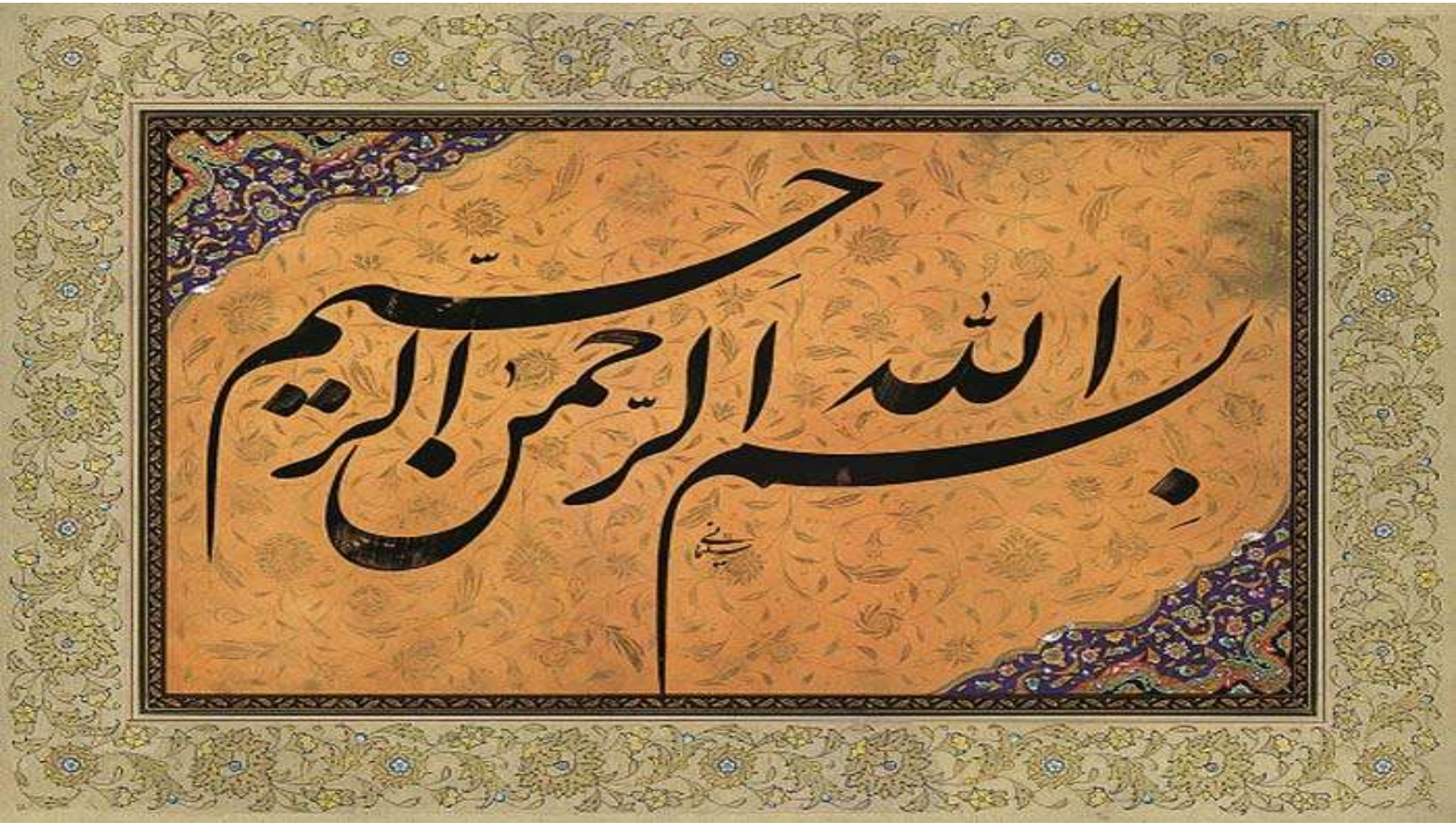
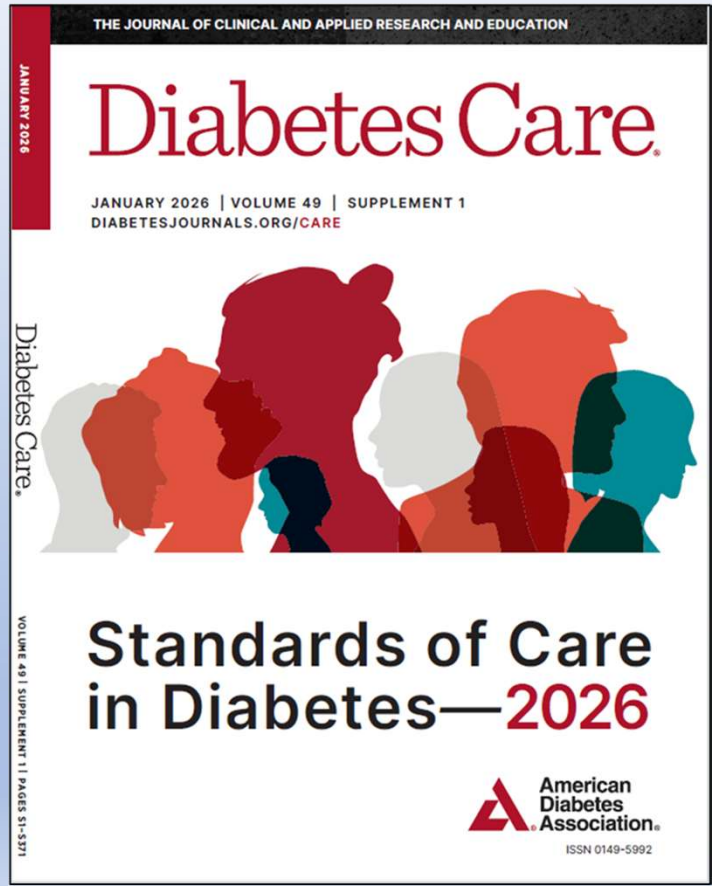

بسم الله الرحمن الرحیم

Microvascular complication of diabetes

Dr sevil Ghaffarzadeh rad

Assisstant professor of endocrinology



DIABETIC RETINOPATHY

- Highly specific neurovascular complication of both type 1 and type 2 diabetes.
- Leading cause of **new-onset blindness** in adults aged 20–74 years in developed countries
- Glaucoma, cataracts, and other ocular disorders occur earlier and more frequently in diabetes
- Prevalence strongly correlated with diabetes duration and glycemic control

Major Risk Factors for Diabetic Retinopathy

- ✓Duration of diabetes (strongest predictor)
- ✓Chronic hyperglycemia
- ✓Diabetic nephropathy
- ✓Hypertension
- ✓Dyslipidemia

- Every **1%** reduction in HbA1c → **30–40%** reduction in retinopathy progression (UKPDS, DCCT/EDIC)

Intensive diabetes management

- Prevents and/or delays onset of diabetic retinopathy
- Slows progression of existing retinopathy
- Reduces need for laser photocoagulation & vitrectomy
- 76% reduction in risk of sustained retinopathy progression (DCCT)
- Long-term beneficial effect persists years after trial (“**metabolic memory”)**

Screening for Diabetic Retinopathy

- Type1 Diabetes :Within **5 years** after diabetes onset
- Type 2 Diabetes :**At the time** of diabetes diagnosis
- Follow-up Screening:No retinopathy + good glycemic control → Every 1–2 years may be considered
- Any level of retinopathy → At least annual dilated exam
- Progressing or sight-threatening DR → More frequent exams (as advised by ophthalmologist)
- interval can be individualized – but never skip annual screening when retinopathy is present.”

Retinopathy (Type 1)

An initial dilated and comprehensive eye examination is recommended once youth have had type 1 diabetes for 3–5 years, provided they are **aged ≥11** years or **puberty has started**, whichever is earlier. **B**

After the initial examination, repeat dilated and comprehensive eye examination **every 2 years**. Less frequent examinations, every 4 years, may be acceptable on the advice of an eye care professional and based on risk factor assessment, including a history of A1C<8% (<64 mmol/mol). **B**

GLP-1 Receptor Agonists and Retinopathy – Facts

- No direct association between GLP-1 RA use and diabetic retinopathy per se

Only significant association: Rapid and large HbA1c reduction (at 3 months > 1 %) → transient early worsening of retinopathy

Key Messages:

- Risk is related to **magnitude** and speed of HbA1c drop, not the drug class itself
- Early worsening phenomenon well-described (especially in patients with pre-existing moderate–severe DR)

Clinical Recommendation:

In patients with high-risk or active proliferative DR:

Gradual HbA1c reduction + close ophthalmologic monitoring in the first year of GLP-1 RA therapy

Diabetic Retinopathy and Special Population Pregnancy

Recommendations:

- Counsel **all** women of childbearing potential with T1DM or T2DM (planning or already pregnant) about risk of development and/or rapid progression of DR

Pregnancy can cause rapid worsening of pre-existing retinopathy, especially if glycemic control is intensified quickly.

Management of DR During Pregnancy

Recommended Eye Exam Schedule (Preexisting T1DM/T2DM):

- Ideally **before** conception (pre-pregnancy counseling)
- 1st trimester (mandatory)
- **Every trimester** until delivery
- Follow-up at 3–6–12 months postpartum (risk persists up to 1 year)

Treatment Considerations:

- Laser photocoagulation: **Safe** and preferred for high-risk PDR or center-involved DME
- Anti-VEGF injections:
  - Only if potential benefit clearly outweighs fetal risk
  - All currently available agents are FDA Pregnancy Category C
  - Theoretical risk to fetal vasculature → use with extreme caution

Treatment of Diabetic Retinopathy

- PRP remains standard for high-risk PDR (especially when anti-VEGF access is limited)
- Macular focal/grid laser = second-line for persistent/non-center-involved DME

Treatment of Diabetic Retinopathy

Condition	Action	Evidence
Any diabetic macular edema (DME)	Urgent referral to retina specialist	A
Moderate NPDR or worse	Prompt referral (precursor to PDR)	A
Any proliferative DR (PDR)	Immediate referral to experienced ophthalmologist	A
Center-involved DME with vision loss	Anti-VEGF = first-line treatment	A
Persistent DME despite anti-VEGF	Macular laser or intravitreal corticosteroid (2nd line)	A
High-risk PDR	Panretinal photocoagulation (PRP) – still indicated	A
Selected PDR cases (especially with DME)	Anti-VEGF injections = reasonable alternative or adjunct to PRP	A
Aspirin for cardioprotection	Continue – NO increased risk of retinal hemorrhage	A

Anti-VEGF vs. Panretinal Photocoagulation forPDR

Outcome (2–5 year follow-up)	Anti-VEGF (mainly aflibercept/ranibizumab)	Panretinal Laser (PRP)
Visual acuity	Non-inferior or superior	Reference
Regression of neovascularization	Faster and more complete	Slower
Peripheral visual field loss	Significantly less	More pronounced
Risk of new or worsening DME	Lower	Higher
Need for vitrectomy	Lower	Higher
Number of visits & injections	Substantially higher (monthly–bimonthly initially)	2–4 sessions total
Risk if patient is lost to follow-up	Severe rebound & vision loss	Lower risk

Anti-VEGF in Non-Proliferative DR

Anti-VEGF in Moderate–Severe NPDR (no DME):**≥50%** reduction in risk of new PDR or center-involved DME at 2 years

Significant improvement in DRSS (Diabetic Retinopathy Severity Scale) ≥2 steps

Vision-preserving strategy for high-risk NPDR patients

Current Status (2026):FDA-approved indication: “Treatment of diabetic retinopathy” (aflibercept, ranibizumab)Real-world use increasing in patients with:**Severe NPDR + poor follow-up likelihood**

Need to avoid PRP side effects (night vision, DME worsening)

Anti-VEGF

- FDA-Approved Anti-VEGF for DR (without DME):
- Aflibercept (Eylea®)Ranibizumab (Lucentis®)

Choosing Between Anti-VEGF and PRP in PDR Practical Algorithm

Prefer Anti-VEGF First

- Center-involved or high-risk DME present
- Patient values peripheral vision & driving
- Monocular patient or high visual demands
- Willing & able to attend frequent visits

Prefer PRP First or Early

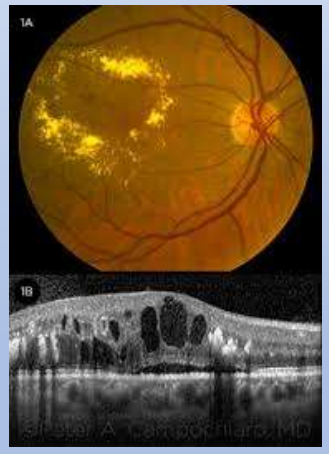
- Good compliance unlikely
- Limited access to monthly injections
- Active neovascularization with traction risk
- Cost/access barriers to anti-VEGF

Treatment of Diabetic Macular Edema (DME)

Center-Involved DME: Anti-VEGF is First-Line Therapy

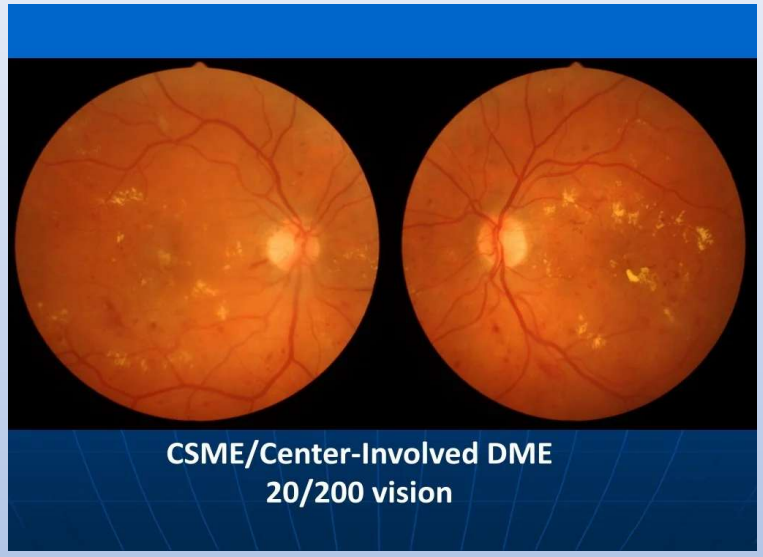
Key Evidence (Level A):

- Anti-VEGF monotherapy > focal/grid laser alone
- Anti-VEGF in NPDR without DME → prevents progression but does **not** improve vision → not routinely recommended



Special Cases:

- Good vision (≥20/25) + center-involved DME → Observation ± deferred anti-VEGF (Protocol V)
- Pregnancy → Laser or observation (anti-VEGF contraindicated)



Systemic Factors That Slow Retinopathy Progression

Intervention	Effect on Retinopathy Progression	Key Trials / Evidence
Blood pressure control	↓ Progression (target <140/90; <130/80 if tolerated)	UKPDS, ACCORD-Eye
Systolic <120 mmHg	No additional benefit vs. <140 mmHg	ACCORD-Eye
Fenofibrate 160 mg/day	↓ Progression by ~30–40%, especially in early DR Strongest benefit if baseline mild–moderate NPDR	FIELD, ACCORD-Eye
GLP-1 RA	↓ Intraocular pressure, possible ↓ risk of glaucoma	

Take-Home Messages

1. Refer immediately if: any DME, ≥ moderate NPDR, or any PDR
2. Anti-VEGF is now first-line for center-involved DME and many PDR cases
3. PRP laser remains essential for high-risk PDR (especially resource-limited settings)
4. Aspirin for CVD protection is safe – do NOT stop because of retinopathy
5. Early referral + modern therapy → >95% of patients keep useful vision

Diabetic neuropathy

Diabetic neuropathy

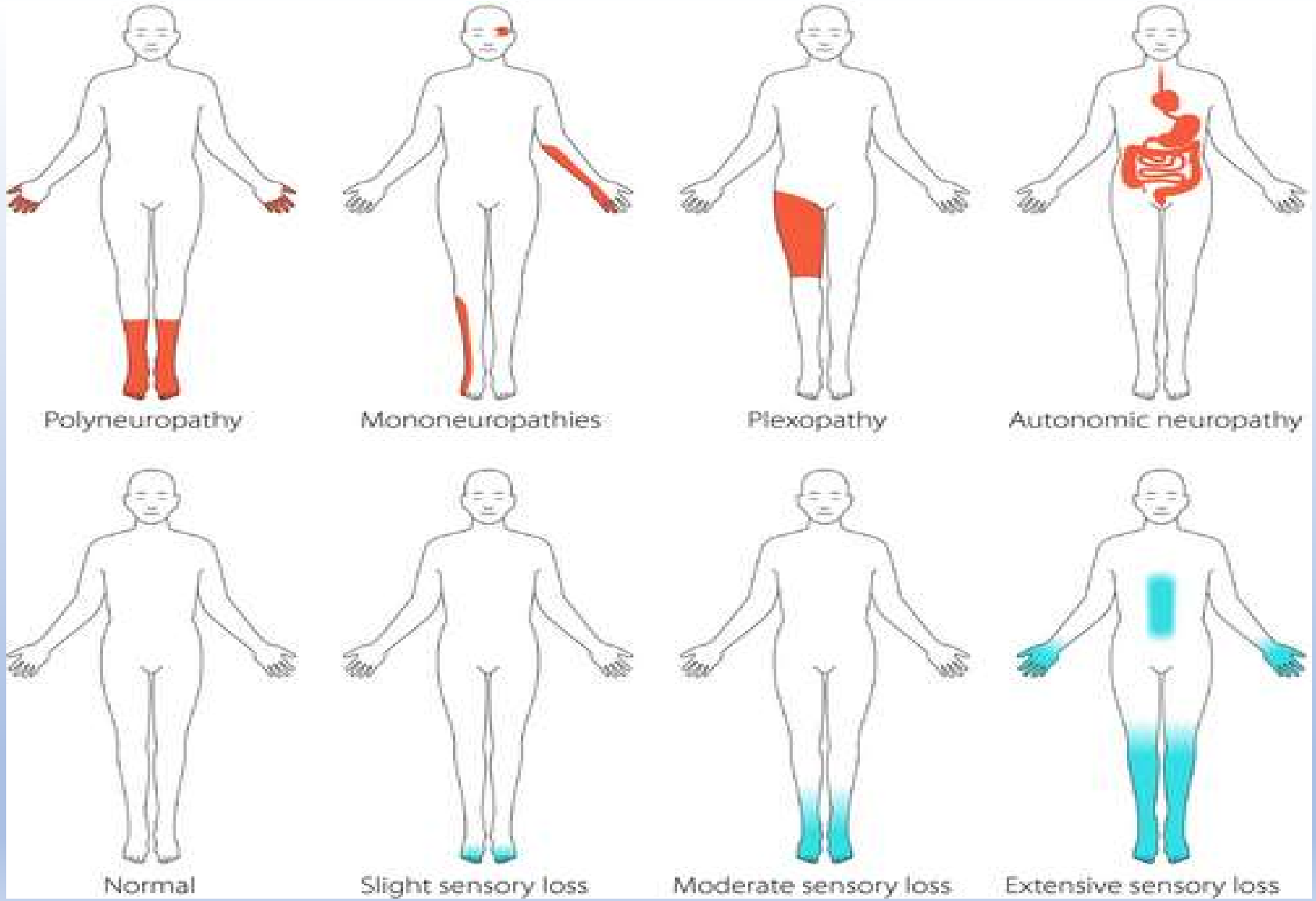
- Microvascular complication of diabetes mellitus (DM)
  Approximately **50%** of persons with longstanding type 1 DM or type 2 DM develop symptomatic neuropathy.
- Subclinical disease may be present in an even higher percentage of patients.
- Usually becomes apparent after 5-10 years of diabetes
- As cause of hospitalization

Risk factors

- Longer duration of diabetes mellitus
- Higher glycated hemoglobin levels
- Hypertension
- Obesity
- Dyslipidemia
- Tobacco use
- Chronic alcohol use
- Taller patient height
- Older age

Classification of diabetic neuropathies

Diffuse neuropathy	Mononeuropathy	Radiculopathy	Other neuropathies
DPN primarily **small** fiber	Isolated **cranial** or **peripheral** neuropathy	**Thoracic** radiculoneuropathy	Pressure neuropathies Entrapment
DPN primarily **large** fiber	Mononeuritis multiplex	**Radiculoplexus** neuropathy	CIDP
DPN **mixed** small and large fiber		diabetic amyotrophy	Acute treatment induced neuropathy
DPN and autonomic neuropathy			


Polyneuropathy
Mononeuropathies
Plexopathy
Autonomic neuropathy
Normal
Slight sensory loss
Moderate sensory loss
Extensive sensory loss

Distal symmetric polyneuropathy

- sensorimotor polyneuropathy ***Motor symptoms are less common***
- Up to **50%** of patients, may be **asymptomatic**
- progressive reduction in the intra epidermal nerve fibers
- this reduction is seen even in persons with prediabetes
- up to one quarter of persons with IGT
- increases with both age and duration of diabetes, and obesity.

How to Diagnose DPN in Daily Practice

Who & When

- Type 2 diabetes → start at diagnosis
- Type 1 diabetes → start 5 years after diagnosis
- Then: **annual assessment in every patient**

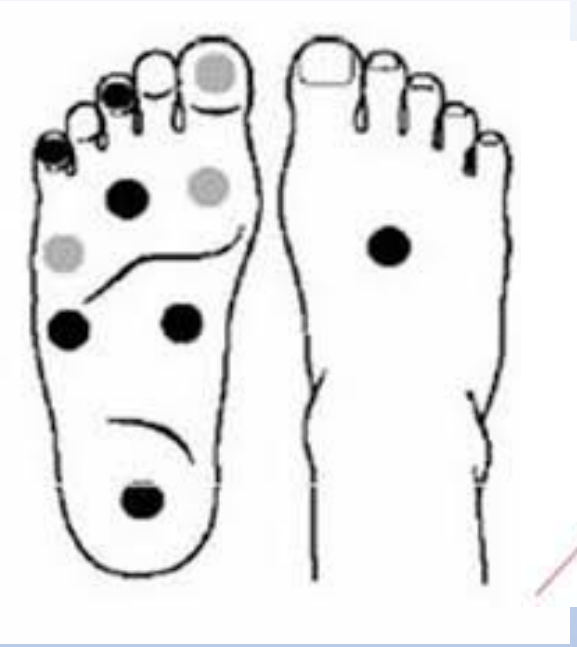
Typical Symptoms

- Small-fiber (early): burning pain, tingling, dysesthesia
- Large-fiber (later): numbness, imbalance, loss of protective sensation (LOPS)

Minimum Required Clinical Tests (2–3 minutes)

Red Flags → Refer to Neurology

- Acute/subacute onset
- Asymmetric or motor-predominant
- Non-length-dependent (proximal > distal)
- Rapid progression
- Always Rule Out Other Causes Alcohol | Chemotherapy | B12 deficiency | Hypothyroidism | CKD | Malignancy (myeloma, paraneoplastic) |HIV | CIDP | Vasculitis



Fiber Type	Test	What It Detects
Small fiber	Pinprick (safety pin)	Pain sensation
	Temperature (cold tuning fork)	Thermal sensation
Large fiber	128-Hz tuning fork (big toe)	Vibration perception
	Ankle reflexes	Large-fiber reflex arc
Protective sensation	10-g monofilament (4–6 sites/foot)	Risk of ulceration & amputation

Diabetic Neuropathy Screening

- History

❑DSPN : Pinprick or temperature: 128-Hz tuning fork, 10-g monofilament

❑Autonomic neuropathy:

- Orthostatic BP
- Resting HR
- Symptoms (ED, gastroparesis, sweating abnormalities)

Neuropathy, Why Screening Actually Matters

1. **Diagnosis of exclusion** → Rule out B12 deficiency, alcohol, hypothyroidism, chemotherapy, monoclonal gammopathy, etc. – many are treatable!
2. **≥50% of DPN is completely asymptomatic** → Silent until ulcer or amputation occurs → Annual 10-g monofilament + 128-Hz fork = prevents 50–80% of amputations
3. **Autonomic neuropathy is treatable symptomatically** → Early recognition improves quality of life (midodrine, fludrocortisone, sildenafil, pyridostigmine, etc.)

Annual 2-minute foot + neuropathy screen saves toes, feet, and lives

“No symptoms” ≠ “no neuropathy”

Risk classification based on the comprehensive foot examination

Category	Ulcer Risk	Characteristics	Frequency
0	Very low	No LOPS and No PAD	Once a year
1	Low	LOPS or PAD	Once every 6-12 months
2	Moderate	LOPS + PAD, *or* LOPS + foot deformity, *or* PAD + foot deformity	Once every 3-6 months
3	High	LOPS or PAD, *and* one or more of the following: ✓ - history of a foot ulcer ✓ - a lower-extremity amputation (minor or major) ✓ - end-stage renal disease	Once every 1–3

Annual Diabetic Foot Examination – What You Must Do in <3 Minutes

Component	How to Do It (quickly)
Inspection	Skin integrity, callus, fissure, infection, deformity
Deformities	Hammer/claw toes, bunions, Charcot, prominent metatarsals
Neurology – LOPS	10-g monofilament (4–6 sites/foot) + ONE of: pinprick, temperature, 128-Hz tuning fork, ankle reflexes
Vascular	Dorsalis pedis & posterior tibial pulses, capillary refill, rubor on dependency
Footwear check	Ill-fitting shoes, walking barefoot

Immediate Podiatry / Multidisciplinary Foot Clinic Referral

Any ONE of these = high risk:

- Loss of protective sensation (LOPS)
- Prior ulcer or amputation
- Foot deformity + neuropathy
- PAD (absent pulses or toe pressure <50 mmHg)
- Charcot foot
- End-stage renal disease / dialysis
- Active smoker with any neuropathy

Plus: Provide therapeutic footwear (custom insoles, depth shoes, rocker soles)

Chronic Diabetic Foot Ulcer Treatment Algorithm

Optimal standard care × 4–6 weeks

(Off-loading + debridement + infection control + perfusion optimisation)

↓ No healing (>50% area reduction)

↓

Adjunctive advanced therapy (choose one or combine):

- **Negative-pressure wound therapy (NPWT/VAC)**
- **Placental membranes (Grafix, EpiFix)**
- **Bioengineered living skin (Apligraf, Dermagraft)**
- **Acellular dermal matrices**
- **Autologous platelet-rich fibrin**
- **Topical oxygen therapy (e.g., EPO)**

↓

Still no closure → consider HBOT, surgery, or clinical trial

Five Pillars of Diabetic Foot Ulcer Treatment

Pillar	Action
1 Off-loading	TCC, irremovable walker, or surgical off-loading
2 Debridement	Sharp weekly debridement of callus & necrotic tissue
3 Infection control	Culture-guided antibiotics (deep swab or tissue); treat osteomyelitis
4 Revascularisation	Angiography + endovascular or bypass if toe pressure <50 mmHg or $TcPO_2$ <40 mmHg
5 Wound physiology	Moist wound healing dressings (collagen, hyaluronic acid, etc.)

Rule of 50% If

- If <50% area reduction after 4 weeks of optimal standard care → start advanced wound therapy

Advanced Wound Therapies

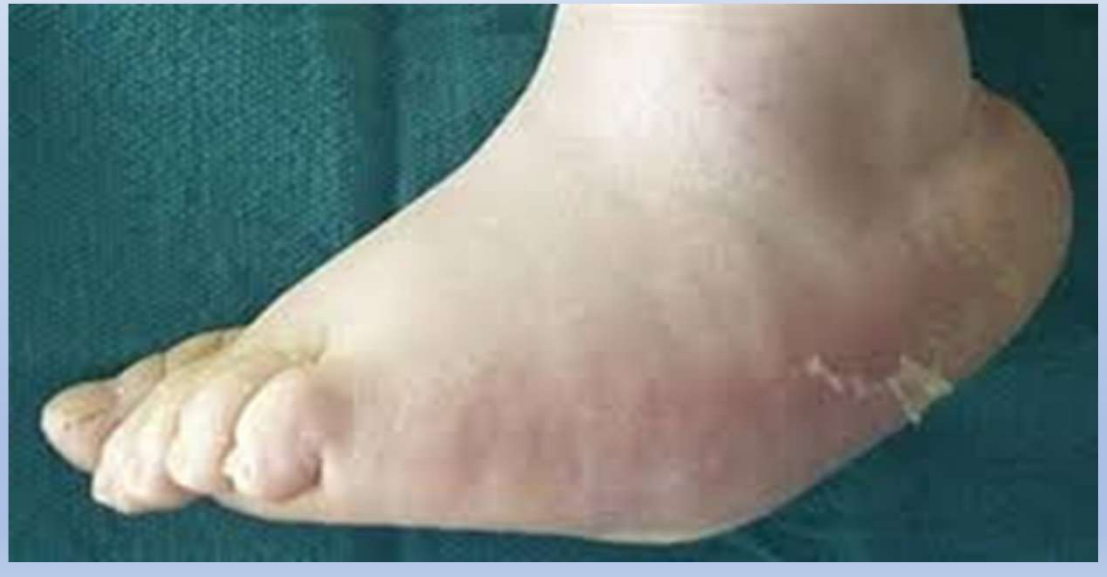
Therapy	Best Evidence (2025)	Typical Indication
Negative-pressure wound therapy (NPWT)	Strong (multiple RCTs)	Deep, large, or post-surgical wounds
Placental membranes (e.g., Grafix, EpiFix)	Strong (RCTs + meta-analyses)	Clean, superficial–moderate depth ulcers
Bioengineered skin (Apligraf, Dermagraft)	Strong	Chronic, non-infected ulcers
Topical oxygen therapy (continuous or cyclical)	Very strong (5+ meta-analyses)	Home-based, non-healing ulcers after 4 weeks
Hyperbaric oxygen (HBOT)	Weak–moderate (only selected neuro-ischemic)	Salvage in severe ischemia + infection

Therapeutic Footwear & Off-Loading

Patient Group	Recommended Footwear	Evidence Summary (2025)
LOPS + deformity or prior ulcer	Extra-depth shoes + custom multidensity insoles	↓ peak plantar pressure 20–40%
Recurrent ulcers despite good shoes	Custom molded shoes + rocker sole or rigid forefoot	↓ recurrence rate in observational studies
Active plantar ulcer	Total contact cast (TCC), removable cast walker, forefoot off-loading shoe	Gold standard – heals 80–90% in 6–12 weeks

Charcot arthropathy

Collaps of the arch of the midfoot and bony prominences leading to fragmentation and sclerosis of bone,new bone formation,subluxation, dislocation, and stress fractures.



Charcot arthropathy

- **Classic Presentation** Warm, red, swollen foot (often 5–10°C warmer than contralateral) ± minor trauma history No open wound X-ray may be normal in first 2–4 weeks
- **Immediate Actions (2026)**
- Total non-weight-bearing (TCC or pneumatic walker with crutches)
- Urgent referral to diabetic foot specialist (same week)
- Serial X-rays/MRI if diagnosis uncertain
- Bisphosphonates (controversial – not routine)
- **Long-term** Custom shoes or surgical reconstruction when stable

Neuropathy Treatment: Prevention First, Symptom Control Second

Intervention	Type 1 Diabetes	Type 2 Diabetes	Evidence
Intensive glucose control	Strongly prevents DPN & CAN	Modestly slows progression	A / C
Weight loss + exercise	↓ Risk & progression	↓ Risk & progression	B
Blood pressure control	↓ Progression	↓ Progression	B
Statin + fenofibrate (if indicated)	↓ Progression	↓ Progression	B

First-Line Drugs for Diabetic Neuropathic Pain (Level A/B)

Drug Class	Examples (starting doses)	Notes
Gabapentinoids	**Pregabalin 150–300 mg/day** **Gabapentin 900–3600 mg/day**	**Titrate slowly; renal dosing essential**
SNRI	**Duloxetine 60 mg/day** **Desvenlafaxine 50–100 mg**	**Best evidence; also helps depression**
Tricyclic antidepressants	**Amitriptyline 25–100 mg HS** **Nortriptyline 25–100 mg HS**	**Cheapest; watch anticholinergic side effects**
Sodium channel blockers	**Valproate 500–1500 mg/day** **Lacosamide 200–400 mg/day**	**Useful add-on or alternative**

Beyond First-Line: What We Actually Use When Initial Drugs Fail

Therapy	Evidence Level	Practical Notes
Sodium channel blockers (lacosamide, valproate, oxcarbazepine)	Moderate	Useful 2nd/3rd line; watch Na^+, mood, weight
Capsaicin 8% patch (Qutenza®)	High (1 RCT)	Excellent for localised foot pain; needs clinic application, 60 min with local anaesthetic
Capsaicin 0.075% cream	Moderate	Over-the-counter; 3–4× daily; burning on application
Lidocaine 5% plaster	Limited	Only for very focal nocturnal foot pain; max 12 h/day
Opioids (oxycodone, morphine, tramadol, tapentadol)	Effective short-term → NOT recommended	AAN, CDC, ADA: risks >> benefits → avoid

Practical Pain Management Algorithm

Patient reports burning, shooting, or electric pain in feet/hands

↓

Step 1 → **Start ONE first-line agent** (most choose **duloxetine** or **pregabalin**)

↓

Titrate to effective dose or maximum tolerated (4–8 weeks)

↓

No or partial relief?

↓

Step 2 → Switch to different class OR combine 2 classes (e.g., **duloxetine + gabapentin**)

↓

Still uncontrolled?

↓

Step 3 → Refer to multidisciplinary pain clinic

→ Consider topical capsaicin 8%, spinal cord stimulation, etc.

Patient & Caregiver Foot Care Education

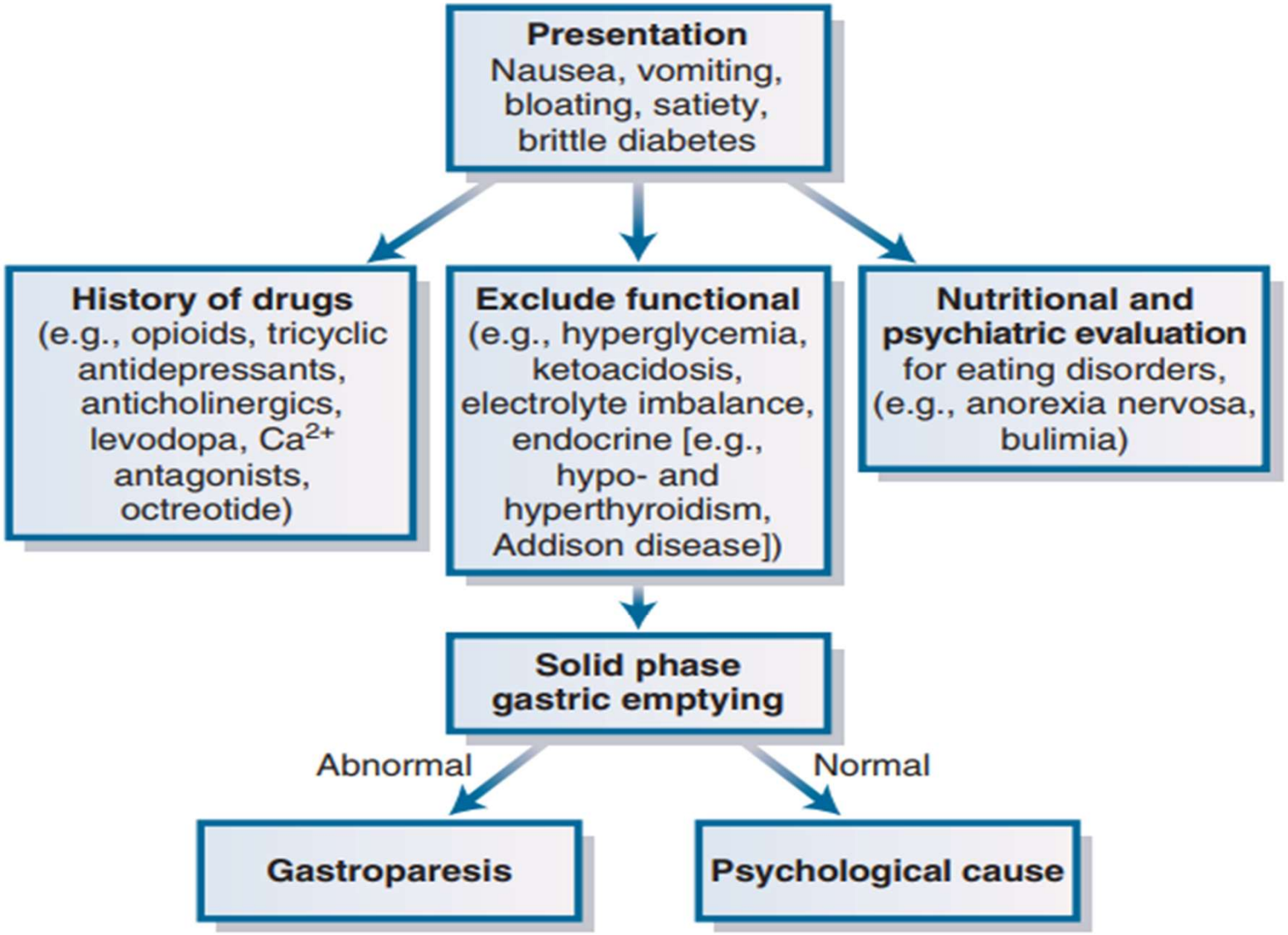
Topic	What to Teach Patients & Families
Daily foot inspection	Use mirror or ask family member Look for cuts, blisters, redness, swelling
Skin & nail care	Moisturise daily (not between toes) Never cut calluses or ingrown nails yourself
Footwear	Never barefoot – even at home No open-toe sandals or flip-flops Check inside shoes daily
Temperature awareness	Don’t use hot water bottles or heating pads Test bath water with elbow
When to call immediately	Any sore, blister, cut that is not healing in 24–48 h New redness/swelling/warmth

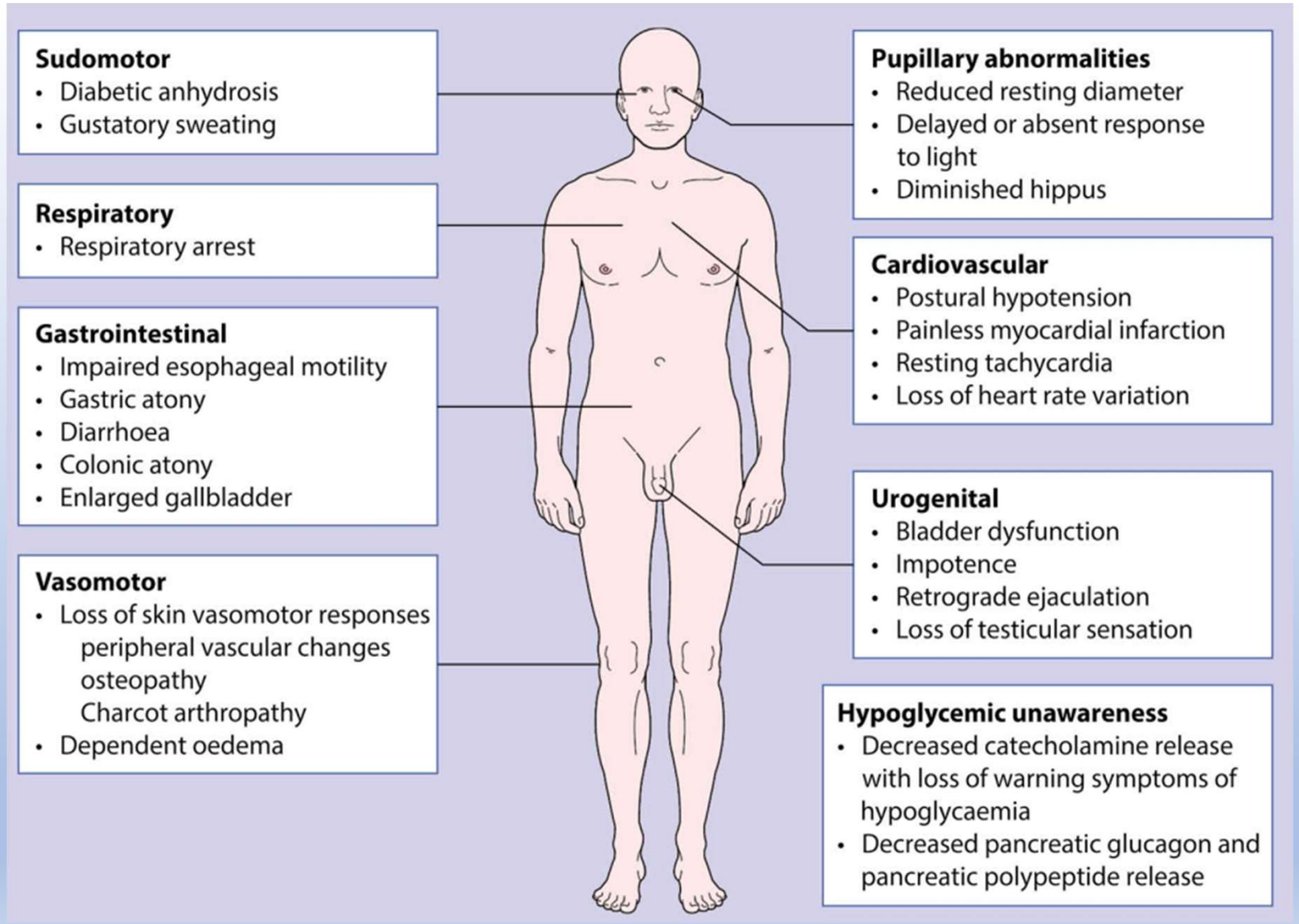
Autonomic Neuropathy

Don’t Miss the Silent Killer of Quality of Life

Screening Timing Same as DPN:

T2DM at diagnosis, T1DM from year 5 → annually


Presentation
Nausea, vomiting, bloating, satiety, brittle diabetes
History of drugs
(e.g., opioids, tricyclic antidepressants, anticholinergics, levodopa, Ca^{2+} antagonists, octreotide)
Exclude functional
(e.g., hyperglycemia, ketoacidosis, electrolyte imbalance, endocrine [e.g., hypo- and hyperthyroidism, Addison disease])
Nutritional and psychiatric evaluation
for eating disorders, (e.g., anorexia nervosa, bulimia)
Solid phase gastric emptying
Abnormal
Normal
Gastroparesis
Psychological cause


Sudomotor
• Diabetic anhydrosis
• Gustatory sweating
Respiratory
• Respiratory arrest
Gastrointestinal
• Impaired esophageal motility
• Gastric atony
• Diarrhoea
• Colonic atony
• Enlarged gallbladder
Vasomotor
• Loss of skin vasomotor responses
peripheral vascular changes
osteopathy
Charcot arthropathy
• Dependent oedema
Pupillary abnormalities
• Reduced resting diameter
• Delayed or absent response to light
• Diminished hippus
Cardiovascular
• Postural hypotension
• Painless myocardial infarction
• Resting tachycardia
• Loss of heart rate variation
Urogenital
• Bladder dysfunction
• Impotence
• Retrograde ejaculation
• Loss of testicular sensation
Hypoglycemic unawareness
• Decreased catecholamine release with loss of warning symptoms of hypoglycaemia
• Decreased pancreatic glucagon and pancreatic polypeptide release

Autonomic Neuropathy

•Resting tachycardia (>100 bpm)
•Orthostatic hypotension (≥20/10 mmHg drop)
•Dry, cracked feet (anhidrosis)

Advanced Testing Only If Symptomatic

•Cardiovagal tests
•QSART (sweat function)
•Gastric emptying study
•Urodynamics
•Impaired hypoglycemia awareness is usually due to recurrent hypoglycemia, **not** autonomic neuropathy.

Autonomic Neuropathy

System	Symptoms to Screen For
Cardiovascular	Orthostatic dizziness, syncope, exercise intolerance
Gastrointestinal	Early satiety, persistent nausea, alternating constipation/diarrhea
Genitourinary	Erectile dysfunction, urinary retention/incontinence, recurrent UTI
Sudomotor	Anhidrosis (dry feet), gustatory sweating, heat intolerance

Objective testing for neuropathy

- **Measurement of nerve-conduction velocities NCV**
- **Quantitative measures of small fiber nerves:**
- **Quantitative sensory testing**

❖**Vibratory Testing Device**

❖**Thermal Sensory Analyzer**

➢**Skin Bx**

➢**OCT (Optical Coherence Tomography)**

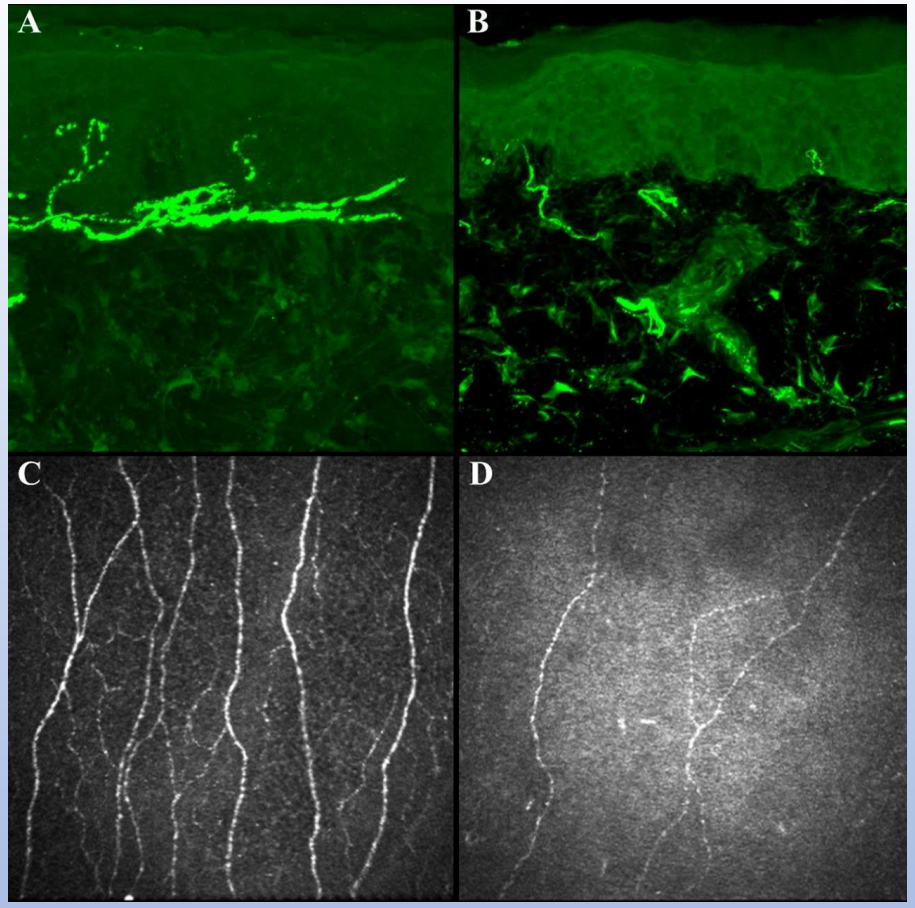
➢**Sudomotor test**

- **Tests of autonomic function** is required to make a definitive diagnosis of neuropathy, although it is not essential for clinical care.

- Quantitative assessment of small fiber damage is key to the early diagnosis and assessment of progression or regression of diabetic sensorimotor polyneuropathy (DSPN).

- Intraepidermal nerve fiber density (IENFD) is the current gold standard, but corneal confocal microscopy (CCM), an in vivo ophthalmic imaging modality, has the potential to be a noninvasive and objective image biomarker for identifying small fiber damage

Quantitative measures of small fiber nerves.



Roni M. Shtein, and Brian C. Callaghan Diabetes 2013;62:25-26

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Cardiovascular Autonomic Neuropathy (CAN) – The Silent Prognostic Marker

- Independent predictor of cardiovascular death and all-cause mortality (even after adjusting for traditional risk factors)
- 5-year mortality in symptomatic CAN: up to 25–50%

- Management Focus Symptom relief (midodrine, fludrocortisone, droxidopa) + aggressive CV risk factor control

Cardiovascular Autonomic Neuropathy

Stage	Clinical Findings	Screening / Diagnosis
Subclinical (early)	↓ Heart rate variability on deep breathing	Only detectable by formal autonomic testing
Clinical	Resting tachycardia (>100 bpm)	Simple office sign
Advanced	Orthostatic hypotension (SBP ↓ ≥20 mmHg or DBP ↓ ≥10 mmHg on standing)	Measure BP lying → standing at 3 min

Gastrointestinal Autonomic Neuropathy

Manifestation	Typical Symptoms / Signs	Diagnostic Approach
Esophageal dysmotility	Dysphagia, heartburn	Rarely needs specific testing
Gastroparesis	Early satiety, nausea, vomiting, erratic glucose	4-hour gastric emptying scintigraphy (gold standard) or ^{13}C-octanoic acid breath test
Chronic constipation	<3 bowel movements/week	Rule out opioids, calcium-channel blockers
Diabetic diarrhea	Explosive watery nocturnal diarrhea	Exclude celiac, bile-acid malabsorption, SIBO
Fecal incontinence	Involuntary leakage	Due to internal anal sphincter dysfunction

Genitourinary Autonomic Neuropathy

Problem	Prevalence / Presentation	Practical Management
Erectile dysfunction (men)	50–75% of men with long-standing diabetes	PDE5 inhibitors (safe), rule out testosterone deficiency
Retrograde ejaculation	Dry orgasm, cloudy urine after intercourse	Alpha-blocker related or autonomic
Female sexual dysfunction	↓ Desire, arousal, lubrication, dyspareunia	Lubricants, flibanserin, local estrogen if post-menopausal
Neurogenic bladder	Urgency, frequency, weak stream, overflow incontinence, recurrent UTI	Urodynamics if recurrent pyelonephritis or palpable bladder

Autonomic Neuropathy Screening Checklist (2 Minutes/Year)

Ask every patient annually:

1. “Any dizziness when standing up quickly?”
2. “Any persistent nausea or feeling full very quickly?”
3. “Any new erectile problems or reduced sexual interest?”
4. “Any change in sweating (feet too dry or face sweating when eating)?”

Examine:

- Resting heart rate (>100 → suspect CAN)
- Lying → standing BP at 3 minutes
- Feet for dryness/cracking (sudomotor dysfunction)

Early detection dramatically improves quality of life and may reduce mortality.

Treating Orthostatic Hypotension (CAN)

Step	Action
1 Always first	Stop offending drugs: opioids, GLP-1 RA, pramlintide, anticholinergics, TCAs
2 Diet	Small-particle, low-fat, low-fibre diet (blended foods, soups, smoothies)
3 Drug (only if severe)	• Metoclopramide 5–10 mg TID (max 12 weeks – FDA black box for tardive dyskinesia) • Erythromycin 200–250 mg TID (short-term only – tachyphylaxis) • Domperidone 10 mg TID (outside US, compassionate use)
4 Refractory	Pyloric Botox (limited evidence), G-POEM, gastric electrical stimulation (not recommended in diabetes)

Erectile & Sexual Dysfunction – Treatment Ladder

Problem	First-Line	Second-Line & Beyond
Erectile dysfunction (men)	PDE5 inhibitors (sildenafil, tadalafil daily or on-demand)	Intra-cavernosal alprostadil, vacuum device, penile prosthesis
Female sexual dysfunction	Education, lubricants, local estrogen (post-menopausal)	Flibanserin, bremelanotide (if desire disorder)
Hypogonadism	Testosterone replacement only if confirmed low T + symptoms	–

Diabetic Kidney Disease (DKD)

Leading cause of end-stage kidney disease (ESKD) worldwide

2–4× increased cardiovascular mortality

Prevalence: **30–40%** in type 2 diabetes **20–30%** in type 1DM

Good news: Progression is preventable and modifiable!

Epidemiology of Diabetes and Chronic Kidney Disease

Persistent albuminuria or **eGFR <60 mL/min/1.73 m²**

- Most common cause of end-stage kidney disease (ESKD) in the United States
- Leading indication for dialysis or kidney transplantation in most countries
- Presence of CKD in diabetes dramatically **increases cardiovascular risk**
- CKD significantly raises healthcare costs in both type 1 and type 2 diabetes

Screening Recommendations

Type 1 diabetes **≥5** years duration

All patients with type 2 diabetes (regardless of treatment) **Annual** assessment of: →

- Spot urine albumin-to-creatinine ratio (UACR)
- Estimated glomerular filtration rate (eGFR)

Monitoring in Established CKD

Frequency of UACR + eGFR monitoring:

- Stage G1–G2: **1–2** times/year
- Stage G3**: 2–3** times/year
- Stage G4–G5: **3–4** times/year

Foundational Therapies

- **Optimized glycemic control → slows CKD progression**
- **Blood pressure control ,Target <130/80 mmHg – Reduce BP variability → ↓ CV and renal risk**

RAS Blockade , When and How

- Moderately increased albuminuria (UACR 30–299 mg/g): ACEi or ARB recommended (B)
- Severely increased albuminuria (UACR ≥300 mg/g) and/or eGFR <60: Strongly recommended, **maximal tolerated dose** (A)
- **NOT** recommended for primary prevention in normotensive, normoalbuminuric patients (A)
- Accept **≤30%** rise in creatinine if no volume depletion (A)

Monitoring During RASi / MRA / Diuretics

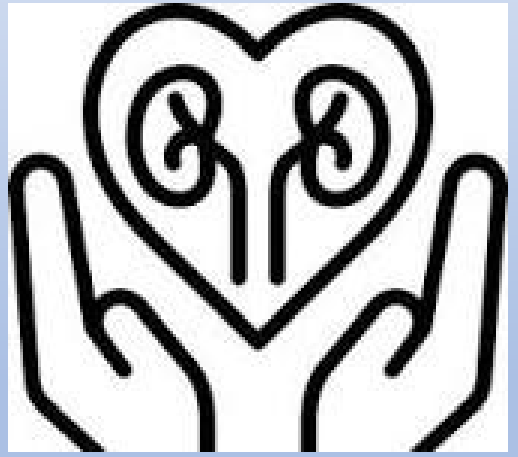
Check at **7–14 days** after initiation or dose increase:

- ✓**Serum creatinine & eGFR**
- ✓**Serum potassium** (ACEi/ARB/MRA), (diuretics → risk of hypokalemia)

Kidney + Cardiovascular Protection: New Pillars

- **SGLT2 inhibitors :**Recommended if **eGFR ≥20** mL/min/1.73 m^2 (A)
- **GLP-1 receptor agonists :**Proven CV and renal benefit (A)
- **Non-steroidal MRA (finerenone) :**In CKD + albuminuria :

If **eGFR ≥25** ,Monitor potassium closely (A)



Albuminuria Target

Aim for **≥30%** reduction in UACR in patients with albuminuria ≥300 mg/g → Strongly associated with slower CKD progression

Nutrition in CKD

Non-dialysis CKD (G3 or higher): Protein intake **0.8 g/kg/day** (same as general population) (A)

Dialysis patients: **1.0–1.2 g/kg/day** (to prevent protein-energy wasting) (B)

When to Refer to Nephrology

Urgent/strong referral (A):

- eGFR **<30** mL/min/1.73 m^2
- Continuously rising UACR or falling eGFR Also consider referral (B):
- Uncertain etiology
- Difficult management (resistant HTN, hyperkalemia, etc.)
- Rapidly progressing kidney disease

When to Suspect Alternative or Additional Causes

Active urinary sediment (RBCs, WBCs, cellular casts)

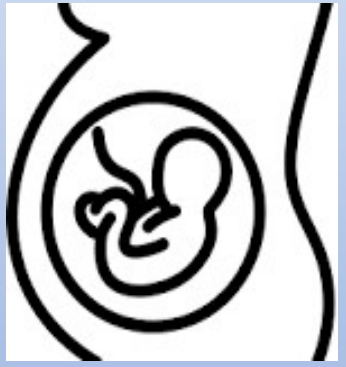
- Rapidly increasing albuminuria or total proteinuria
- Nephrotic-range proteinuria (>3.5 g/day)
- Rapidly decreasing eGFR **(>5 mL/min/1.73 m^2 per year or >30% in <6–12 months)**
- Absence of retinopathy **in type 1 diabetes** (very rare for pure DKD)
- Onset of kidney disease <5 years after type 1 diabetes diagnosis
- Signs/symptoms of systemic disease (e.g., rash, arthritis, positive ANA, low complement)
- In these cases: **Early nephrology referral ± kidney biopsy strongly recommended**

Practical Referral Thresholds & Timing
2025 Referral Algorithm – “Don’t Wait Until Dialysis”

Clinical Scenario	Recommended Action
eGFR <30 mL/min/1.73 m²	Refer immediately
Rapid eGFR decline (>5 mL/min/year)	Refer urgently
Persistent UACR increase despite four pillars	Refer within weeks
Resistant hypertension or refractory hyperkalemia	Refer now
Unexplained active urinary sediment	Refer for consideration of biopsy
Stage 3 CKD (eGFR 30–59) + complications	Consider early referral

Special Situations

- Pregnancy planning: Avoid ACEi/ARB/MRA/SGLT2i → Switch to safer agents before conception (B)
- Sexually active individuals of childbearing potential: Reliable contraception or alternative agents



Assessment of Albuminuria

- Preferred method: **Spot urine albumin-to-creatinine ratio (UACR)** in a random sample
- Timed (4-h or 24-h) collections: more burdensome, no added accuracy → not recommended
- Albumin-only dipstick or immunoassay (without creatinine): cheaper but high false ± due to hydration variability
- Normal: UACR <30 mg/g Cr
- Moderately increased: 30–299 mg/g Cr
- Severely increased: ≥300 mg/g Cr

- UACR is a **continuous risk marker** , even values within “normal” range predict outcomes

Confirming Albuminuria

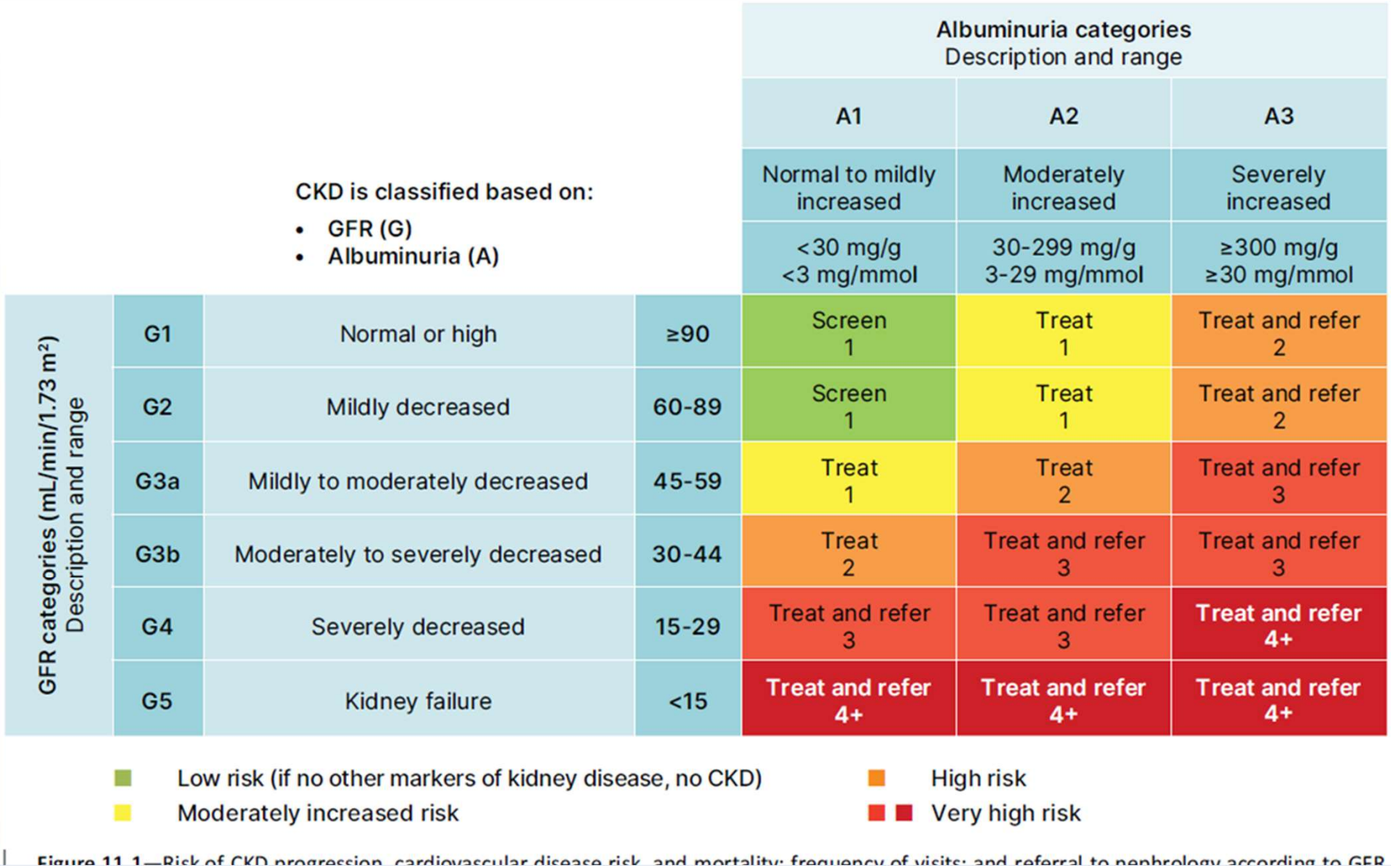
- High biological day-to-day variability of urinary albumin excretion (>20%)
- Diagnosis of moderately or severely increased albuminuria requires: → **≥2 out of 3 abnormal UACR specimens** collected within 3–6 months
- Transient elevations of UACR may be caused by: → **Exercise** <24 h, **infection**, **fever**, **CHF**, **marked hyperglycemia**, **menstruation**, **severe hypertension**
- Recent studies: significant week-to-week variability → **trend over time is more important than single value**
- Target in treatment: ≥30% sustained UACR reduction strongly linked to slower CKD progression
- Always interpret UACR in clinical context and repeat when confounding factors are present

Assessment of eGFR

Estimated Glomerular Filtration Rate (eGFR)

Routinely calculate eGFR from serum creatinine using validated equations

- Use the **2021 CKD-EPI creatinine equation (refitted without race coefficient)** for all patients
- Race is a social, not biological construct → race-based equations no longer recommended
- Abnormal eGFR: persistently <60 mL/min/1.73 m^2
- eGFR calculators freely available (nkdep.nih.gov or NKF website)
- **In adults >70 years: clinical significance of eGFR 45–59 without albuminuria is debated**
- Report both eGFR and UACR together for complete kidney risk stratification



CKD is classified based on:

- GFR (G)
- Albuminuria (A)

GFR categories (mL/min/1.73 m²) Description and range				Albuminuria categories Description and range		
				A1	A2	A3
				Normal to mildly increased	Moderately increased	Severely increased
				<30 mg/g <3 mg/mmol	30-299 mg/g 3-29 mg/mmol	≥300 mg/g ≥30 mg/mmol
	G1	Normal or high	≥90	Screen 1	Treat 1	Treat and refer 2
	G2	Mildly decreased	60-89	Screen 1	Treat 1	Treat and refer 2
	G3a	Mildly to moderately decreased	45-59	Treat 1	Treat 2	Treat and refer 3
	G3b	Moderately to severely decreased	30-44	Treat 2	Treat and refer 3	Treat and refer 3
	G4	Severely decreased	15-29	Treat and refer 3	Treat and refer 3	**Treat and refer 4+**
	G5	Kidney failure	<15	**Treat and refer 4+**	**Treat and refer 4+**	**Treat and refer 4+**

Low risk (if no other markers of kidney disease, no CKD)
Moderately increased risk
High risk
Very high risk

Figure 11.1—Risk of CKD progression, cardiovascular disease risk, and mortality; frequency of visits; and referral to nephrology according to GFR

Staging of Chronic Kidney Disease in Diabetes

- **Stages G1 and G2:** **eGFR ≥60 mL**/min/1.73 m² **but only if albuminuria is present**
- **Stages G3–G5:** defined exclusively by progressively **lower eGFR (<60 → <15)**
- *At **any given eGFR**, the degree of albuminuria is a powerful independent predictor of: → Cardiovascular disease (CVD) → CKD progression → All-cause mortality*
- KDIGO recommendation :use **combined eGFR + albuminuria staging** (A1–A3) at all levels
- Combined staging is **more accurate for risk stratification** than eGFR alone, despite added complexity
- Both parameters **must be quantified** to guide: → Antihypertensive choice (especially RAS inhibitors) → Glucose-lowering therapy (SGLT2i, GLP-1 RA, finerenone) → Medication dose adjustment or contraindications
- Additional prognostic factors to consider: → Rate of historical eGFR decline → Etiology of kidney damage (diabetes vs. non-diabetic or mixed causes)

Acute Kidney Injury (AKI) in People with Diabetes

- Patients with DM have significantly higher risk of AKI
- **Common precipitating factors:**

➢ Pre-existing CKD→ NSAIDs, iodinated contrast agents

➢ Dehydration, sepsis, surgery

➢ Medications affecting renal hemodynamics (diuretics, ACEi/ARB)

SGLT2 inhibitors: initial concern about volume depletion → not confirmed in large RCTs (even in advanced CKD or high CV risk)

Non-steroidal MRAs (**finerenone**): do NOT increase AKI risk in landmark trials

- Early recognition and treatment of AKI is critical → AKI strongly predicts progression to CKD, CV events, and mortality
- Important distinction:→ ≤30% rise in serum creatinine after starting ACEi/ARB (or during intensive BP control) is hemodynamic and expected→ NOT true AKI
  Do NOT stop ACEi/ARB for creatinine rise ≤30% unless clear volume depletion or hyperkalemia is present

Rationale for Regular Monitoring of UACR & eGFR

- ✓Detect new-onset CKD at the earliest reversible stage
- ✓Monitor rate of CKD progression
- ✓Detect acute kidney injury (AKI) or superimposed kidney disease
- ✓Stratify cardiovascular and kidney risk
- ✓Guide medication dose adjustment and contraindications
- ✓Decide timing of nephrology referral
- ✓Assess response to renin-angiotensin system (RAS) blockade

UACR as a Therapeutic Target and Monitoring Tool

Annual quantitative UACR is in **all** patients with

Diagnosis of albuminuria→ Starting or up-titrating ACEi/ARB

Achieving BP target

Early rise in UACR often precedes eGFR decline

Reduce **UACR to <300** mg/g or **≥30%** reduction from baseline → improved renal & CV outcomes

Titrate ACEi/ARB (and other therapies) to maximally tolerated doses to achieve maximum UACR reduction

Primary Prevention of CKD in Diabetes

two proven primary prevention strategies for diabetic kidney disease:→ **Intensive glycemic control (A1C ≈7%)**

→ **Blood pressure control (target <130/80 mmHg)**

Routine use of RAS inhibitors solely for primary prevention is NOT recommended

SGLT2 inhibitors and finerenone: not studied nor recommended for primary prevention

Prevent CKD by preventing albuminuria : focus on glucose + BP first

Sodium, Potassium & Individualized Nutrition
Sodium and Potassium Management in Diabetic CKD

- **Sodium restriction**: **<2,300 mg/day** (ideally <2,000 mg if hypertension or volume overload) → helps BP and CV risk
- Individualize **potassium** intake based on: → Serum potassium levels → eGFR (especially <60) → Use of ACEi/ARB/MRA/SGLT2i/diuretics → Comorbidities and medications
- All dietary interventions should be **personalized** using: → Current blood pressure → Laboratory results (K^+, bicarbonate, etc.) → Medication list → Presence of edema or heart failure

Interventions that lower albuminuria

- Blood glucose management
- Blood pressure management
- Treatment with ACE inhibitors or ARBs
- Smoking cessation
- Weight loss
- Changes in eating patterns (decreased salt intake and/or protein intake)
- Treatment with SGLT2 inhibitors, MRAs, or GLP-1 RAs

ACEi / ARB: When Are They Strongly Indicated?

- UACR ≥300 mg/g + **hypertension** → **strongly recommended**, maximal tolerated dose
- UACR ≥**300 mg**/g + **eGFR <60** → **strongly recommended** (reduces progression to ESKD)
- UACR 30–299 mg/g + hypertension → **recommended** (slows progression to UACR ≥300 and CV events)
- Proven benefit even in advanced CKD (eGFR <30) – recent trials show mortality & ESKD reduction
- ACEi and ARB have **equivalent** renal & CV benefits
- **Do NOT combine ACEi + ARB** → no benefit, increased hyperkalemia & AKI (ONTARGET, VA NEPHRON-D)

Practical Monitoring When Using ACEi/ARB

- Check serum creatinine & potassium **7–14 days** after initiation or dose increase
- Acceptable: creatinine rise ≤30% without hyperkalemia or volume depletion
- Continue therapy if rise is ≤30%

Stop only if:

- **>30–40% acute rise + clinical suspicion of AKI**
- **Symptomatic hypotension**
- **Life-threatening hyperkalemia**
- **In advanced CKD (eGFR <30)**
- ***benefits still outweigh risks in most patients***

Direct Kidney Effects of Glucose-Lowering Medications

- **SGLT2 inhibitors** (e.g., empagliflozin, canagliflozin, dapagliflozin):

✓*direct renal benefits independent of glucose lowering*

- Mechanisms: ↓ renal glucose reabsorption, ↓ weight, ↓ systemic & intraglomerular BP, ↓ albuminuria, slows eGFR declineAdditional effects: ↓ oxidative stress (>50%), ↓ angiotensinogen, ↓inflammasome activity
- **GLP-1 receptor agonists (RAs)** (e.g., semaglutide, liraglutide):
- improve kidney outcomes via anti-inflammatory & hemodynamic effects
- No unique renoprotective effects seen with other classes (DPP-4i, sulfonylureas, insulin) in primary prevention trials

Selection of Glucose-Lowering Agents in CKD: Key Considerations

ADA/KDIGO Consensus

Tailor therapy to: CKD stage (eGFR limitations), CV/CKD progression risk, hypoglycemia avoidance

- Dose adjustments required for eGFR <60 mL/min/1.73 m^2 (most agents)
- **Metformin** :Contraindicated if eGFR <30 , Reassess benefits/risks at eGFR <45 , Do not initiate if eGFR <45 → Temporarily hold before iodinated contrast if eGFR 30–60
- Base selection on: CV/kidney risks, weight effects, adverse events, cost, patient preferences
- Ongoing trials: more data on CKD/CV outcomes expected soon

Practical 2026 Algorithm: Agents for T2D + CKD

- High CKD progression risk (**albuminuria**, **eGFR loss history**):

  Start SGLT2i (eGFR ≥20)
- High CV risk: Add/prioritize GLP-1 RA
- Advanced CKD (eGFR <30): Prefer GLP-1 RA for glycemic control (↓ hypo)
- Background: Maximize ACEi/ARB first
- Individualize: Comorbidities, preferences, cost – reassess regularly

Non-steroidal MRA: A New Pillar in Diabetic CKD

Finerenone

First non-steroidal mineralocorticoid receptor antagonist (nsMRA) proven for diabetic CKD

- Different from spironolactone/eplerenone:

➢ ***lower hyperkalemia risk, better kidney & heart selectivity***

- Indicated in type 2 diabetes + CKD with albuminuria (UACR ≥30 mg/g)
- Added on top of maximal tolerated ACEi/ARB + SGLT2i
- Reduces CKD progression and cardiovascular events (especially heart failure)
- Recommended if eGFR **≥25** and serum **K^+ ≤4.8** mmol/L

Now part of the "Four Pillars" of modern DKD therapy: RASi + SGLT2i + GLP-1 RA + nsMRA

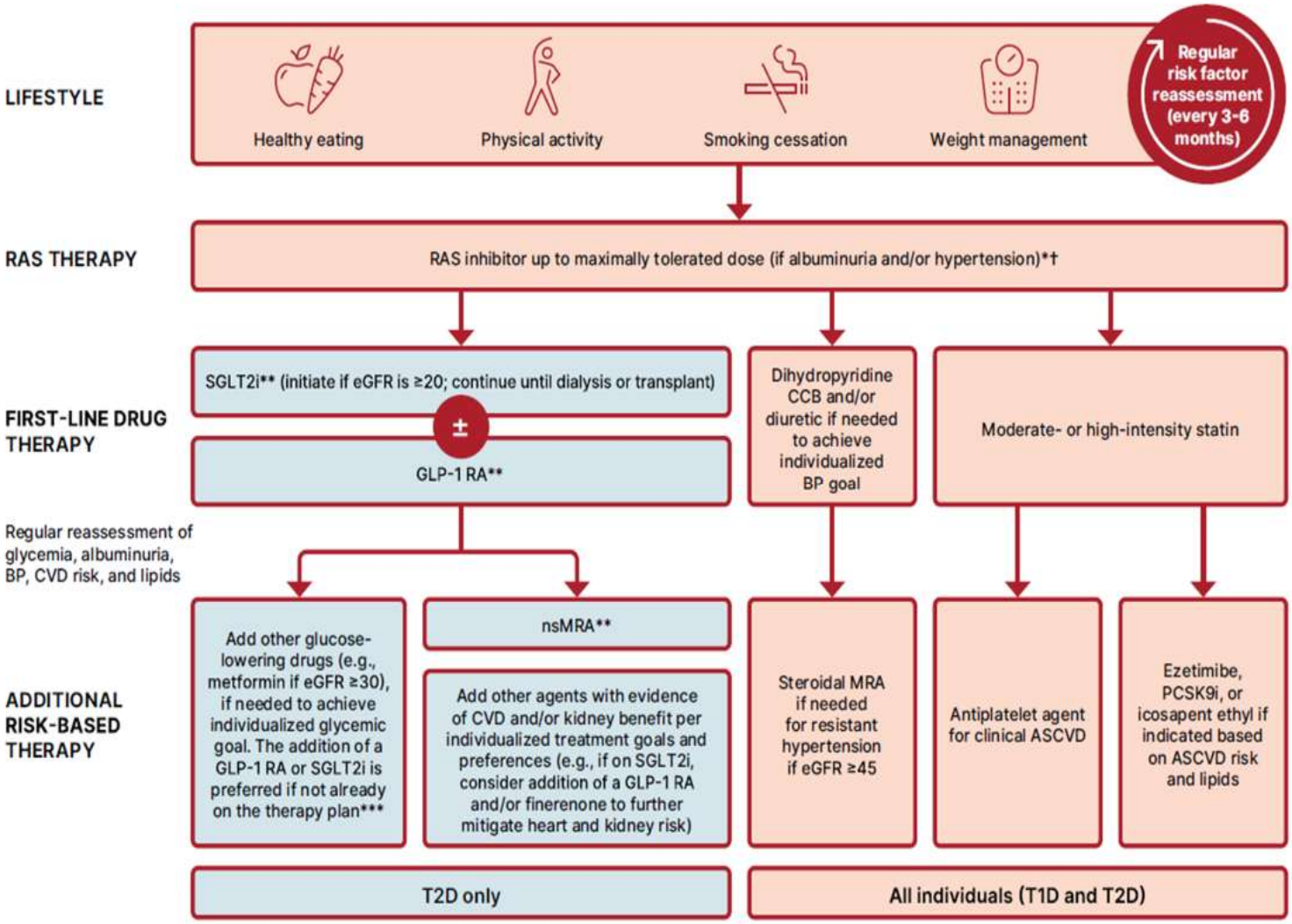
ADA/KDIGO 2026 – Non-steroidal MRA Use

- Recommend finerenone in adults with **T2D + CKD + albuminuria (UACR ≥30** mg/g)
- Add on top of maximal tolerated ACEi/ARB ± SGLT2i ± GLP-1 RA
- Starting dose: → **10 mg** daily if eGFR 25–59

  20 mg daily if eGFR ≥60

Monitor K^+ at **1–4 weeks** after start or dose increase

- Continue unless K^+ **>5.5–6.0** mmol/L or **symptomatic hyperkalemia**
- Acceptable mild hyperkalemia (5.1–5.5) often manageable with diet/low-K binders



*The majority of participants in SGLT2i, GLP-1 RA and nsMRA kidney outcome trials were receiving background optimized RAS inhibitor therapy.

**With demonstrated benefit in this population

***Glucose-lowering efficacy of GLP-1 RAs is preserved at low eGFR; glucose-lowering efficacy of SGLT2i is diminished at lower eGFR.

Figure 11.2

Microvascular Complications

Area	2025 Must-Do Action
Retinopathy	Anti-VEGF first-line for DME & most PDR Fenofibrate in dyslipidemia + early DR
Neuropathy screening	Annual 10-g monofilament + 128-Hz fork + 4 autonomic questions
Pain management	Duloxetine / pregabalin / amitriptyline first → never opioids
Foot exam	Every visit if LOPS or prior ulcer
Ulcer treatment	5 pillars + <50% healing at 4 weeks → advanced therapy (topical O_2 rising fast)
Prevention	Intensive glucose (T1DM), ABC control, smoking cessation, therapeutic shoes