CVD Prevention
in Patients whit DM

Care Delivery Systems:

- 33-49% of patients still do not meet targets for A1C, blood pressure, or lipids
- Only14% of patients meet targets for all A1C, BP, lipids, and nonsmoking status
- Progress in CVD risk factor control is slowing
- System-level improvements are needed

Lipid in Diabetes

TG 

HDL 

LDL 

- Plasma levels of LDL are increased in some but not all subjects. the hyperlipidemia in type 2 diabetes is often characterized by an increase in small, dense LDLs which are particularly atherogenic
- a portion of the plasma LDL undergoes glycosylation, which can increase binding to arterial wall proteoglycans and susceptibility to oxidation.

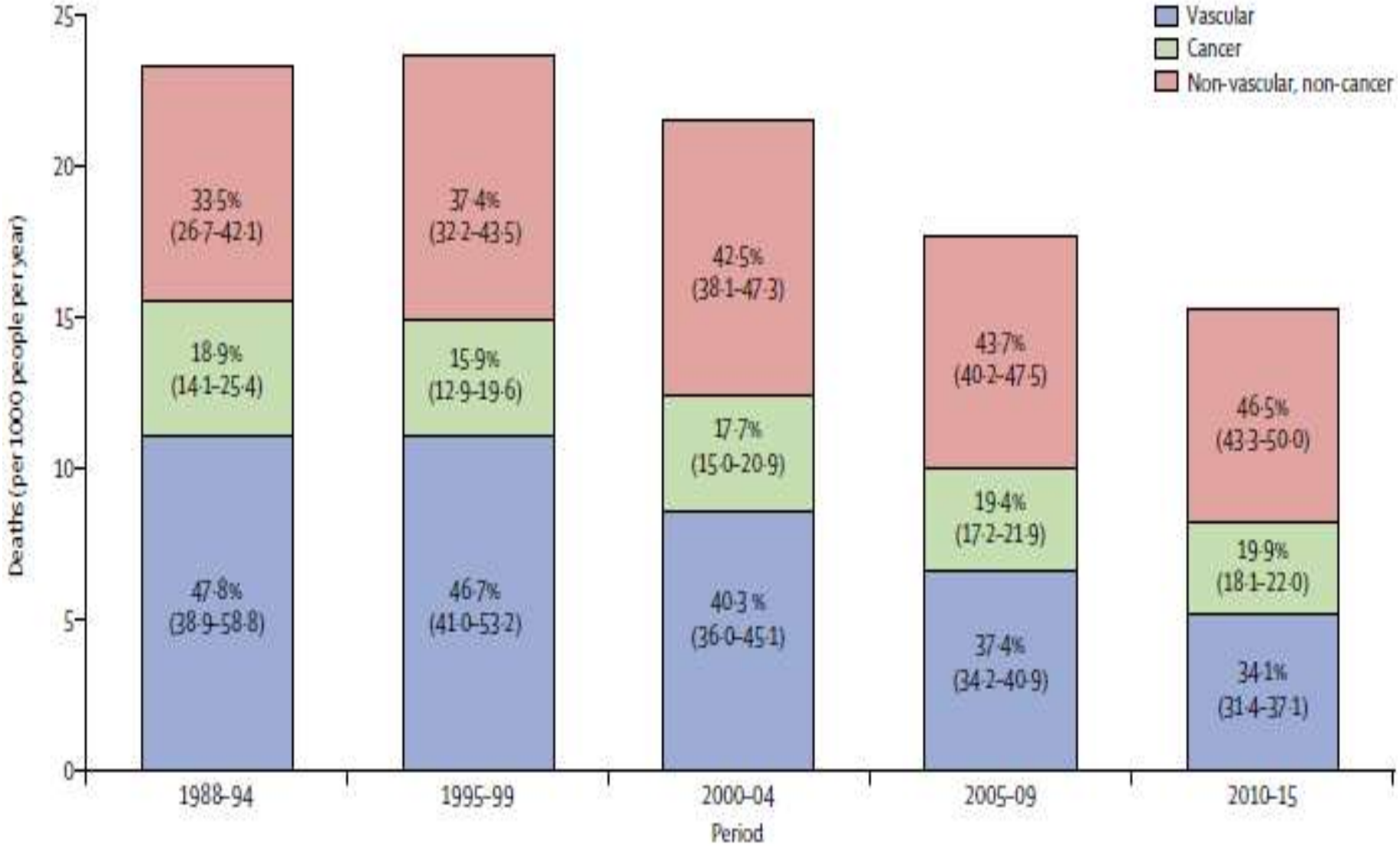
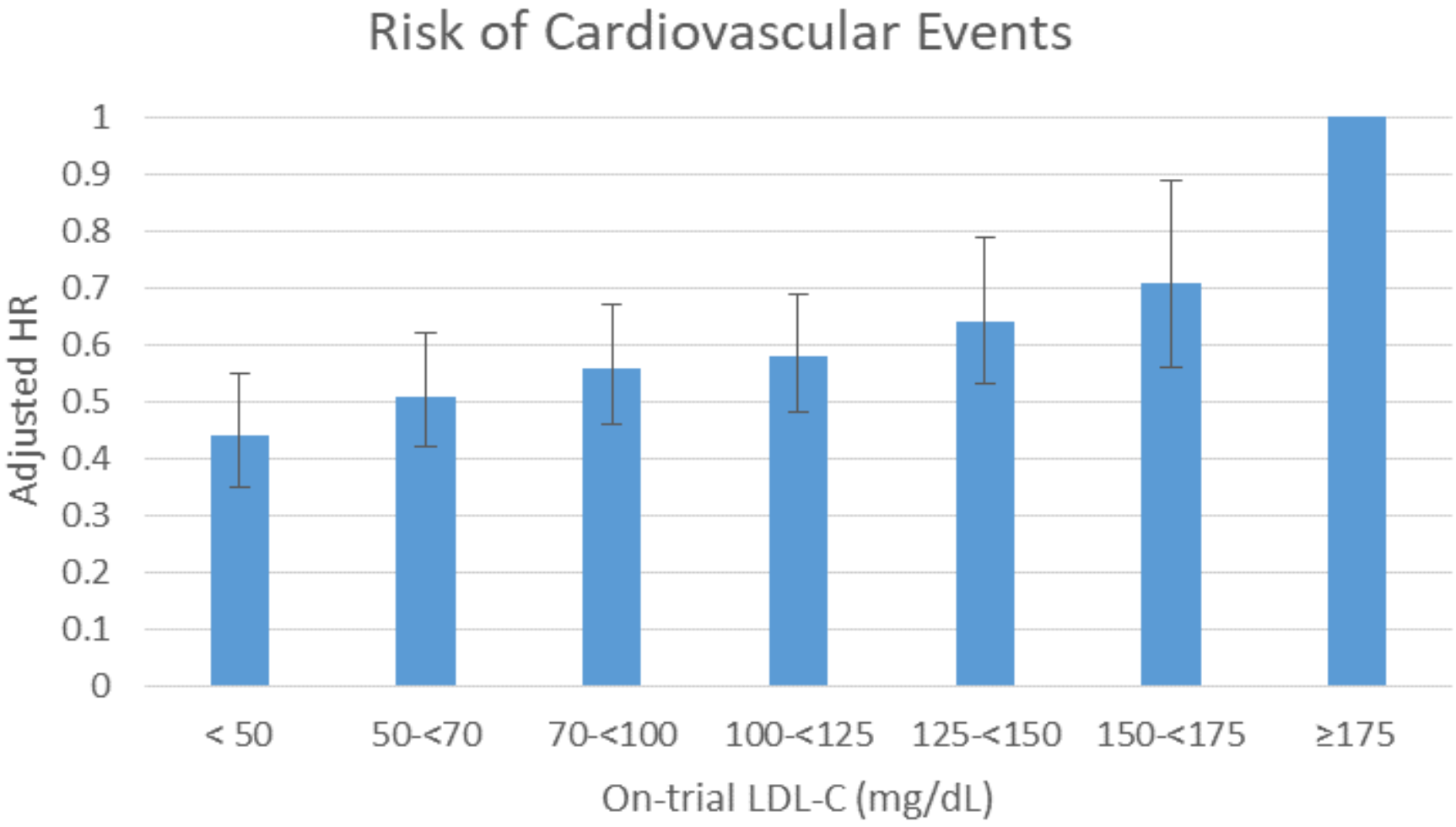


Figure 1: **Deaths due to vascular, cancer, and non-vascular, non-cancer causes among US adults diagnosed with diabetes**
Numbers in bars represent % of total deaths (95% CI).

https://doi.org/10.1016/S0140-6736(18)30314-3

Lowering LDL-cholesterol and CV benefits: Is there a limit to how low LDL-C needs to be for optimal health benefits?



https://doi.org/10.1002/cpt.1133

Outpatient Management:

- ✓ Lifestyle modification
- ✓Lipid management
- ✓ Bp control
- ✓ Cigar discontinuous
- ✓ Glycemic control

Table 4.2—Assessment and treatment plan*

Assess risk of diabetes complications

- ASCVD and heart failure history
- ASCVD risk factors (see **Table 10.2**) and 10-year ASCVD risk assessment
- Staging of chronic kidney disease (see **Table 11.1**)
- Hypoglycemia risk (**Table 4.3**)

Goal setting

- Set A1C/blood glucose target
- If hypertension present, establish blood pressure target
- Diabetes self-management goals (e.g., monitoring frequency)

Therapeutic treatment plan

- Lifestyle management
- Pharmacologic therapy (glucose lowering)
- Pharmacologic therapy (cardiovascular disease risk factors and renal)
- Use of glucose monitoring and insulin delivery devices
- Referral to diabetes education and medical specialists (as needed)

ASCVD, atherosclerotic cardiovascular disease. *Assessment and treatment planning is an essential component of initial and all follow-up visits.

LDL calculated

Fried Ewald equation :

LDL-C = (total cholesterol – HDL-C) – triglycerides / 5

Other Lipid Targets

- Triglycerides
- Non-HDL-C: Total cholesterol minus HDL-C
- Non-HDL cholesterol may predict atherosclerotic CVD risk better than LDL-C alone[a,b]

a. Hoenig MR. *Vasc Health Risk Manag*. 2008;4:143-56.[18]
b. NLA website. 2014.[7]

Non–**HDL-C** targets are 30 mg/dL higher than established LDL-C risk levels .

Calculate non–**HDL-C** (total cholesterol minus HDL-C) in patients with moderately elevated triglycerides (200 to 500 mg/dL), diabetes mellitus, and/or established CAD .

Recommendations: Lipid Management

- In adults not taking statins, a screening lipid profile is reasonable:
  - ➢At diabetes diagnosis
  - ➢At the initial medical evaluation
  - ➢And every 5 years, or more frequently if indicated
- Obtain a lipid profile at initiation of statin therapy, and periodically thereafter.

Recommendations: Lipid Management

To improve lipid profile in patients with diabetes, recommend lifestyle modification A, focusing on:

Weight loss (if indicated)

Reduction of saturated fat, trans fat, cholesterol intake Increase of ω-3 fatty acids, viscous fiber,
plant stanols/sterolsIncreased physical activity.

Recommendations: Lipid Management

- Intensify lifestyle therapy & optimize glycemic control for patients with:
  - Triglyceride levels ≥150 mg/dL (1.7 mmol/L) and/or
  - HDL cholesterol <40 mg/dL (1.0 mmol/L) in men and <50 mg/dL (1.3 mmol/L) in women
- For patients with fasting triglyceride levels ≥ 500 mg/dL (5.7 mmol/L), evaluate for secondary causes and consider medical therapy to reduce the risk of pancreatitis.

Intensity of Statin Therapy

High-Intensity Statin Therapy*	Moderate-Intensity Statin Therapy*	Low-Intensity Statin Therapy*
Daily dose lowers LDL-C, on average, by approximately ≥ 50%	**Daily dose lowers LDL-C, on average, by approximately 30% to < 50%**	**Daily dose lowers LDL-C, on average, by < 30%**
• Atorvastatin (40†) to 80 mg	• Atorvastatin 10 (20) mg	• Simvastatin 10 mg
• Rosuvasatin 20 (40) mg	• Rosuvastatin (5) 10 mg	• Pravastatin 10 to 20 mg
	• Simvastatin 20 to 40 mg‡	• Lovastatin 20 mg
	• Pravastatin 40 (80) mg	• Fluvastatin 20 to 40 mg
	• Lovastatin 40 mg	• Pitavastatin 1 mg
	• Fluvastatin XL 80 mg	
	• Fluvastatin 40 mg twice daily	
	• Pitavastatin 2 to 4 mg	

*Individual responses to statin therapy varied in RCTs and should be expected to vary in clinical practice. There might be a biologic basis for a less-than-average response.
†Evidence from 1 RCT only: down-titration if unable to tolerate atorvastatin 80 mg in IDEAL (Pedersen et al).
‡Although simvastatin 80 mg was evaluated in RCTs, initiation of simvastatin 80 mg or titration to 80 mg is not recommended by the FDA because of the increased risk for myopathy, including rhabdomyolysis.

Stone N, et al. *J Am Coll Cardiol*. 2014;63:2889-2934.

Recommendations for statin and combination treatment in adults with diabetes:

Age	ASCVD or 10-year ASCVD risk ≥ 20%	Recommended statin intensity and combination treatment
< 40 years	No Yes	None High In patients with ASCVD, if LDL cholesterol ≥ 70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)
≥ 40 years	No Yes	Moderate High In patients with ASCVD, if LDL cholesterol ≥70 mg/dL despite maximally tolerated statin dose, consider adding additional LDL-lowering therapy (such as ezetimibe or PCSK9 inhibitor)

Lipid Management:
Treatment of Other Lipoprotein Fractions or Targets.

10.26 For patients with fasting triglyceride levels ≥500 mg/dL (5.7 mmol/L), evaluate for secondary causes of hypertriglyceridemia and consider medical therapy to reduce the risk of pancreatitis C

10.27 In adults with moderate hypertriglyceridemia (fasting or nonfasting triglycerides 175-499 mg/dL), clinicians should address and treat lifestyle factors (obesity and metabolic syndrome), secondary factors (diabetes, chronic liver or kidney disease and/or nephrotic syndrome, hypothyroidism), and medications that raise triglycerides C

Lipid Management:
Other Combination Therapy.

10.28 Combination therapy (statin/fibrate) has not been shown to improve atherosclerotic cardiovascular disease outcomes and is generally not recommended A

10.29 Combination therapy (statin/niacin) has not been shown to provide additional cardiovascular benefit above statin therapy alone, may increase the risk of stroke with additional side effects, and is generally not recommended A

Diabetes Mellitus in Adults

Recommendations for Patients With Diabetes Mellitus		
COR	**LOE**	**Recommendations**
IIa	B-R	In adults with diabetes mellitus who have multiple ASCVD risk factors, it is reasonable to prescribe high-intensity statin therapy with the aim to reduce LDL-C levels by 50% or more.
IIa	B-NR	In adults older than 75 years of age with diabetes mellitus and who are already on statin therapy, it is reasonable to continue statin therapy.
IIb	C-LD	In adults with diabetes mellitus and 10-year ASCVD risk of 20% or higher, it may be reasonable to add ezetimibe to maximally tolerated statin therapy to reduce LDL-C levels by 50% or more.

However, lipid goals for all patients should be personalized by levels of risk .

Choose the Right Statin

Not All Statins Are Created Equal

How are they different?

- Strength at starting dose
- Way they are metabolized
- Hydro/lipophilic

Statin Pharmacokinetics

	Bio-Availability	Half-Life, h	CYP450 Metabolism	Solubility
Lovastatin	< 5%	2 to 3	3A4	Lipophilic
Simvastatin	< 5%	2	3A4	Lipophilic
Pravastatin	17%	1.5 to 2	none	Hydrophilic
Fluvastatin	24%	1	2C9	Hydrophilic
Atorvastatin	12%	14	3A4	Lipophilic
Rosuvastatin	20%	20	2C9	Hydrophilic
Pitavastatin	43% to 51%	12	2C9, 2C8	Slightly hydrophilic

Courtesy of Joyce L. Ross, MSN, CRNP, CLS, FNLA
Chapter 5: Pharmacology of Lipid-Lowering Medications. *Pharmacist's Guide to Lipid Management*, 2nd edition, 2014.

Statin Dose Adjustment Based on Renal Function

Statin	GFR 60-90 ml/min/1.73m^2	GFR 15-59 ml/min/1.73m^2	GFR <15 ml/min/1.73m^2	Notes
Atorvastatin	No	No	No	
Fluvastatin	No	Not defined	Not defined	↓ dose to one-half at GFR < 30 ml/min/1.73m^2, not to exceed 40 mg/day
Lovastatin	No	↓ to 50%	↓ to 50%	↓ dose to one-half at GFR < 30 ml/min/1.73m^2, not to exceed 20 mg per day unless careful monitoring
Pravastatin	No	No	No	Start at 10 mg/day for GFR < 60 ml/min/1.73m^2
Rosuvastatin	No	5-10mg	5-10 mg	Start at 5 mg/day for GFR < 30 ml/min/1.73m^2, max dose 10 mg/day
Simvastatin	No	No	5 mg	Start at 5mg if GFR < 30 ml/min/1.73m^2
Pitavastatin	No	1-2 mg	1-2 mg	Dose should not exceed 2 mg a day if GFR < 30 ml/min/1.73m^2

Harper CR, Jacobson TA. *J Am Coll Cardiol*. 2008;51:2375-2384.

abidi Cardio Thrombosis

Selected Drug Interactions That Increase Statin Levels

Statin	Interacting Agent[a]	Fold Increase in Statin AUC %[a]
Atorvastatin	Diltiazem	51†
Lovastatin*	Amiodarone	1.8
	Conivaptan	3.0
	Diltiazem	3.6
	Dronedarone	3.9
	Gemfibrozil	2 to 3
	Verapamil	3.6
Simvastatin*	Amiodarone	1.8
	Amlodipine	1.8
	Conivaptan	3.0
	Diltiazem	4.6
	Dronedarone	3.9
	Gemfibrozil	2 to 3
	Ranolazine	1.9
	Ticagrelor	2 to 3
	Verapamil	2.5
	Warfarin	≤ 30% change in INR
Pitavastatin	Gemfibrozil	1.5
Pravastatin	Gemfibrozil	2.0
Rosuvastatin	Gemfibrozil	1.6 to 1.9

Least CYP450 interactions[b]

Interpreting AUC ratio increase:[c]
- Weak: >1.25 – <2.0
- Moderate: >2.0-<4.9
- Strong: >5.0

*"Sensitive" statins. Up to 5-fold increase in statin AUC when administered with strong CYP3A4 inhibitors.[b] †51% increase in AUC of atorvastatin. Combination is reasonable but use caution/monitor.

a. Wiggins BS, et al. *Circulation.* 2016;134:e468-e495; b. *Pharm Lett/Prescr Lett.* 2012;28;6:280606; c. Kellick KA, et al. *J Clin Lipidol.* 2014;8:S30–S46.

Recommendations for drug treatment of patients with hypertriglyceridemia

Recommendations	Class[a]	Level[b]
Statin treatment is recommended as the first drug of choice to reduce CVD risk in high-risk individuals with hypertriglyceridaemia [TG levels >2.3 mmol/L (>200 mg/dL)].[355]	I	B
In high-risk (or above) patients with TG levels between 1.5–5.6 mmol/L (135–499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2×2 g/day) should be considered in combination with a statin.[194]	IIa	B
In primary prevention patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	B
In high-risk patients who are at LDL-C goal with TG levels >2.3 mmol/L (>200 mg/dL), fenofibrate or bezafibrate may be considered in combination with statins.[305–307,356]	IIb	C

2019 ESC/EAS Guidelines for the management of dyslipidaemia: lipid modification to reduce cardiovascular risk. Eur Heart J 2019