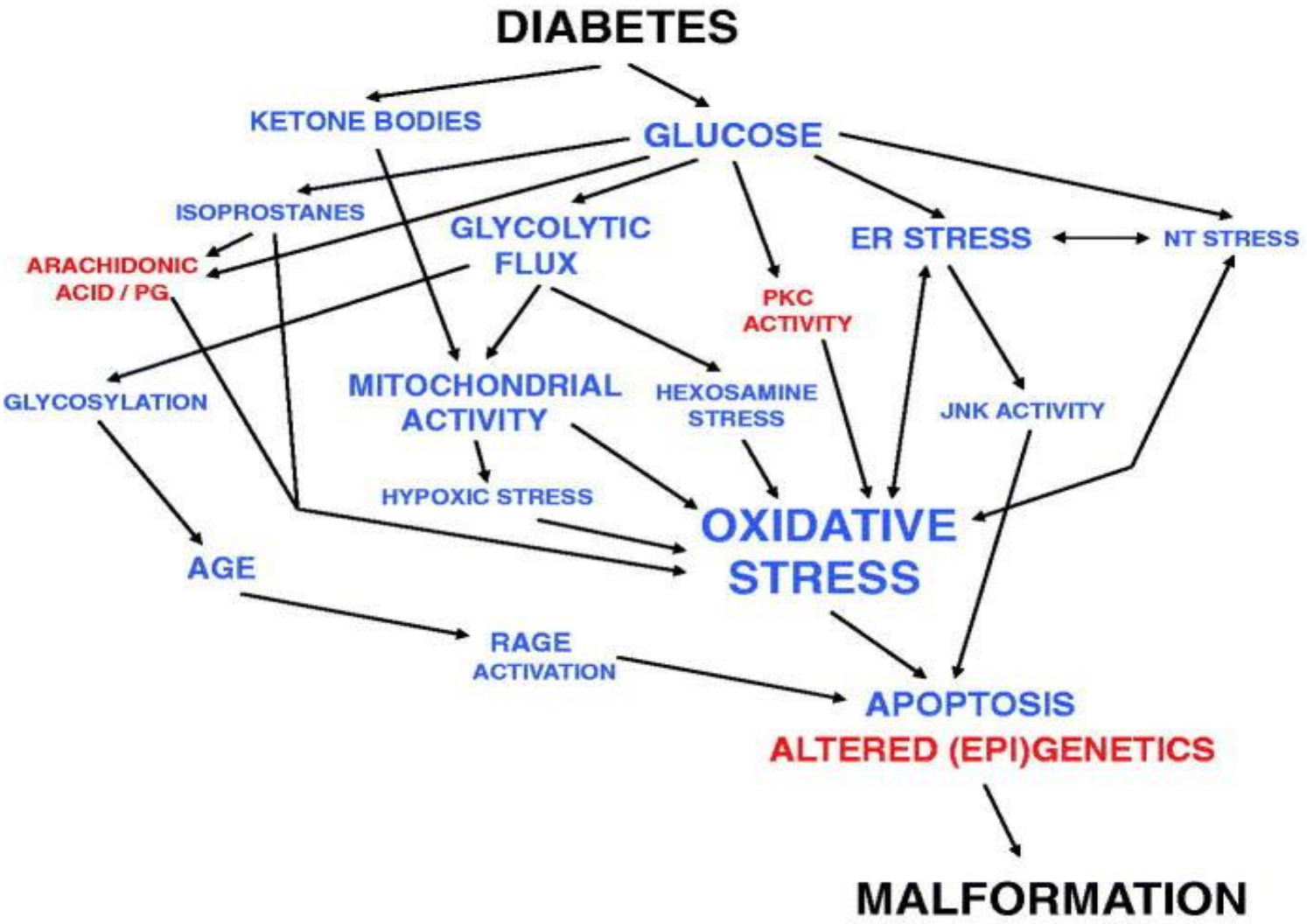
BEFORE BIRTH: High glucose is teratogenic



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Diabetic embryopathy (before 7/40)

Vertebral anomalies

Anorectal malformation

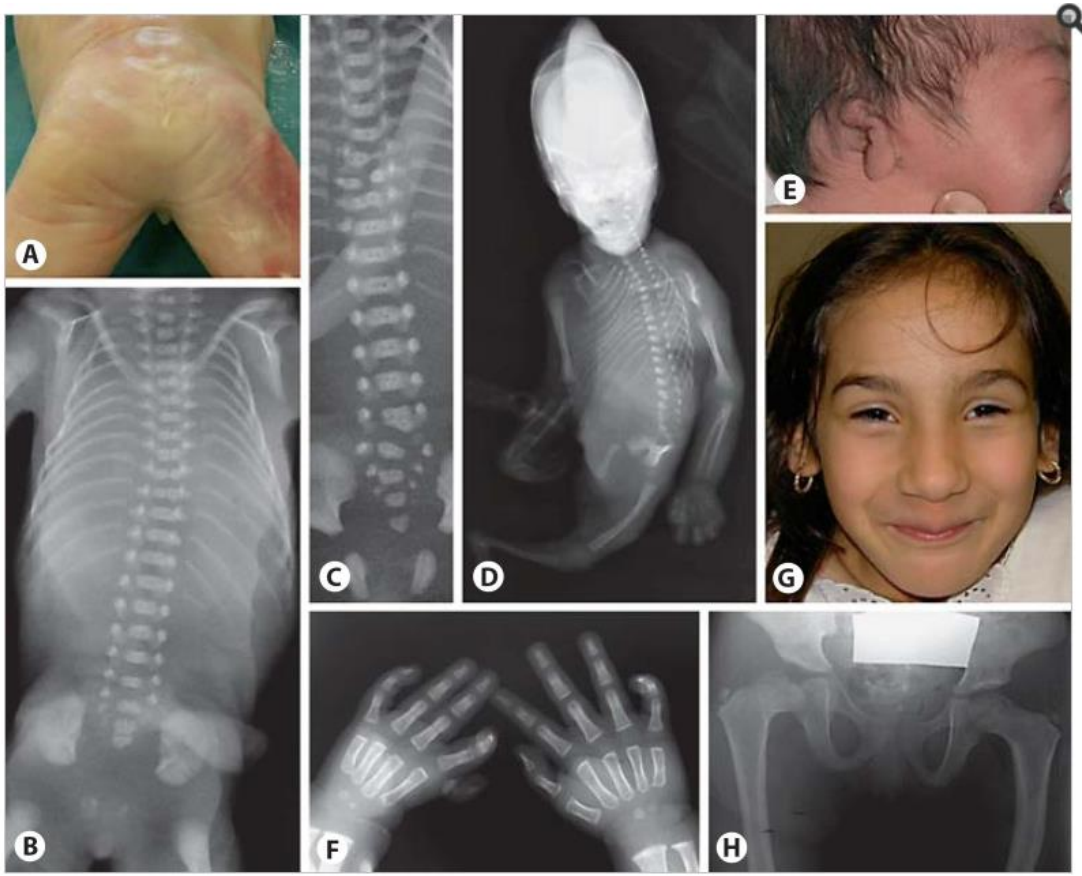
Cardiovascular anomalies

Tracheo-oesophageal fistula

Esophageal atresia

Renal anomalies

Limb defects



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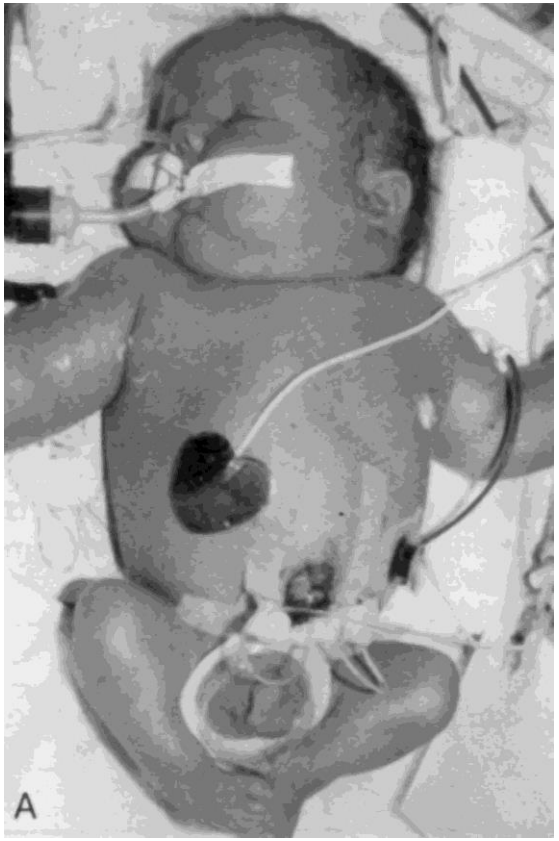
Risk of Birth Defects



Birth defect	Relative frequency
Nonblastogenic malformations	
Bifid tongue	undetermined[a]
Cleft lip ± cleft palate	2.92[b]
Facial dysmorphism	undetermined[c]
Hydrocephaly	8.80[b]
Hypertrophic cardiomyopathy (congenital)	15.10–61.60
Septo-optic dysplasia	undetermined[a]
Blastogenic malformations	
Anorectal atresia/stenosis	2.81–4.70[b]
Caudal dysgenesis	53.00–200.00
Congenital heart defects	up to 18.24[d]
Costovertebral segmentation defects	26.30–39.30[e]
Holoprosencephaly	6.00–10.20
Longitudinal limb defects	up to 6.47[f]
Microtia/anotia/hemifacial microsomia	2.40–3.75
Neural tube defects	2.90[b, g]
Renal adysplasia	3.10–10.43[h]
Sirenomelia	undetermined[b, i]
Thymus aplasia	29.62
Urorectal septum malformation	undetermined[a]

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Mol Syndromol. 2013 Feb; 4(1-2):74-86

Role of maternal nutrition: a double edged sword

GLUCOSE
AMINOACIDS
KETONES

Triglycerides

Metformin

Insulin

Glucagon

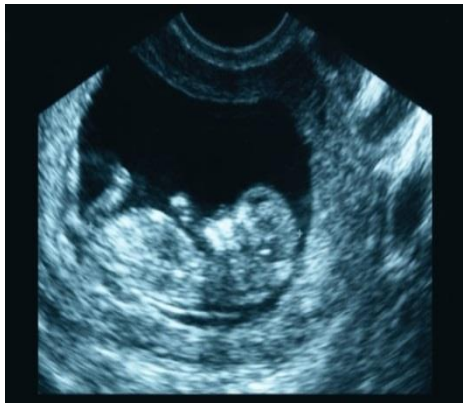
PLACENTA

Barrier, facilitator and an active producer of hormones and factors

GLUCOSE
AMINOACIDS
KETONES

Free fatty acids

Metformin



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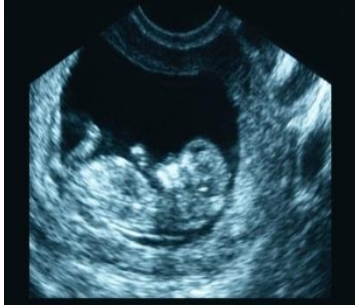
Freinkel N. The Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*

Maternal hyperglycemia and over nutrition



GLUCOSE
AMINOACIDS
KETONES

Triglycerides

Insulin
Glucagon

PLACENTA

GLUCOSE
AMINOACIDS
KETONES

Free fatty acids

Foetal hyperinsulinemia

Excessive foetal growth

macrosomia

Changes in epigenetics and origin of DM/Obesity/metabolic syndrome in the adulthood?

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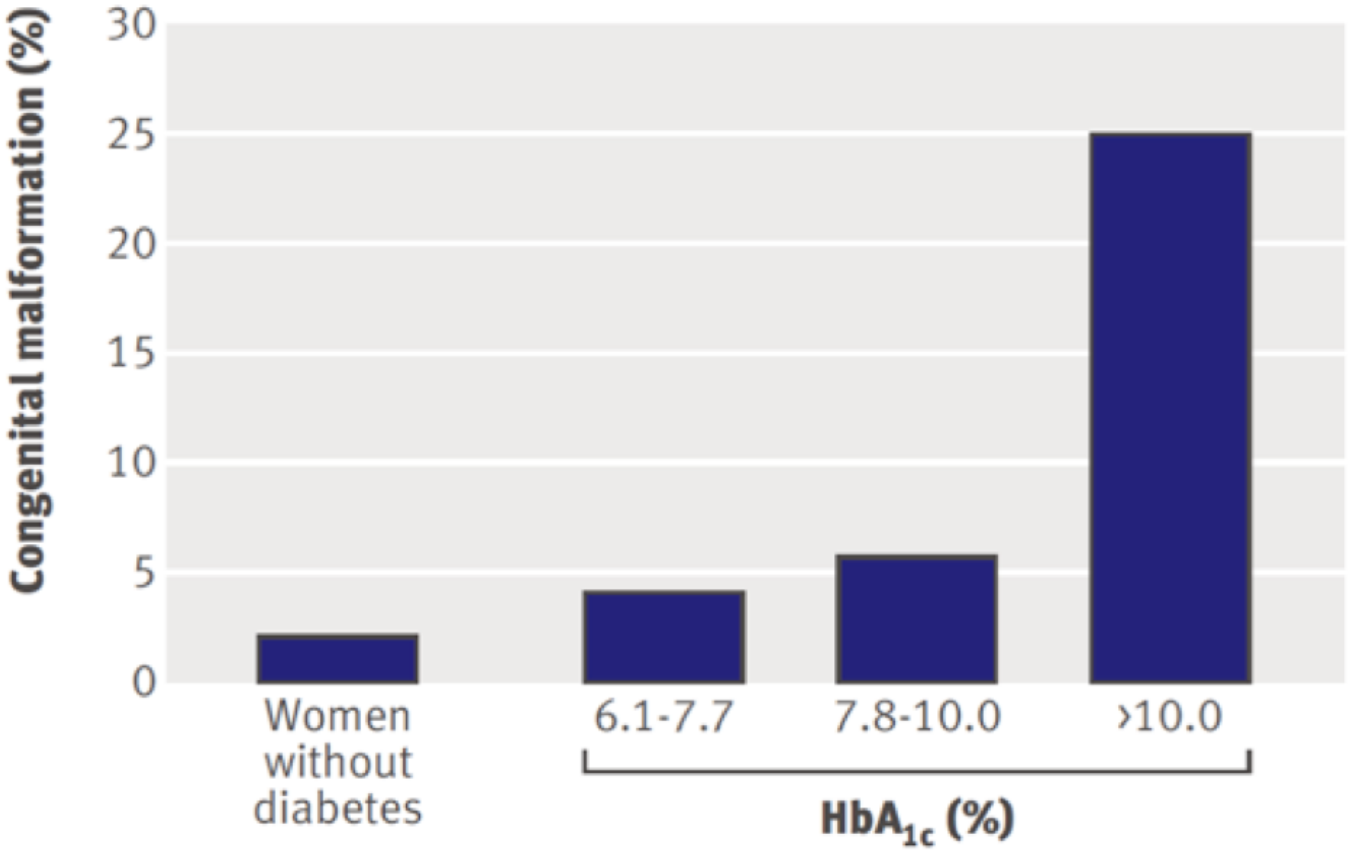
Freinkel N. The Banting Lecture 1980. Of pregnancy and progeny. *Diabetes*

Malformation rates halved with every 1% reduction in HbA1c



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BMJ 2007;334:742-45

Inkster, M. E. *et al*. *BMC Pregnancy Childbirth,* 6 30 (2006).

Pre-conception counselling

- significantly lower prevalence of major congenital anomalies in women who attended for pre-pregnancy counselling (2.1% vs 6.5%; RR 0.36, 95% CI 0.22-0.59)
- CEMACH (UK):
  - Only 35% of women with pregestational diabetes received preconception counselling
  - 37% had a measurement of HbA1c level within the 6 month period before pregnancy
  - less than 39% were taking folic acid before conception.

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Ray JG, O'Brien TE, Chan WS. Q J Med 2001; 94: 435-444.
Confidential Enquiry into Maternal and Child Health. (London, 2005).

Pre-conception counselling

- Contraception until care optimised
- General
  - Smoking cessation, alcohol minimisation, weight control
  - Folate 5mg daily for at least 1 month prior
- Specific
  - Check B12 if on metformin
  - Tight BGL control
    - Fasting 4-5.5, 1 hr <8, 2h <7mmol/l
    - HbA1c <6%-7%
  - Complication screening – eye, proteinuria, TSH
  - Review medications
    - Stop ACEI, ARB, statin, beta-blocker
      - Control BP (prazosin, labetolol, nifedipine, methyldopa)
    - Stop OHA (except metformin)
    - Stop GLP-1 analogues
    - Commence insulin therapy when BGL levels are outside the target

First trimester (T1D/T2D) adverse effects

- Glycaemic disturbance with nausea and pregnancy
  - recurrent hypoglycaemia, DKA

- Increased risk of miscarriage (twice more likely)
  - Hyperglycaemia, maternal vascular disease including placental insufficiency, immunogenic factors and dysmorphogenesis

- Congenital malformation

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Second and third trimester

Effects on Diabetes (risks to mother)

- Increased risk of retinopathy, nephropathy, HT, CVS effects
  -rapid HbA1c drop, angiogenic factors, anaemia, HT and alteration in blood volume
- Increasing insulin requirement (often 2-3 times the pre-pregnancy dose)
- Hypoglycaemia unawareness

Effects on Pregnancy

- PIH, Pre-eclampsia, renal dysfunction
- Pre-term labour, use of steroids
- labour intervention including caesarean section

Effects on foetus

- Macrosomia
- Birth injuries
  -Shoulder dystocia, fractures, brachial plexus injuries, birth asphyxia
- Still birth
- Neonatal hypoglycaemia, seizures, jaundice

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Does maternal hypoglycaemia affect foetus adversely?

- No systematic studies
- potentially teratogenic in first trimester (animal studies)
- Foetal brain can utilise lactate
- Avoid prolonged severe hypoglycaemia (BGL<3)
- Safe to use glucagon

Antenatal management for T1D and T2D

- Best managed in MDT setting with diabetes physician and obstetricians
- regular reviews (at least 2 weekly)
- Fasting BGL target 4-5.5, 2hr post prandial <7mmol/l
- ketone testing if BGL>10mmol/l
- Monitor biochemical parameters (HbA1c, EUC, Urine ACR, FBC)
- retinal screening each trimester
- Sonography (Dating scan, anomaly scan, cardiac scan and growth scans)
- Aim to deliver around 38-39 weeks

Intra- and post partum

- Peri-partum: close monitoring and strict glycaemic control (BGL 4-6mmol/l) -IV insulin/dextrose/KCl
- Most require <50% insulin following delivery
  - Halve insulin dosage or return to pre-pregnancy dosage
- Safe to breast feed but beware of hypoglycaemia
  - Many women with T2DM may be managed on diet alone whilst breast feeding
- Monitor BGL regularly
- Advise contraception, arrange clinical review 6-8 weeks
  - ARB/ACEi/statin excreted into breast milk

Gestational Diabetes

- Affects 12-20% of pregnancy
- High Risk groups: age >30, BMI, previous GDM, previous macrosomic baby, family history, ethnic group, glycosuria, PCOS – screen with f. BGL and HbA1c ASAP
- Universal screening at 24-28 weeks unless high risk – earlier screening (refer to Health pathway)
- GDM diagnosed at 24-28 weeks on 75g OGTT based on 1 positive criteria [OR 1.75]

fasting $\geq$ 5.1 1h $\geq$10 2h $\geq$ 8.5

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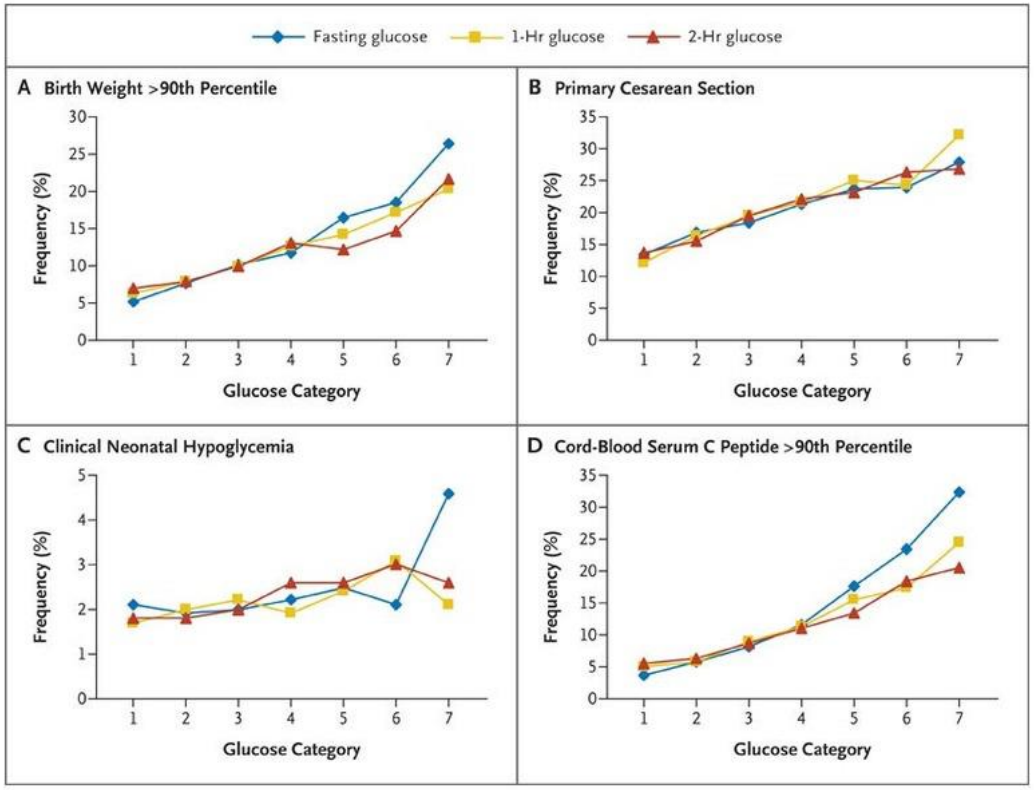
Hyperglycemia and Adverse Pregnancy Outcomes



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Treatment of GDM

Target: fasting BGL <5.1, 2h <6.7mmol/l

- Nutritional advice
- Moderate exercise (walking, swimming)
- BGL monitoring – 4 times a day
- metformin (crosses placenta but appears to be safe)
- Insulin therapy

Start Protaphane before bed and titrate to keep fasting BGL <5.2

Add NovoRapid with meals if prandial readings are >6.7mmol/l

- Fetal monitoring – US 4th wkly, Growth centile, Amniotic fluid index

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When to deliver

- Higher rates of unexplained late fetal death

- Balance between premature delivery and increased fetal death
  - T1DM 36-38 weeks
  - T2DM 38-40 weeks

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Post-pregnancy care: GDM

- Cease all treatment once placenta delivered
- Encourage breastfeeding
- OGTT at 6 weeks postpartum
  - Up to 50% will develop T2DM over next 5 yrs
- Lifestyle advice to delay development of T2DM
- Screen 1-3yrly for development of diabetes
- Recurrence rates up to 68%
  - Future pregnancies – screen at diagnosis
  - Repeat at 16-18 + 28/40

HNELHD Pregnancy Guideline 2017

- Available on intranet
- ** Includes IV insulin protocol for labour/steroids
- High risk women should be delivered in center with NICU

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Microvascular Complications

- Diabetic Peripheral Neuropathy
- Diabetic Autonomic neuropathy
- Diabetic Retinopathy
- Diabetic Nephropathy
- Diabetic foot disease*

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Macrovascular Complications

- IHD
- PVD
- Stroke
- Cardiac failure*

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Peripheral neuropathy

- Common
  - symptomatic neuropathy at least 10% prevalence
  - asymptomatic PN widely present

- Length dependent, symmetric (Glove and stocking)
- Thoracic and lumbar polyradiculopathy (Diabetic amyotrophy)
- Cranial (commonly oculomotor) and peripheral nerve palsy (median)
- Mononeuritis multiplex
- Treatment induced neuropathy (insulin neuritis)

Diagnosis

- History
- Foot examination

  - Pin prick, temperature, 10g monofilament = small fibre function

  - Vibration (125Hz), proprioception, pressure and reflexes = large fibre
- Ankle and knee reflexes, muscle power and gait
- And finally inspect the FOOTWARE!

- Nerve Conduction studies only if diagnosis in doubt or to exclude other causes

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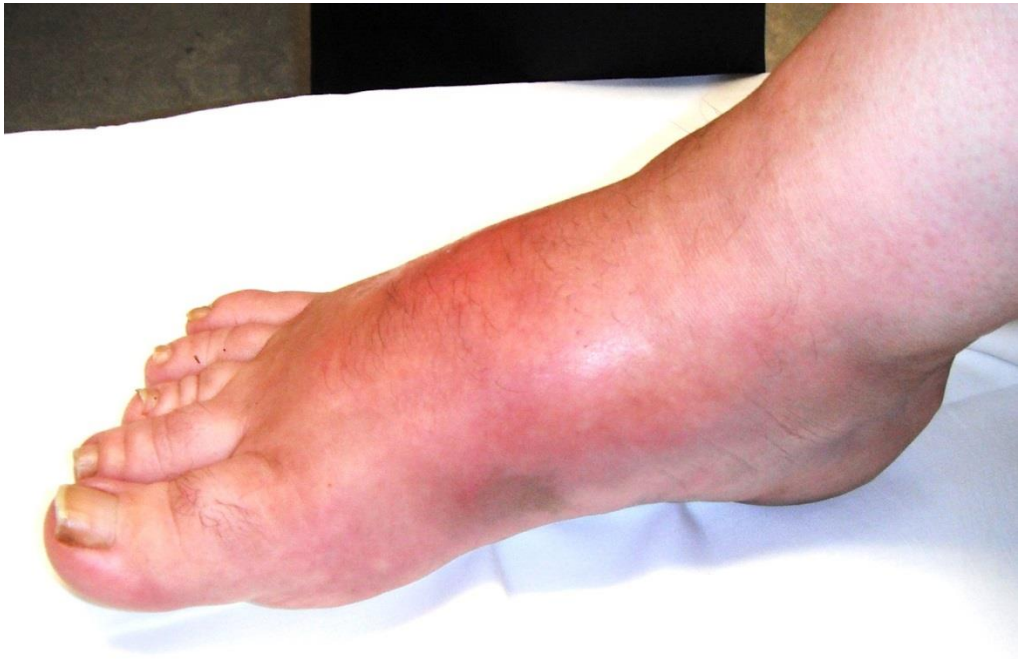
Management

- Most important: foot protection and prevention of ulcers!
- Engage podiatrists for treatment and surveillance
- Improve glycaemia, B12 deficiency, lipids, BP and lifestyle
- Pain relief as needed (pregabalin, low dose amitriptyline, duloxetine, venlafaxine, gabapentin)
- Capsaicin cream
- Avoid opiates
- Most patients settle down with improved glycaemia and time



With thanks to Dr Chris Sankoorikal

THE DIABETIC FOOT

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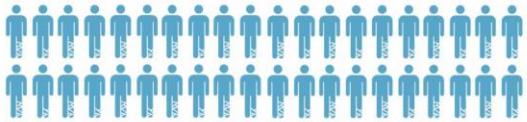
2016 NATIONAL DIABETES WEEK

10-16 July

DURING THIS WEEK....



OVER **400**

People have been diagnosed with diabetic foot disease

7,000

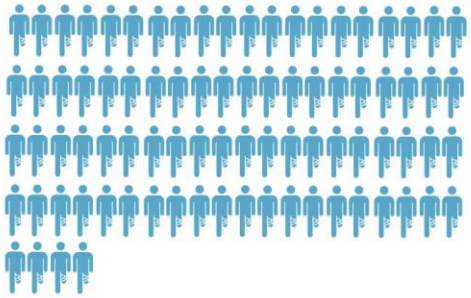
Hospital beds have been used due to diabetic foot disease

$7 MILLION

has been spent on diabetic foot disease hospitalisations

84 PEOPLE

have had an **amputation** as a result of diabetic foot disease.



28

people have **lost their lives** as a result of diabetic foot disease.

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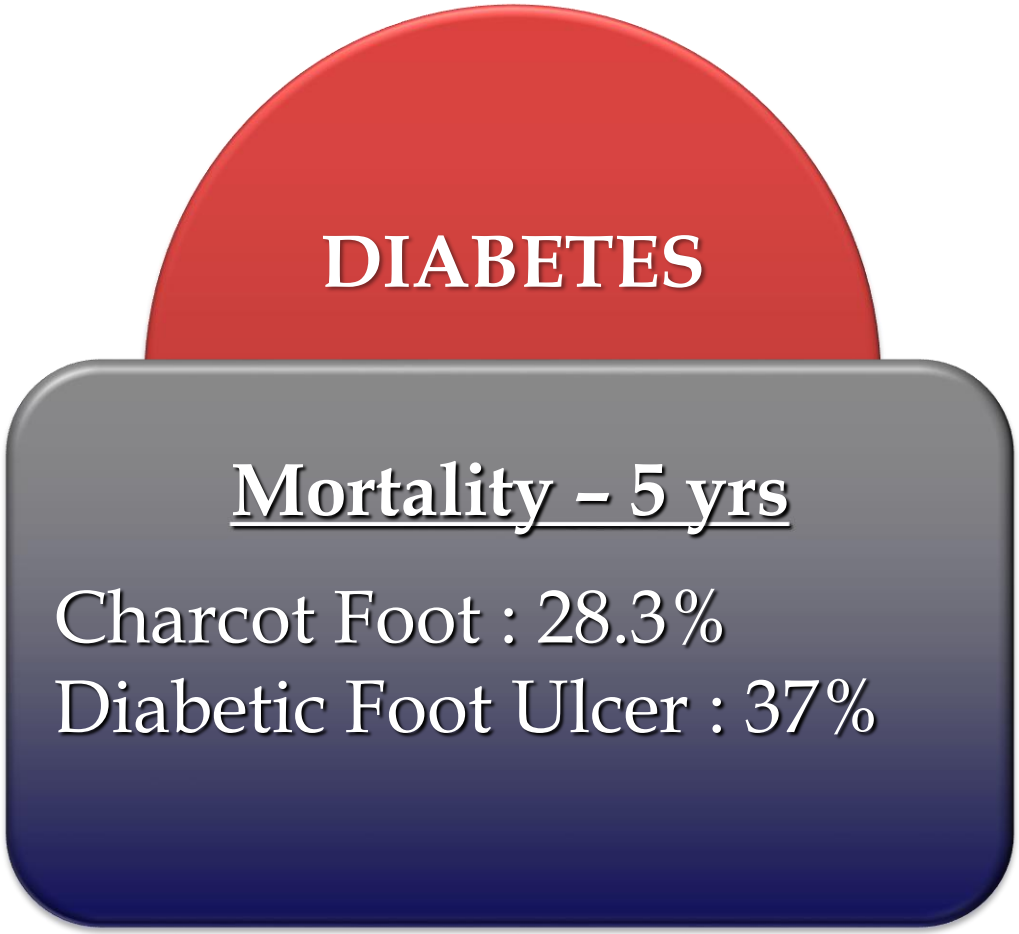
nationaloffice@diabeticfootaustralia.org
www.diabeticfootaustralia.org

DiabeticFoot Australia

5yr survival with breast cancer 90%



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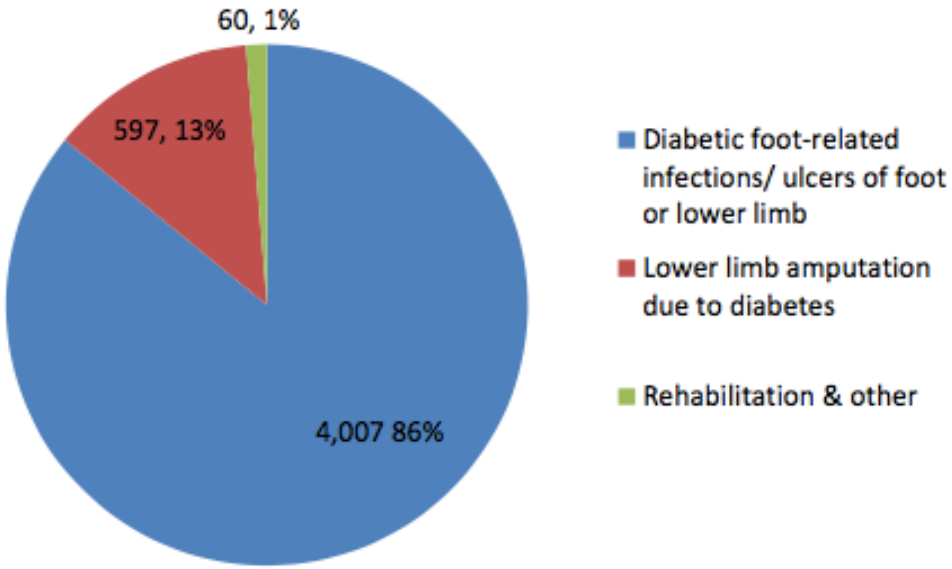
1.Sinha et al
2.Fabrin et al
3. Cofield et al
4. M W Sohn et al 2009

Local data

- Diabetic foot procedures had the highest average length of stay of 20 days.

- Cost for diabetic foot procedures doubled between 2012-13 and 2014-15



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Diabetic foot ulcer

- Neuropathy
  - Sensory
  - Autonomic
- Vascular ischemia
  - 25% asymptomatic
- Trauma
  - Infection
- Impaired immunity

Box 1 | Key components of the diabetic foot exam

Evidence of past and/or present ulcers

Foot shape

- Prominent metatarsal heads/claw toes
- Hallux valgus
- Muscle wasting
- Charcot deformity

Dermatological

- Callus
- Erythema
- Sweating

Neurological

- 10 g monofilament at four sites on each foot and one of the following:
  - Vibration using 128 Hz tuning fork
  - Pinprick sensation
  - Ankle reflexes
  - Vibration perception threshold

Vascular

- Foot pulses
- Ankle brachial index (if indicated)
- Doppler wave forms

Revascularisation

- Restoration of skin perfusion is considered to be a critical component of treatment.
- In individuals with critical ischaemia who did not undergo revascularization had a rate of major amputation of 23%-46% and a rate of wound healing of 53% at 1 year.
- Toe pressure <60mmHg – unlikely to heal without revascularisation

Management principles

- Any systemic sepsis: need admission
- Commence antibiotics if infection suspected
- **OFF LOAD**
- Wound care
- Revascularisation
- Optimise glycaemic management
- High risk foot clinic referral ASAP

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Pathophysiology – Charcot's

Autonomic Dysregulation
Hyperemia
AV Shunting
Increased Bone resorption

↓ Proprioception
↓ Vibration & Pain
+
Repetitive stress - Insensate joint
Microfractures

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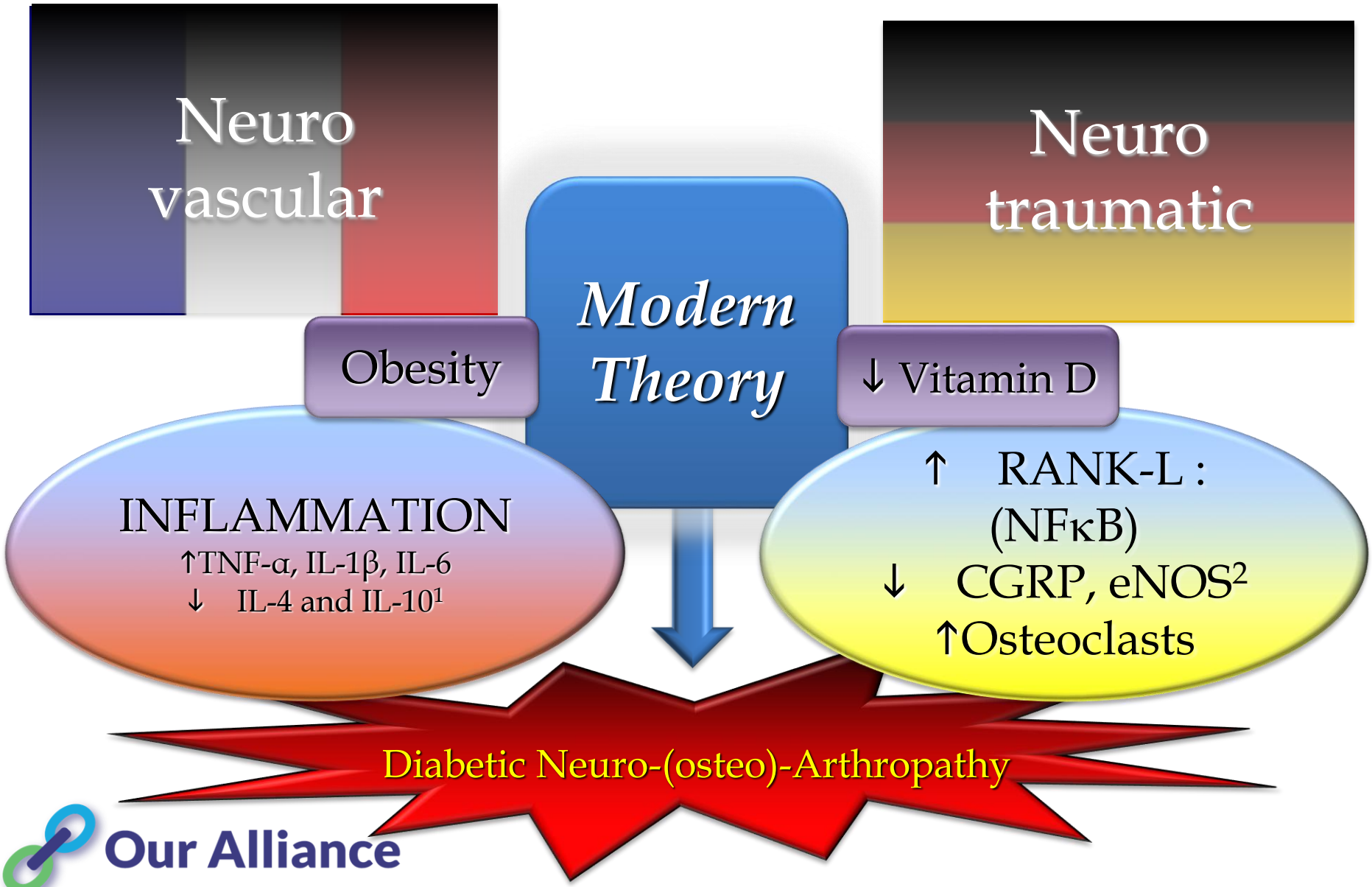
Pathophysiology



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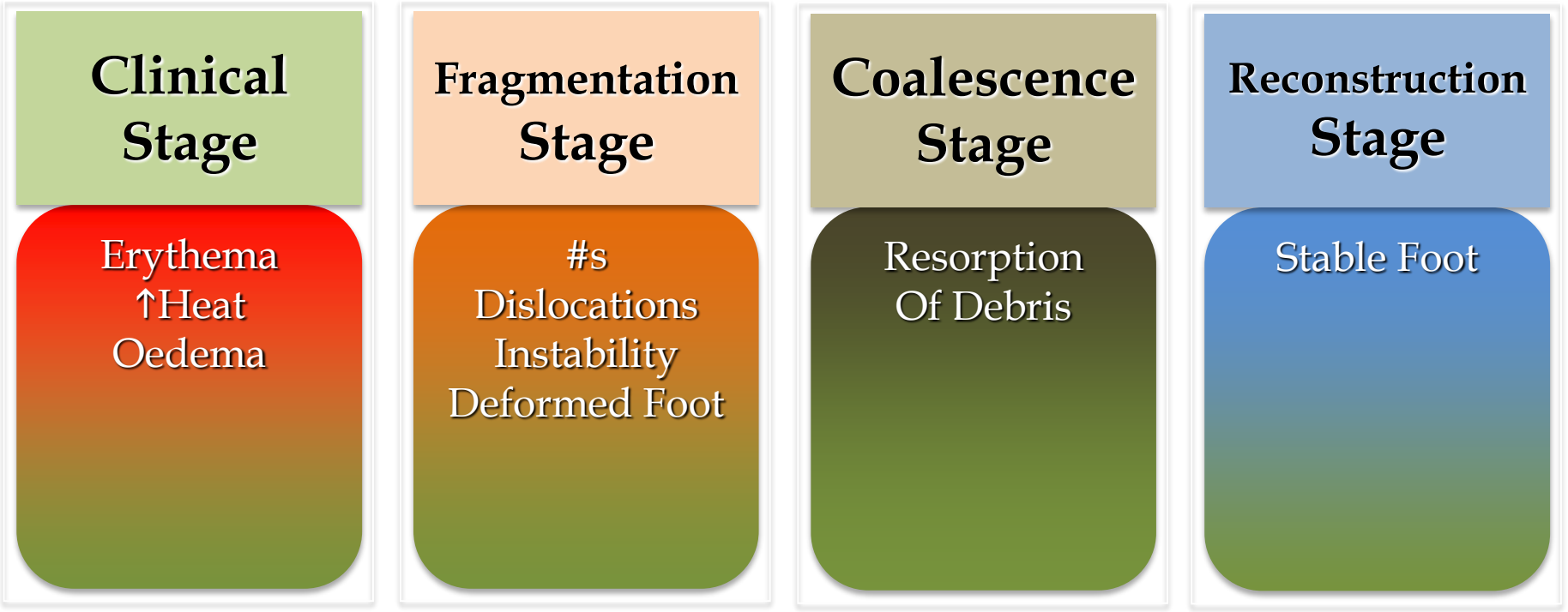
Eichenholtz Classification -
Clinical Progression



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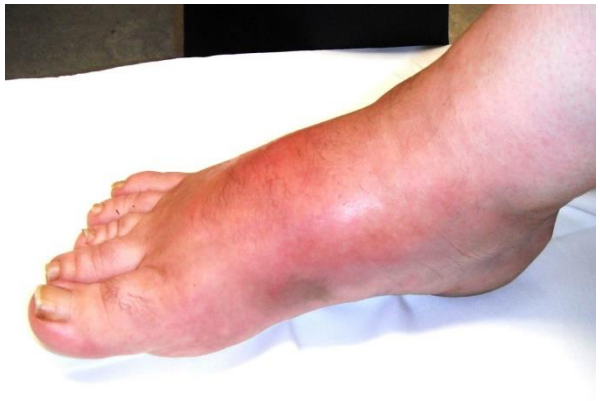
Adapted from Kelikian AS Operative treatment of foot and ankle 1999 : 153



Clinical Stage

Erythema
↑Heat
Oedema

Early Detection

High Index of Suspicion –Neuropathy
Age : 5th-6th decade
Diabetes ~10years
Overweight
Osteopenia*

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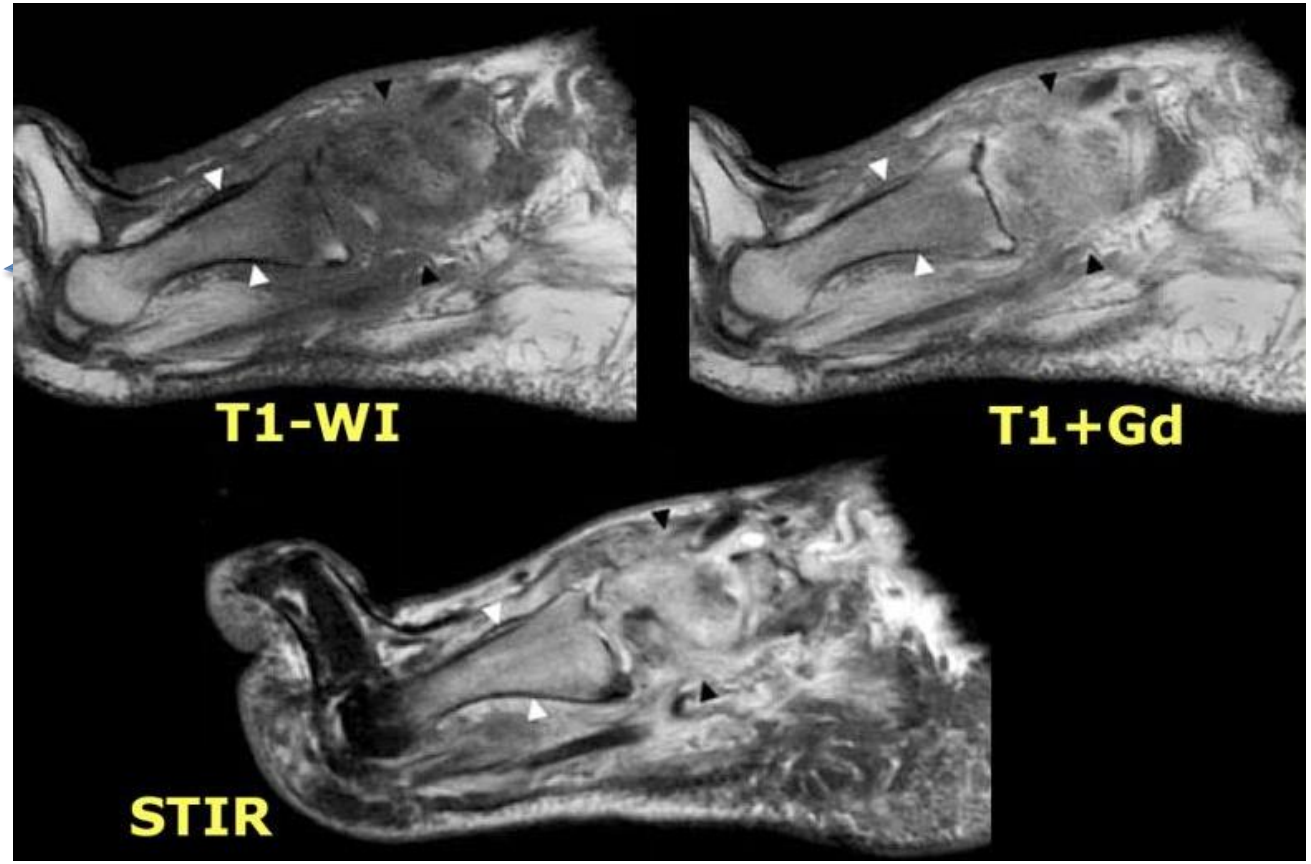
Adapted from Kelikian AS Operative treatment of foot and ankle 1999 : 153

Clinical Stage

Erythema
↑Heat
Oedema

NO weight bearing,
Close Observation
TCC/PPRC



Kelikian AS. Operative treatment of the foot and ankle. Stamford, Conn.: Appleton & Lange,

Eichenholtz Classification

Clinical Progression

Clinical Stage	Fragmentation Stage	Coalescence Stage	Reconstruction Stage
Erythema ↑Heat Oedema NWB, Observation TCC/PPRC	#s Dislocations Instability Deformed Foot TCC/PPRC	Resorption Of Debris TCC - CROW	Stable Foot Surgical intervention for removal of bony prominences

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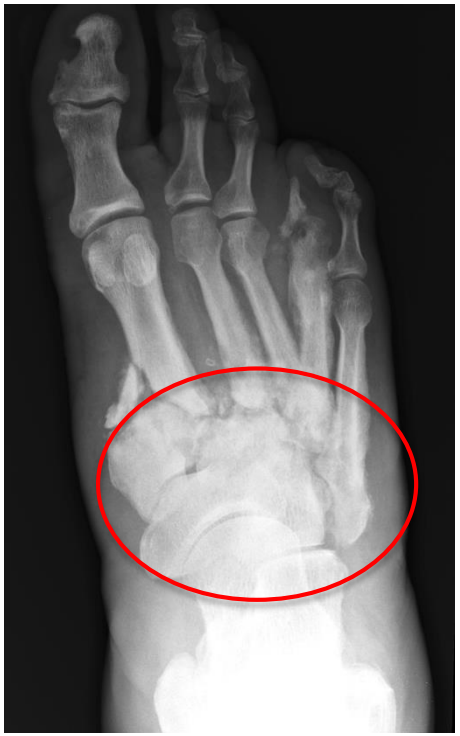
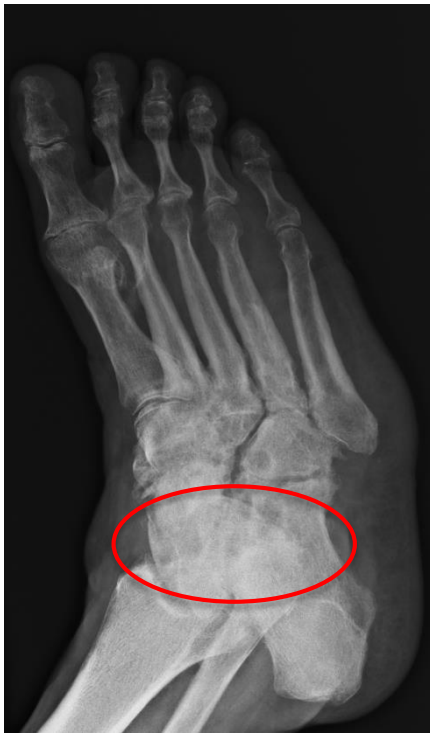
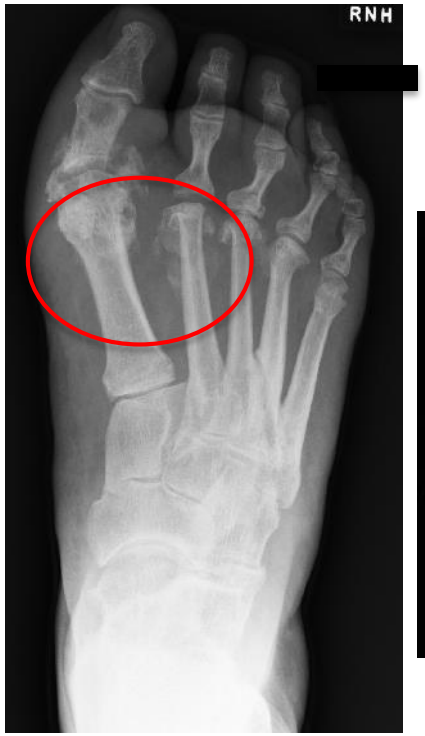
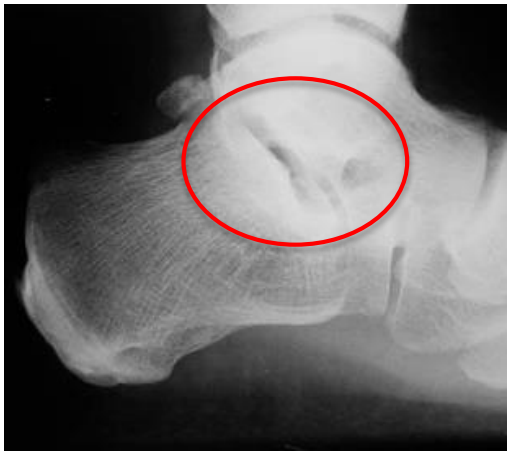
Adapted from Kelikian AS Operative treatment of foot and ankle 1999 : 153

Imaging









Midfoot – 60%

Forefoot

Hindfoot – 30%

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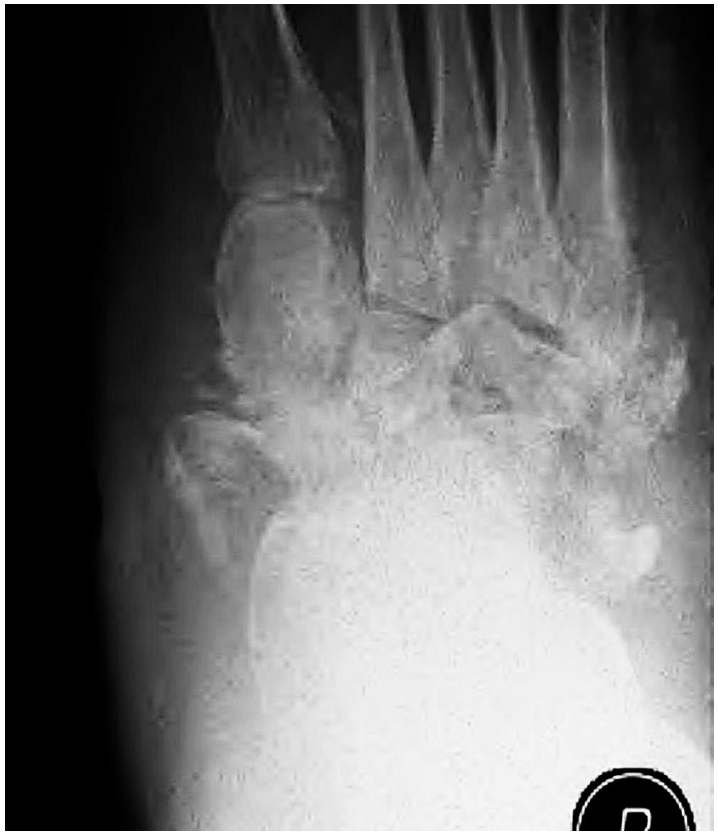

Coalescence Stage

Resorption
Of Debris

TCC - CROW

Demineralisation of bone
Periarticular fragmentation
Joint dislocation

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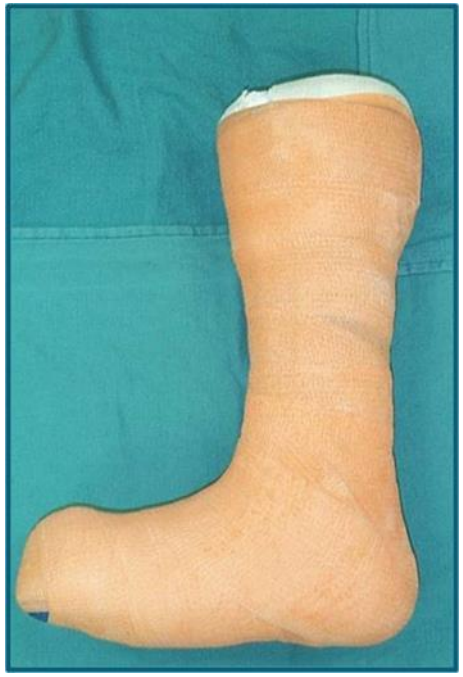
Treatment

- Immobilisation (Mean duration ~18 weeks)



Total Contact Cast

Prefabricated Pneumatic Removable Cast

Charcot Removable Orthotic Walker

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Amstrong DG et al, Diabetes Medicine 1997 May;14(5):357-63

Surgical Indications

1. Severe deformity unable to brace

2. Marked instability

3. Ulcers
   - aim to try and heal ulcer first
   - may be caused by fixed bony deformity

4. Soft tissues at risk

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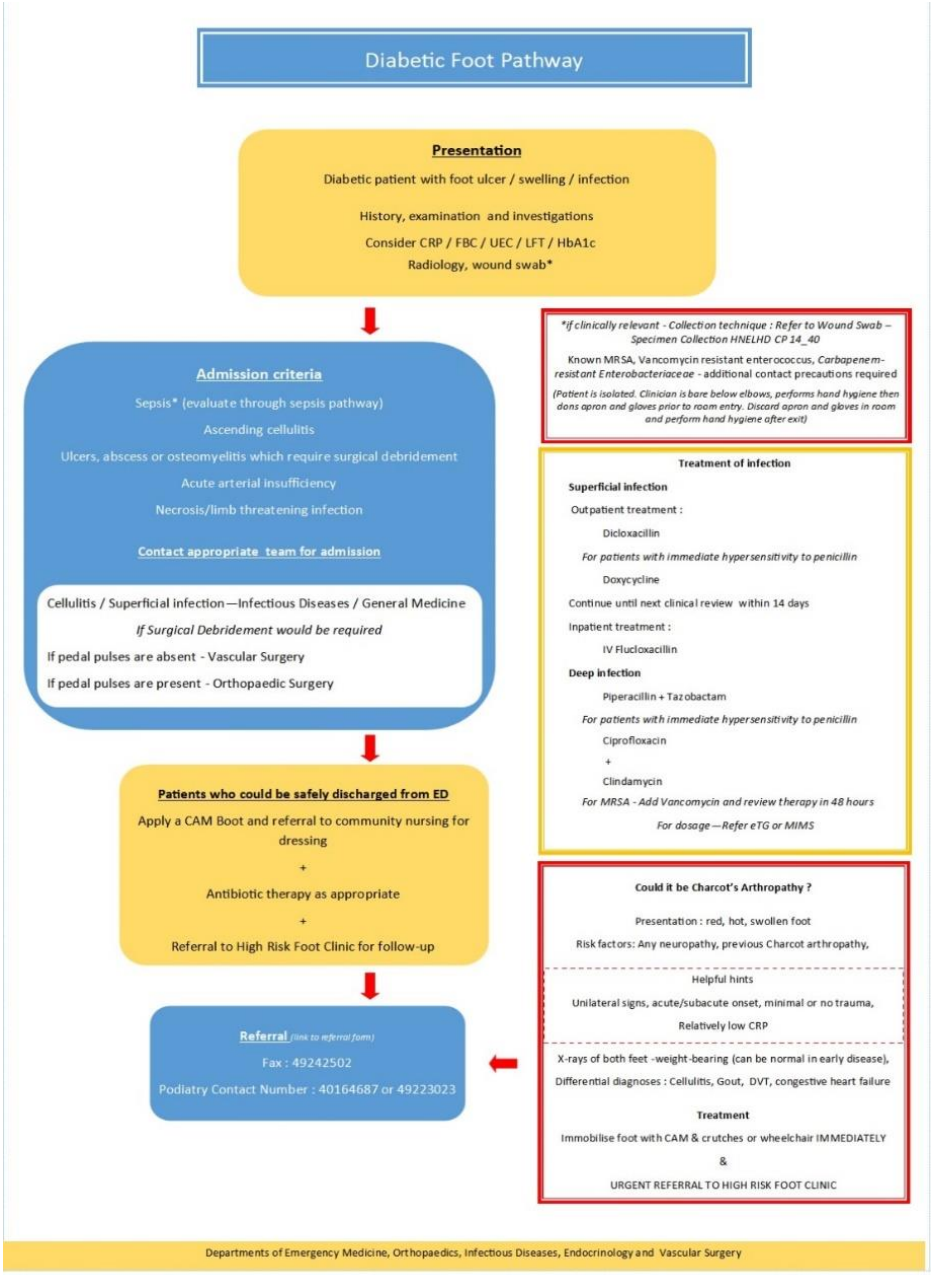

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See Diabetes Foot Screening HealthPathway

Take Home Points

- Recognise : Charcot's Neuroarthropathy should be considered whenever there is an inflamed foot with background neuropathy
- Clinical clue: warm foot with bounding pulses
- Early Disease – minimal radiological changes (may need MRI – Foot)
- Offloading – cornerstone of management

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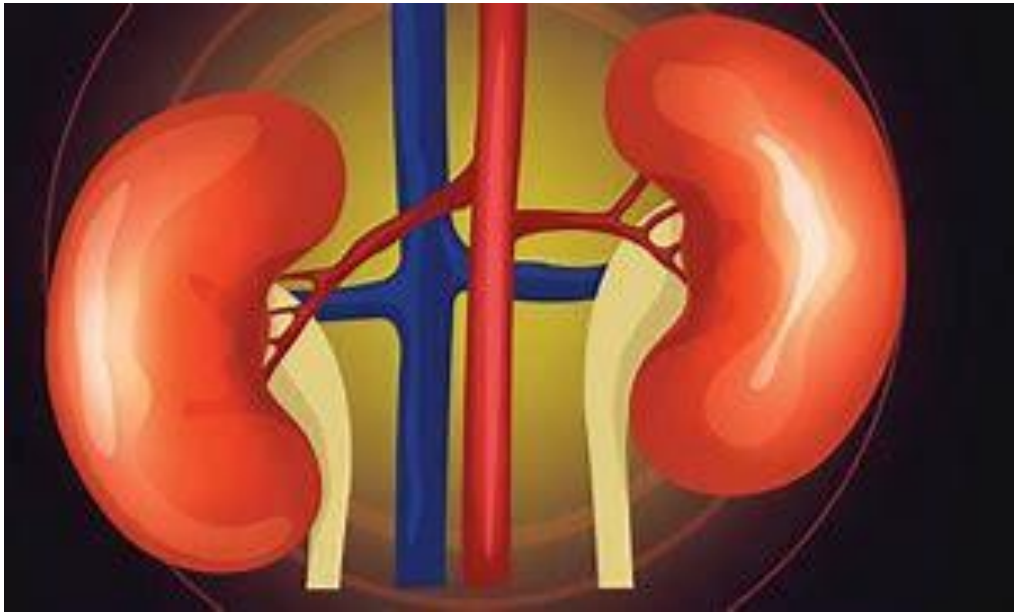
Autonomic neuropathy

- Wide spread or local autonomic nervous system dysfunction
- Cardiovascular: postural hypotension, resting tachycardia, exercise intolerance, intra operative instability, MI and sudden death
- GI: gastroparesis, diarrhoea or constipation
- Genitourinary: bladder dysfunction, ejaculatory or erectile dysfunction, orgasm failure, dyspareunia

Autonomic neuropathy

- Difficult to manage
  - Dietary modifications
  - Lifestyle modifications – compression stockings
  - Drugs: midodrine, domperidone, prucalopride
- May improve with sustained glycemic control over time

Diabetic nephropathy



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Natural History of Diabetic Nephropathy

	Designation	Characteristics	GFR (minimum)	Albumin Excretion	Blood Pressure	Chronology
Stage 1	Hyperfunction and hypertrophy	Glomerular hyperfiltration	Increased in type 1 and type 2	May Be Increased	Type 1 normal Type 2 normal hypertension	Present at time of diagnosis
Stage 2	Silent stage	Thickend BM Expanded mesangium	Normal	Type 1 normal Type 2 may be <30-300 mg/d	Type 1 normal Type 2 normal hypertension	First 5 years
Stage 3	Incipient stage	Microalbuminuria	GFR begins to fall	30-300 mg/d	Type 1 increased Type 2 normal hypertension	6-15 years
Stage 4	Overt diabetic nephropathy	Macroalbuminuria	GFR below N	>300 mg/d	Hypertension	15-25 years
Stage 5	Uremic	ESRD	0-10	Decreasing	Hypertension	25-30 years

What is microalbuminuria?

- Microalbuminuria = leakage of small quantities of albumin into the urine (below detection on dipstick) due to increased permeability in the glomeruli
- Common causes: diabetic kidney disease, Hypertension, glomerulonephritis
- “False” positive can occur after vigorous exercise, fever, sexual intercourse, UTI, menses so retesting is needed to confirm
- microalbuminuria is potentially reversible with improved glycaemia, BP control, ACE inhibition, SGLT2i and GLP1-RA however once macroalbuminuria occurs progression to end stage renal disease inevitable

Diagnosis, classification and staging of CKD

		Albuminuria stage		
Kidney function stage	**GFR (mL/min/1.73m^2)**	**Normal (urine ACR mg/mmol) Male: < 2.5 Female: < 3.5**	**Microalbuminuria (urine ACR mg/mmol) Male: 2.5-25 Female: 3.5-35**	**Macroalbuminuria (urine ACR mg/mmol) Male: > 25 Female: > 35**
1	≥90	Not CKD unless haematuria, structural or pathological abnormalities present		
2	60-89			
3a	45-59			
3b	30-44			
4	15-29			
5	<15 or on dialysis			

Risks of progressive CKD denoted as low (green), moderate (yellow), high (orange) and very high (red).

[For specific management plans refer to Chronic Kidney Disease Management in General Practice [1]]

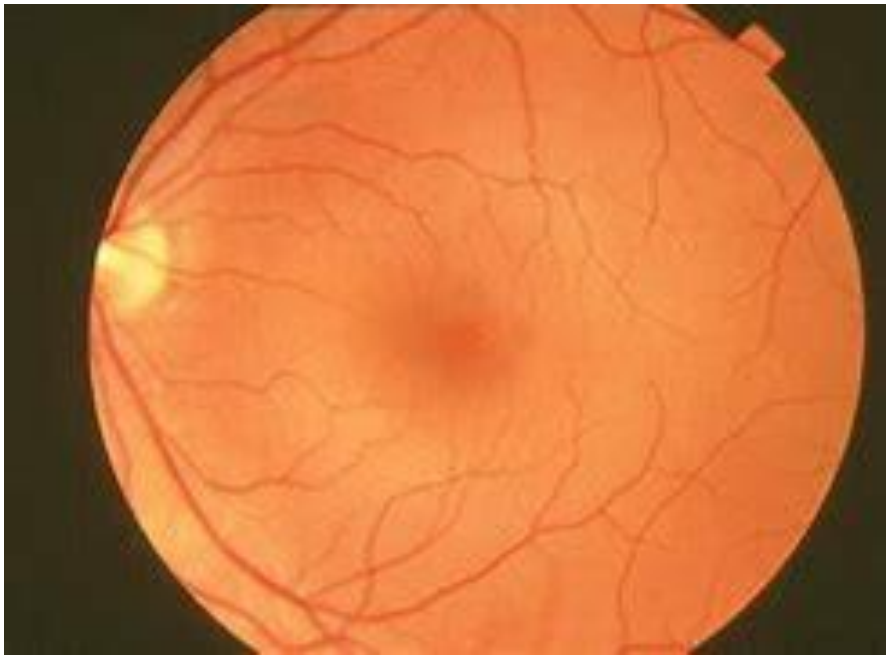
Note:

- **For patients with CKD, the combination of a low GFR and albuminuria or proteinuria places them at a greater risk of CKD progression at all ages, than those with just low GFR, albuminuria or proteinuria.**
- **A measured or estimated GFR <45 mL/min/1.73m^2 is associated with increased risks of adverse renal, cardiovascular and other clinical outcomes, irrespective of age.**

Diabetic renal disease

- Check urine ACR for ALL patients with diabetes at least annually
- If Microalbuminuria confirmed, maximise ACEI (ARB) and start SGLT2i if no contraindication (eGFR>15*)
- Improve glucose control and other vascular risks
- Specialist management required
  - Progressive microalbuminuria (ACR>30mg/mmol)
  - reduction in GFR (<30ml/min)
  - Nephrotic syndrome: overt proteinuria (ACR >300mg/mmol) or hypoalbuminemia
  - Other signs of kidney failure : Anemia, acidosis, hyperkalemia
- Occasionally renal biopsy is warranted to exclude other causes

Diabetic retinopathy



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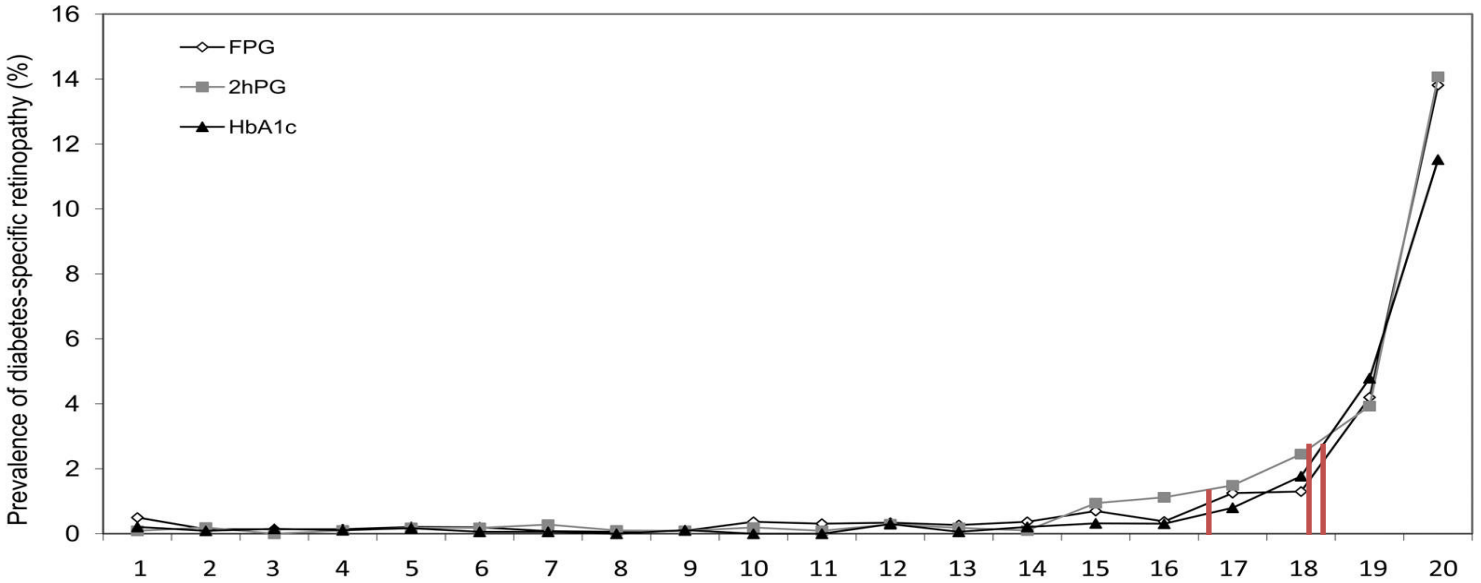
Diabetic Retinopathy

Prevalence of diabetes-specific retinopathy (moderate or more severe retinopathy) by vigintiles of the distribution of FPG, 2-h PG, and A1C.



	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
FPG (mmol/L)	1.7-	4.5-	4.7-	4.8-	4.9-	5.1-	5.2-	5.2-	5.3-	5.4-	5.5-	5.6-	5.7-	5.8-	6.0-	6.2-	6.4-	6.9-	7.7-	10.1-
2-h PG (mmol/L)	1.1-	4.3-	4.9-	5.3-	5.7-	6.0-	6.3-	6.6-	6.9-	7.2-	7.7-	8.0-	8.5-	9.1-	9.8-	10.7-	11.9-	13.4-	15.9-	19.9-
HbA1c (%)	3.1-	4.6-	4.7-	4.9-	5.0-	5.0-	5.1-	5.2-	5.3-	5.3-	5.4-	5.5-	5.6-	5.7-	5.8-	5.9-	6.1-	6.3-	6.8-	7.9-

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Stephen Colagiuri et al. Dia Care 2011;34:145-150

American Diabetes Association.

Diabetic Retinopathy

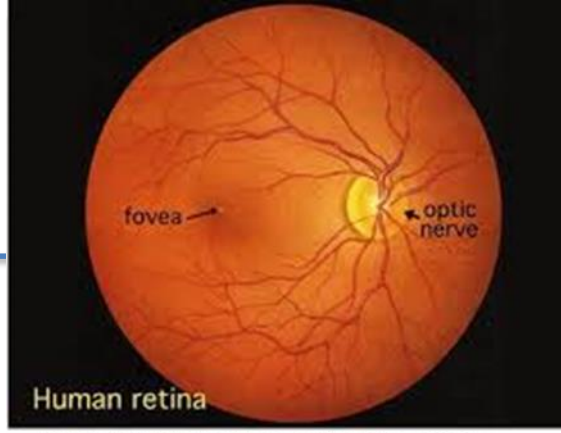
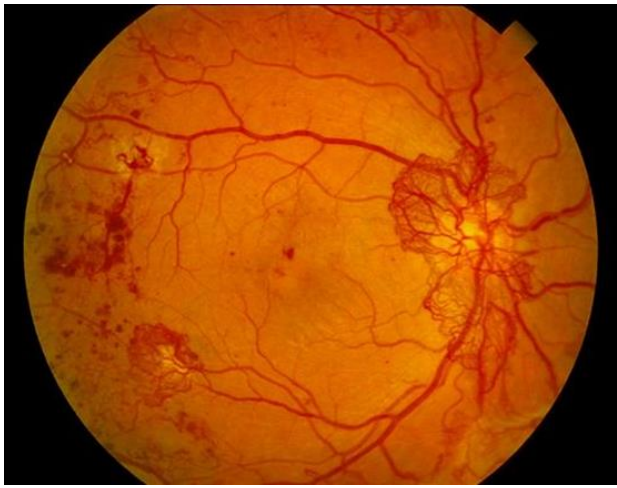
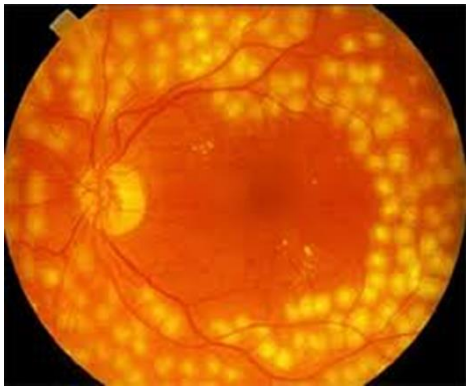


Figure 1. A view of the retina seen though an ophthalmoscope.

- Risk factors:
  - Duration of diabetes
  - Degree of glycaemia (variability of glycaemia)
  - Hypertension, Hyperlipidemia, Smoking
  - African-American
  - Pregnancy
- Screening: at least every 12-18 month
- Prevention:
  - Fenofibrate slows progression in T2DM
  - Mediterranean diet appear beneficial
  - ?Omega 3 supplementation
  - Macuvision (macular oedema)





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Erectile dysfunction

- Male erectile dysfunction is very common in diabetes
- Multifactorial including vascular and neurogenic, compounded by smoking, alcohol, obesity, low testosterone
- Inability to sustain erection, premature/ delayed/retrograde/absent ejaculation
- Female sexual dysfunction is also being recognised

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Macrovascular disease

- IHD (15%) PVD (30%) and CVD
- Atherosclerosis induced
- Duration of DM and degree of metabolic risk control
- Smoking and family history
- Macrovascular disease start at prediabetes

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Treatment

- Counselling should include partners whenever possible
- Treatment may or may not work
- Consider PDE5 inhibitors – daily or PRN
- Caverject injections
- Penile pump
- Referral to Endocrinology or Urology

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Newer agents and vascular complications of Diabetes

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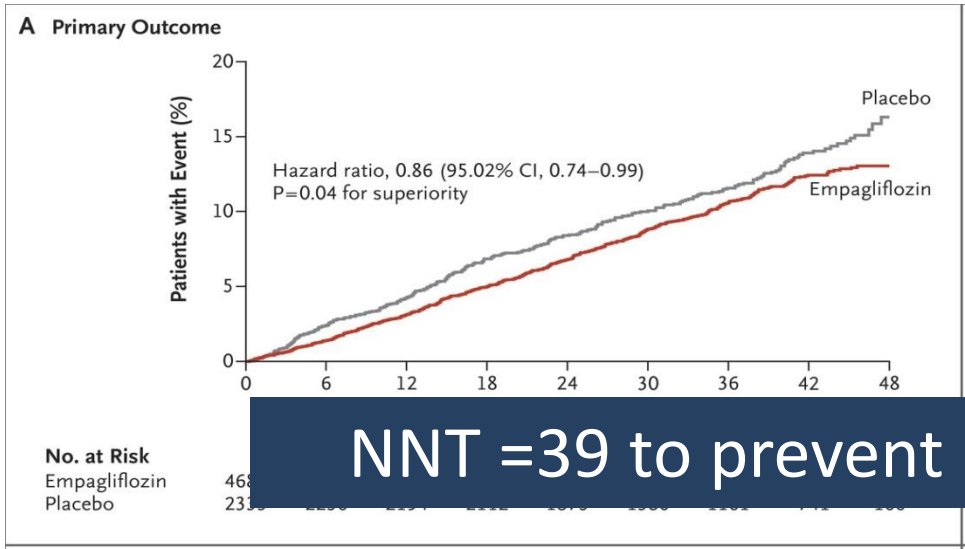
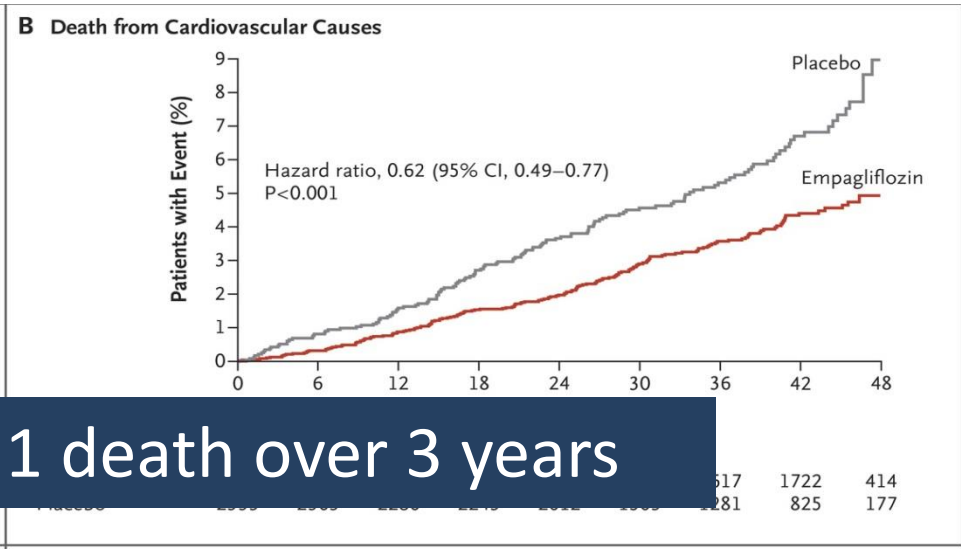
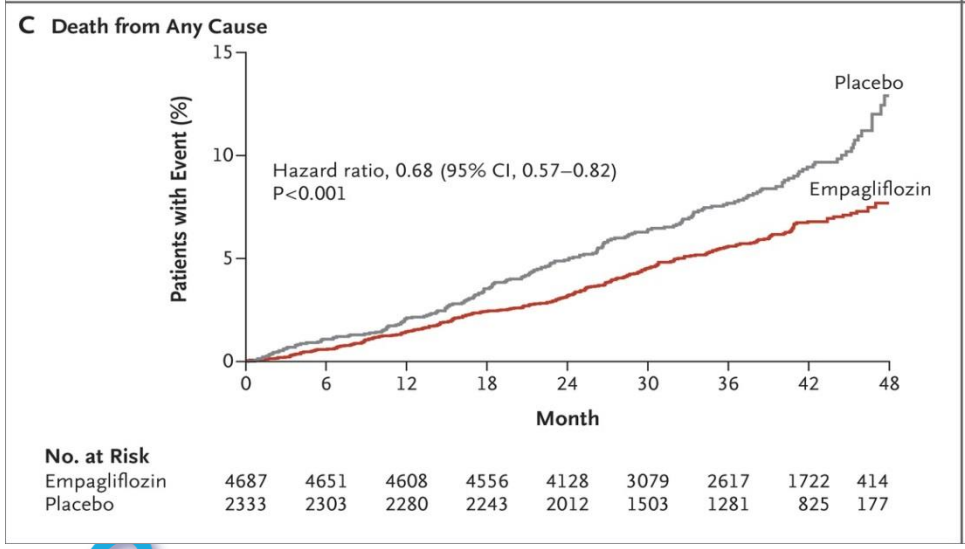
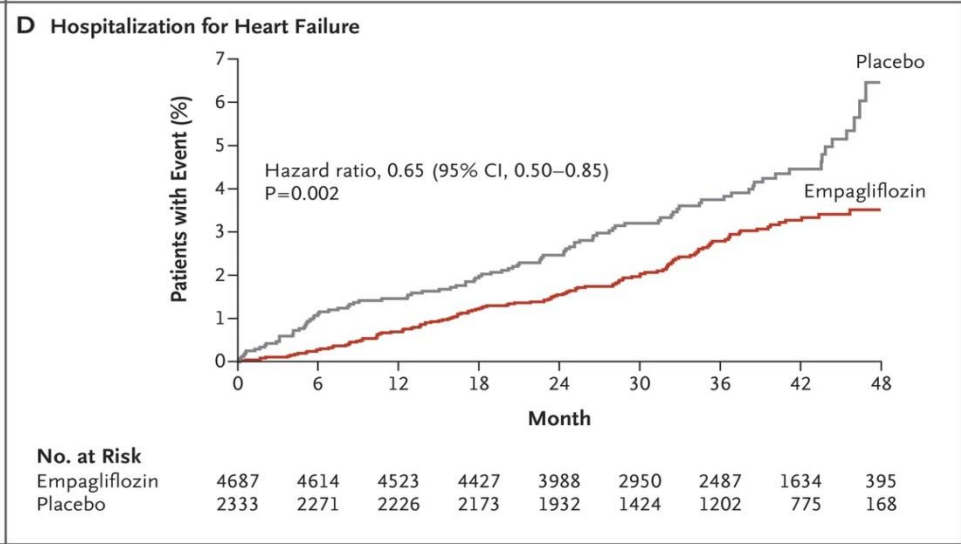
EMPA-REG: Cardiovascular Outcomes And Death From Any Cause.





NNT =39 to prevent 1 death over 3 years

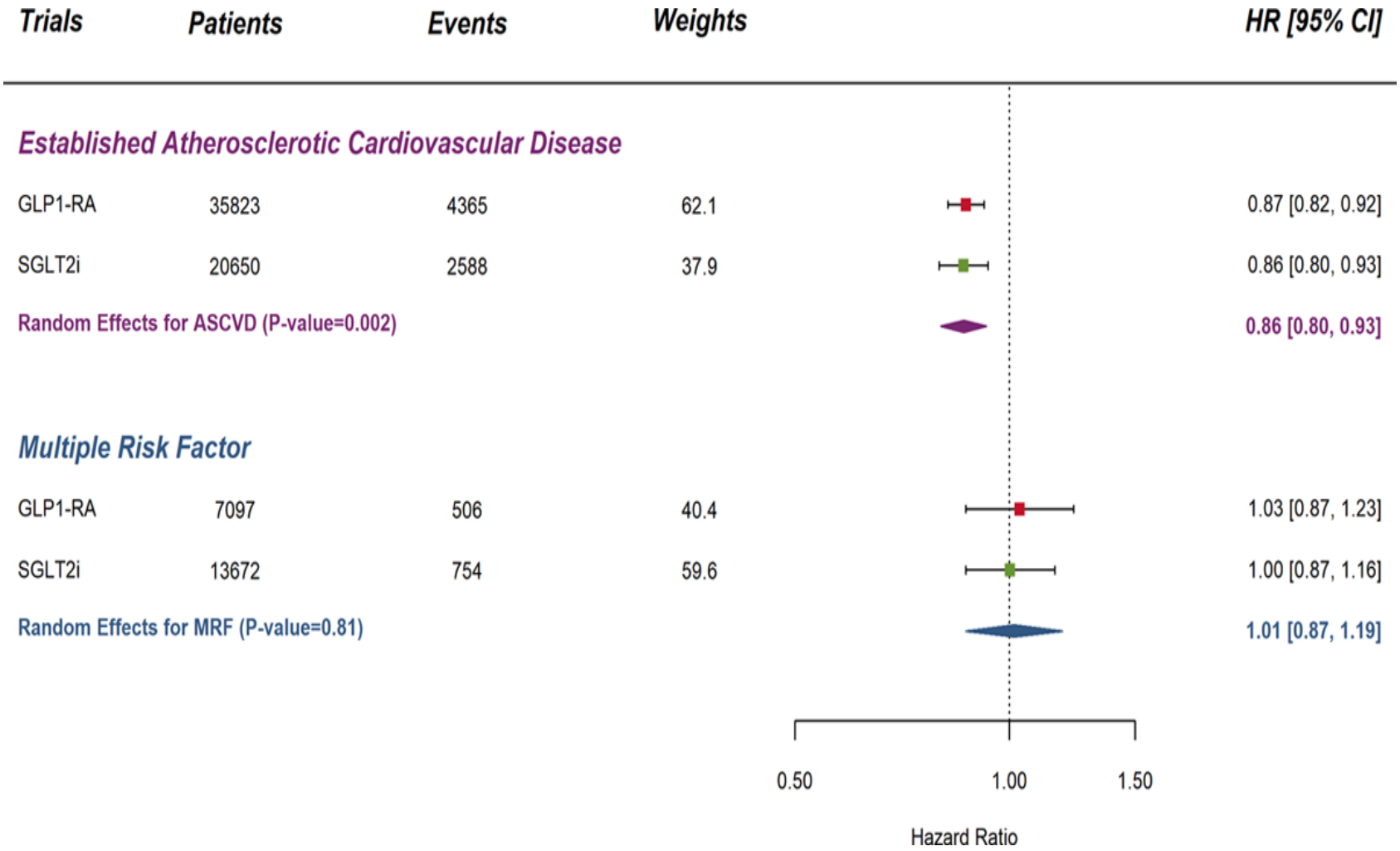




Zinman B et al. N Engl J Med 2015;373

The NEW ENGLAND JOURNAL of MEDICINE

CVOT MACE/mortality



Comparison of the Effects of Glucagon-Like Peptide Receptor Agonists and Sodium-Glucose Cotransporter 2 Inhibitors for Prevention of Major Adverse Cardiovascular and Renal Outcomes in Type 2 Diabetes Mellitus, Volume: 139, Issue: 17, Pages: 2022-2031, DOI: (10.1161/CIRCULATIONAHA.118.038868)

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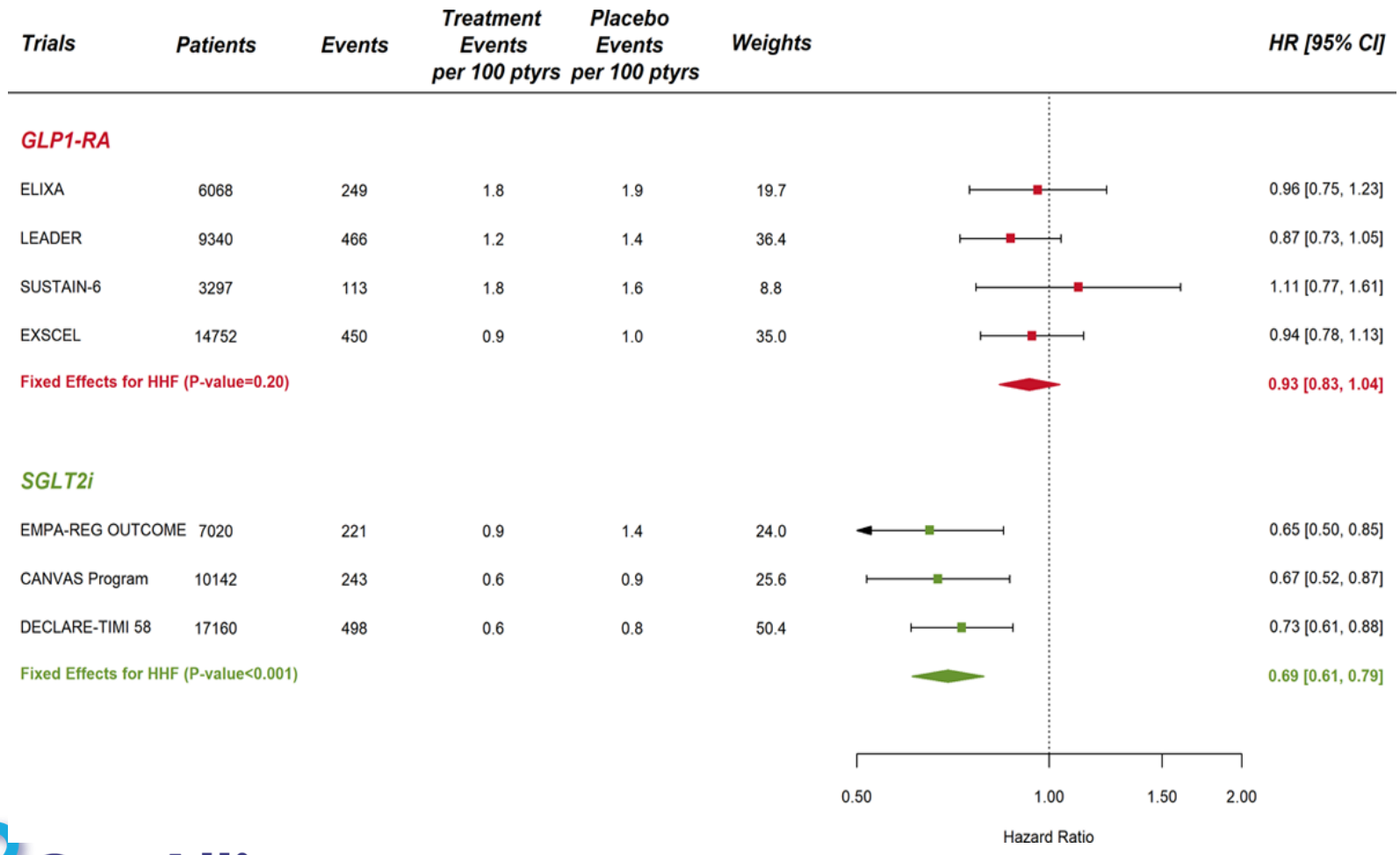
Heart Failure



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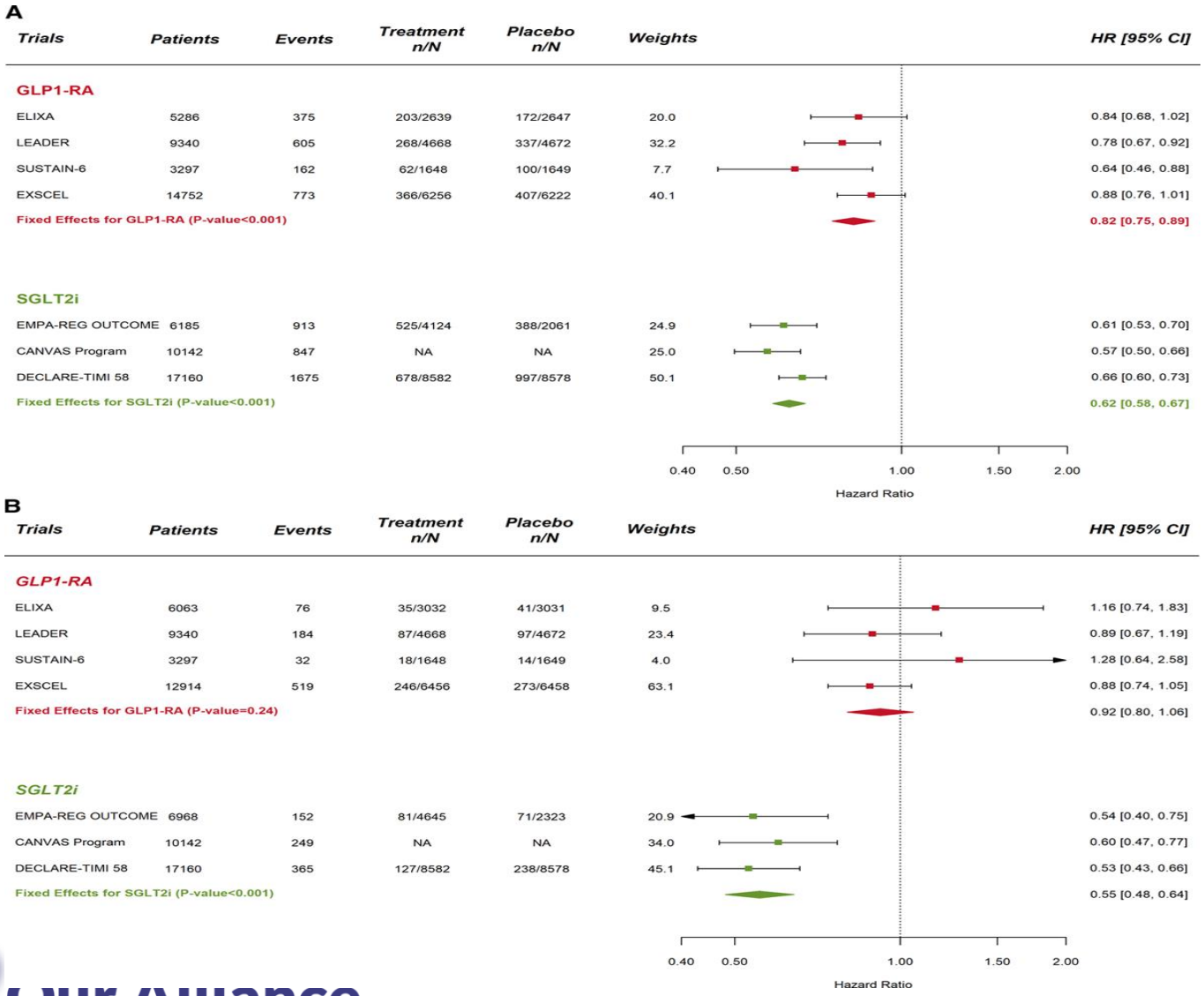
Renal outcome



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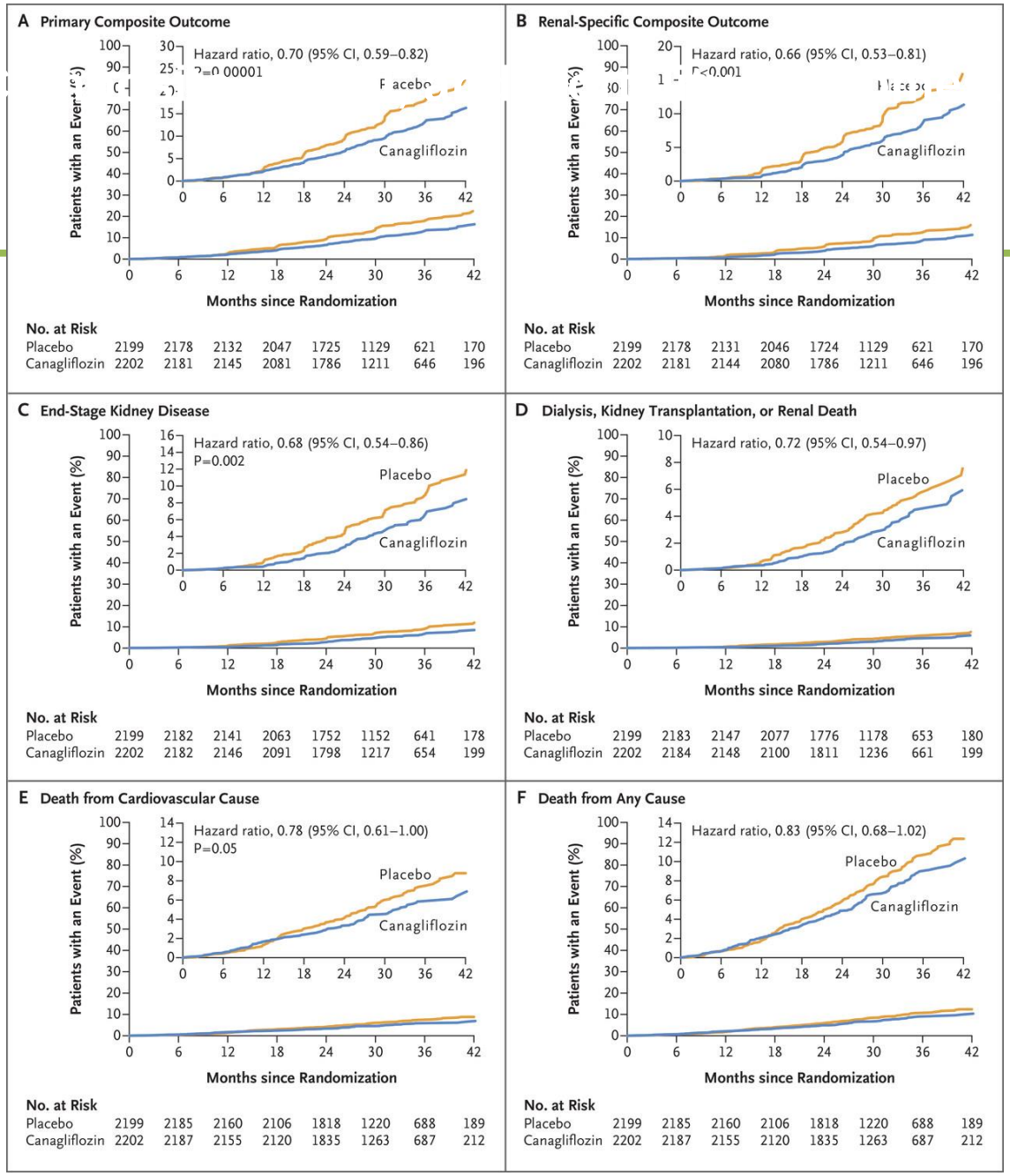

V Perkovic et al. N Engl J Med 2019;380:2295-2306.

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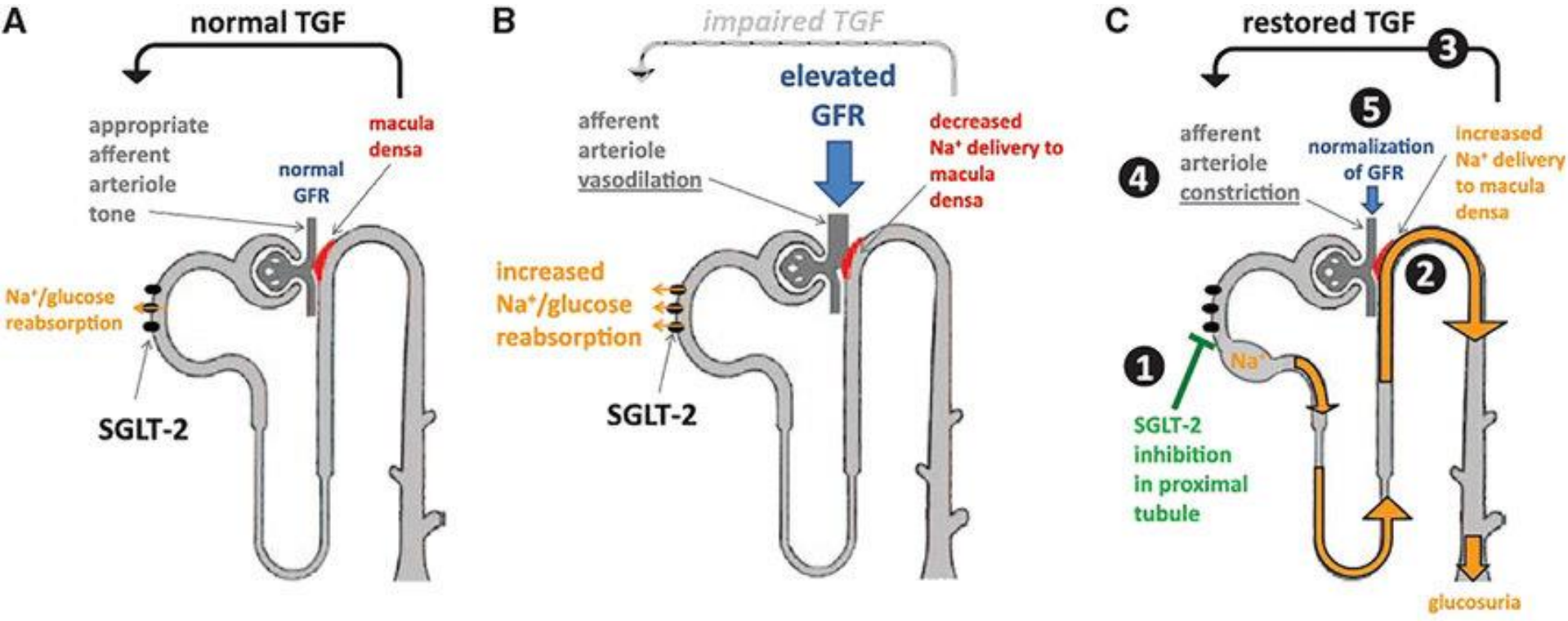

Normal physiology

Hyperfiltration in early stages of diabetic nephropathy

SGLT-2 inhibition reduces hyperfiltration via TGF

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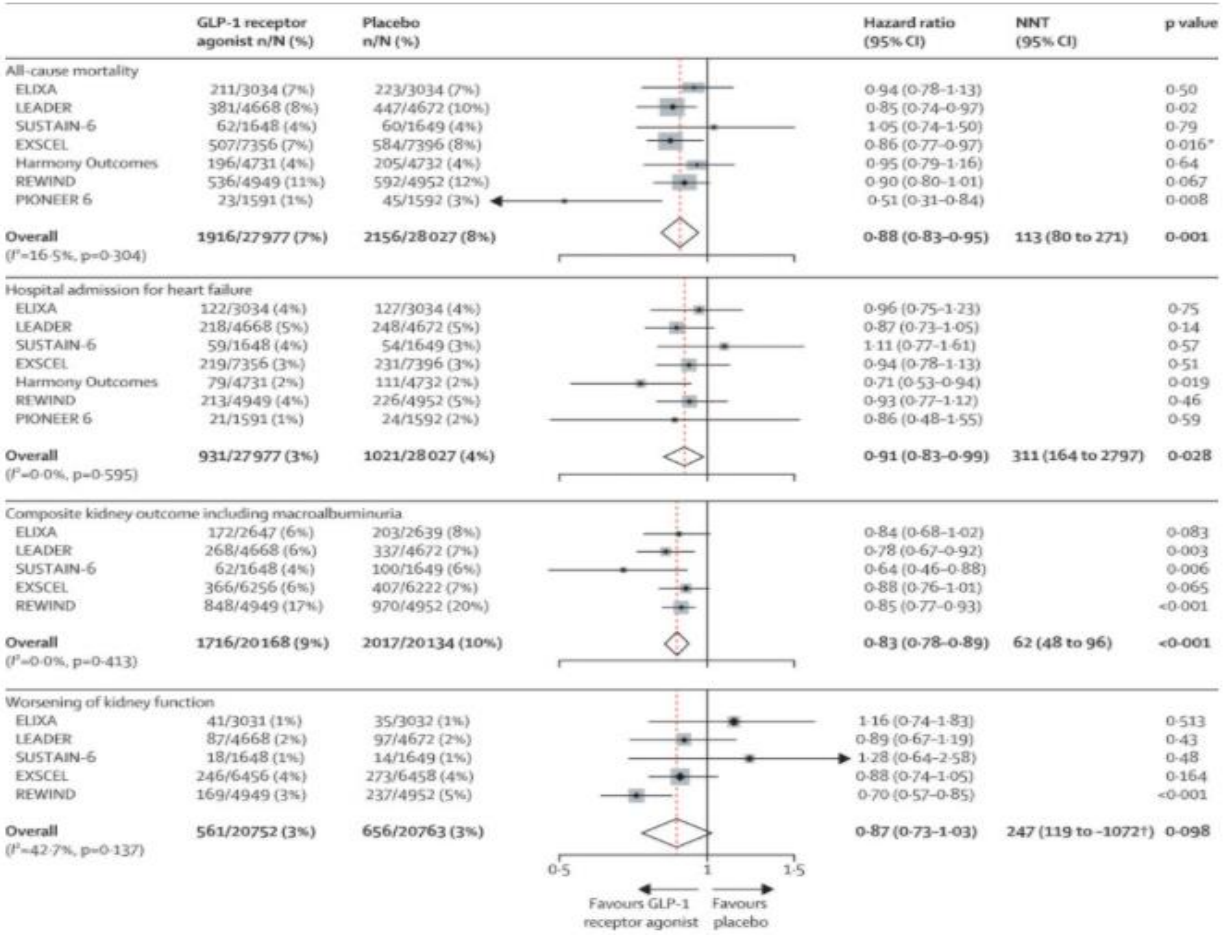
Cardiovascular, mortality, and kidney outcomes with GLP-1 receptor agonists in patients with type 2 diabetes: a systematic review and meta-analysis of cardiovascular outcome trials
Lancet Diabetes and Endocrinology V 7 10, OCTOBER 2019 776- 785
Soren Kristensen et al.



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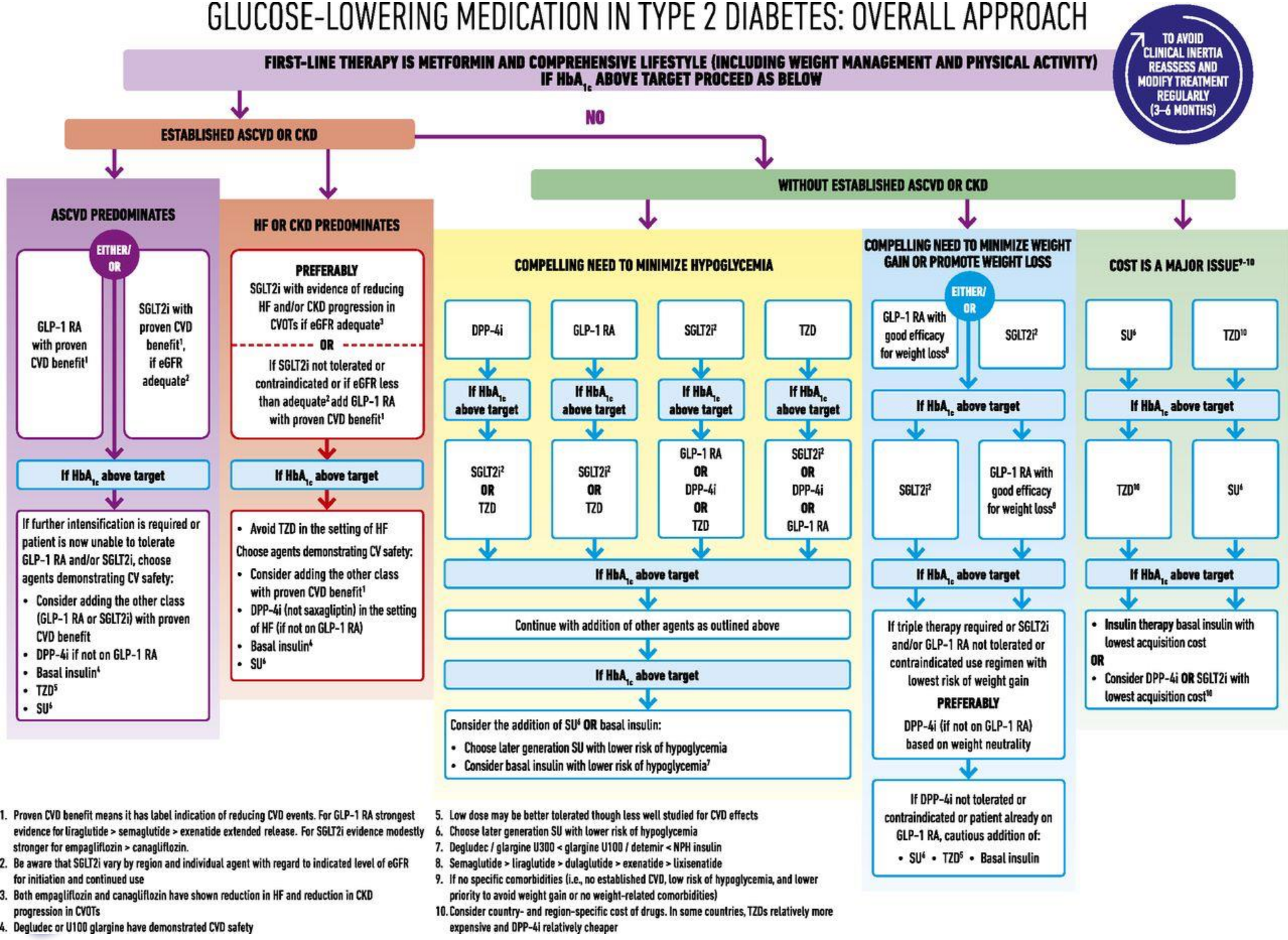
GLUCOSE-LOWERING MEDICATION IN TYPE 2 DIABETES: OVERALL APPROACH



1. Proven CVD benefit means it has label indication of reducing CVD events. For GLP-1 RA strongest evidence for liraglutide > semaglutide > exenatide extended release. For SGLT2i evidence modestly stronger for empagliflozin > canagliflozin.
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 hypoglycemia
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 hypoglycemia, 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

Take home messages

- Diabetic complications is very common
  - SCREEN to make a difference
- Progression may not be stepwise
- BP, glucose and weight control is important
- Think acute Charcot when you see a swollen foot
- Remember the BABY!

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Questions ?

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