Hypertension / Dyslipidemia In Diabetics

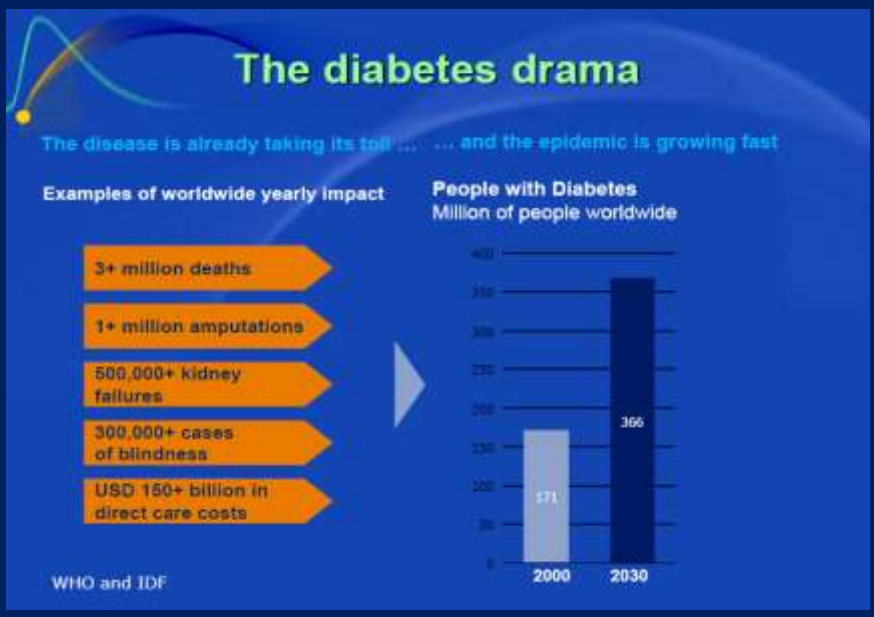
Bassem Zarif

Agenda

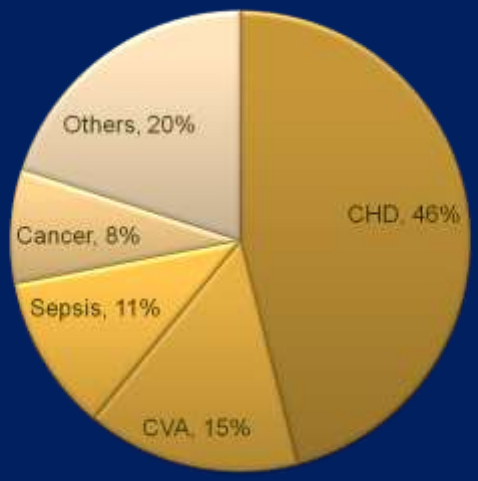
- 1- Reading the epidemiology: Burden of DM and burden when HTN, HC added.
- 2- Reading the underlying pathophysiology: Interacting mechanisms.
- 3- Evidence based studies.
- 4-What Guidelines said in this complex scenario.

Agenda

- 1- Background for the risk.
- 2- Interacting mechanisms.
- 3- Evidence based studies.
- 4- Guidelines.



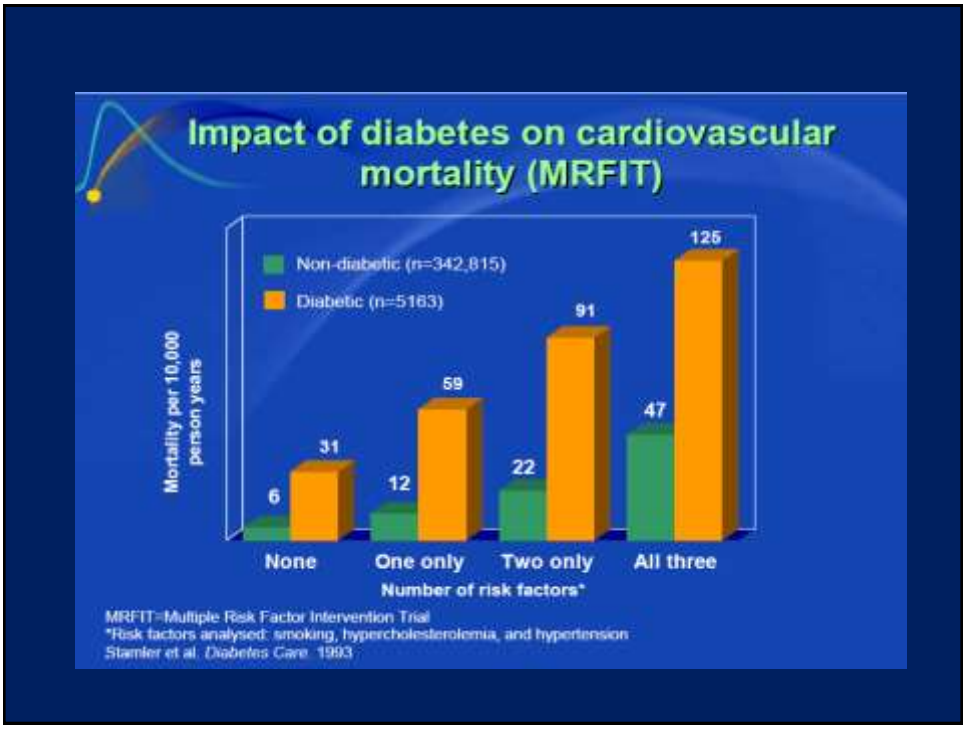
Causes of death in Diabetes

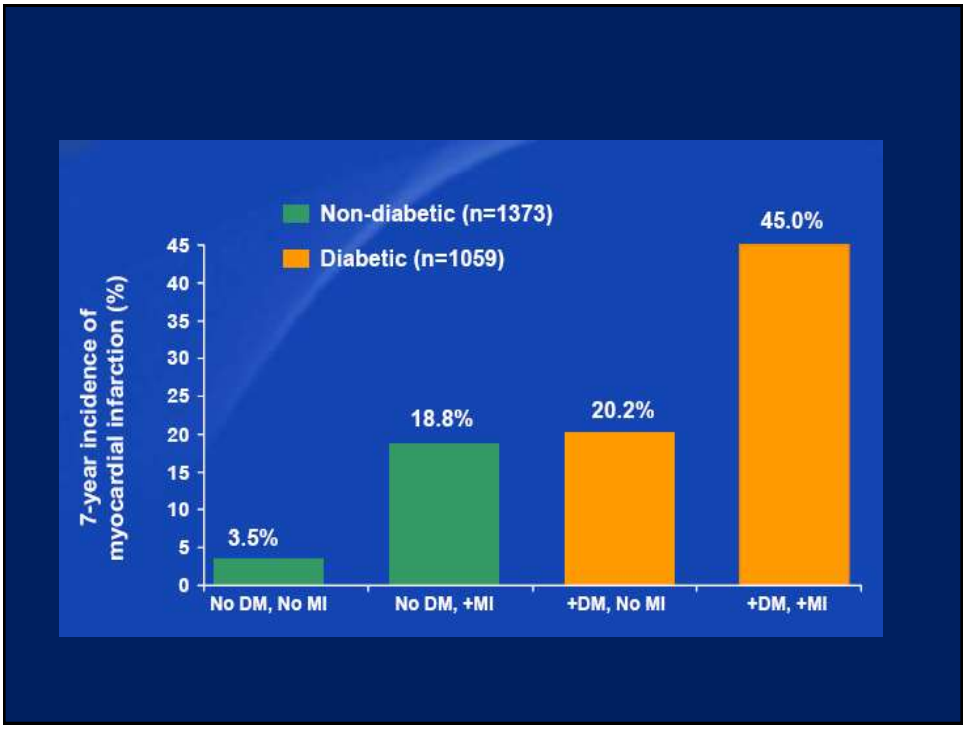


Cardiovascular risk factors in people with diabetes

- Dyslipidaemia[1]
- Hypertension[2,3]
- Hyperinsulinaemia / insulin resistance[4,5]
- Central obesity[6-8]
- Cigarette smoking[2,9,10]
- Hyperglycaemia[11,12]
- Postprandial hyperglycaemia[13]

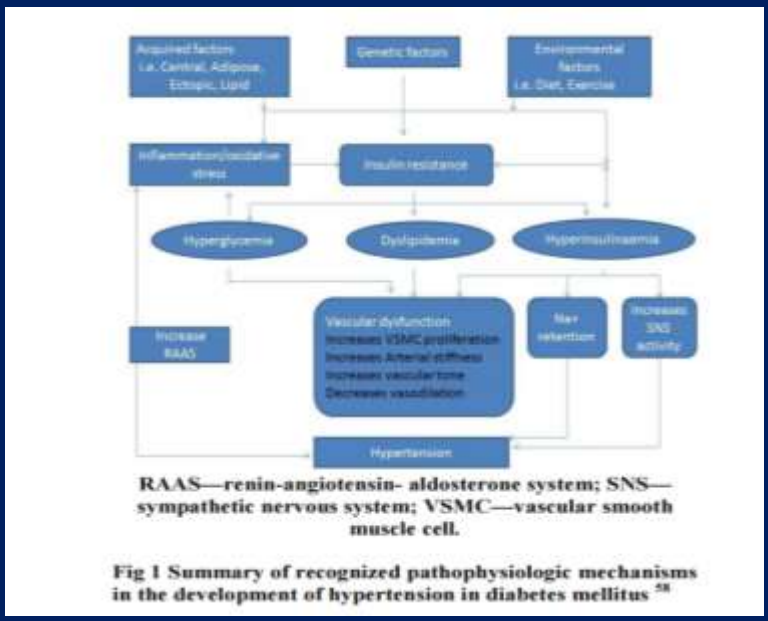
1. Grundy. *Circulation*. 1997
2. Grundy et al. *Circulation*. 1999
3. Chobanian et al. *Hypertension*. 2003
4. Reaven. *Diabetes* 1988
5. Reaven. *Physiol Rev*. 1995
6. Laakso. *Diabetes Rev*. 1995
7. Stunkard. *Am J Med*. 1996
8. Despres. *Bailleres Clin Endocrinol Metab*. 1994
9. Neaton, Wentworth. *Arch Intern Med*. 1992
10. Heitzer et al. *Circulation*. 1996
11. Haffner. *Diabetes Care*. 1998
12. Cohen. *Circulation*. 1993
13. Ceriello et al. *Nutr Metab Cardiovasc Dis*. 2006


Impact of diabetes on cardiovascular mortality (MRFIT)
Non-diabetic (n=342,815)
Diabetic (n=5163)
Mortality per 10,000 person years
6
31
12
59
22
91
47
125
None
One only
Two only
All three
Number of risk factors*
MRFIT=Multiple Risk Factor Intervention Trial
*Risk factors analysed: smoking, hypercholesterolemia, and hypertension
Stamler et al. Diabetes Care 1993


Non-diabetic (n=1373)
Diabetic (n=1059)
7-year incidence of myocardial infarction (%)
45
40
35
30
25
20
15
10
5
0
3.5%
18.8%
20.2%
45.0%
No DM, No MI
No DM, +MI
+DM, No MI
+DM, +MI

Agenda

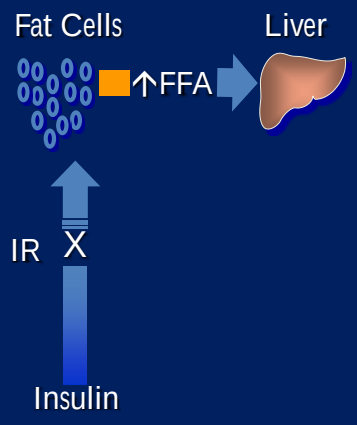
- 1- Background for the risk.
- 2- Interacting mechanisms.
- 3- Evidence based studies.
- 4- Guidelines.



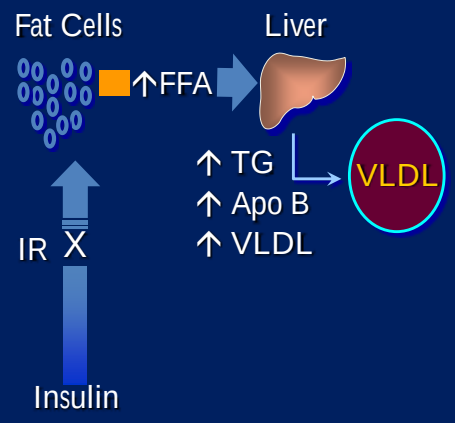
RAAS—renin-angiotensin- aldosterone system; SNS—sympathetic nervous system; VSMC—vascular smooth muscle cell.

Fig 1 Summary of recognized pathophysiologic mechanisms in the development of hypertension in diabetes mellitus [58]

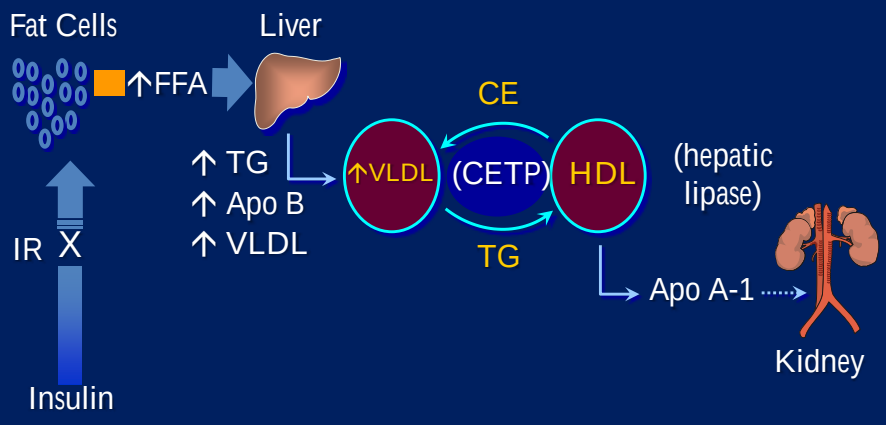
Mechanisms of DM Dyslipidemia



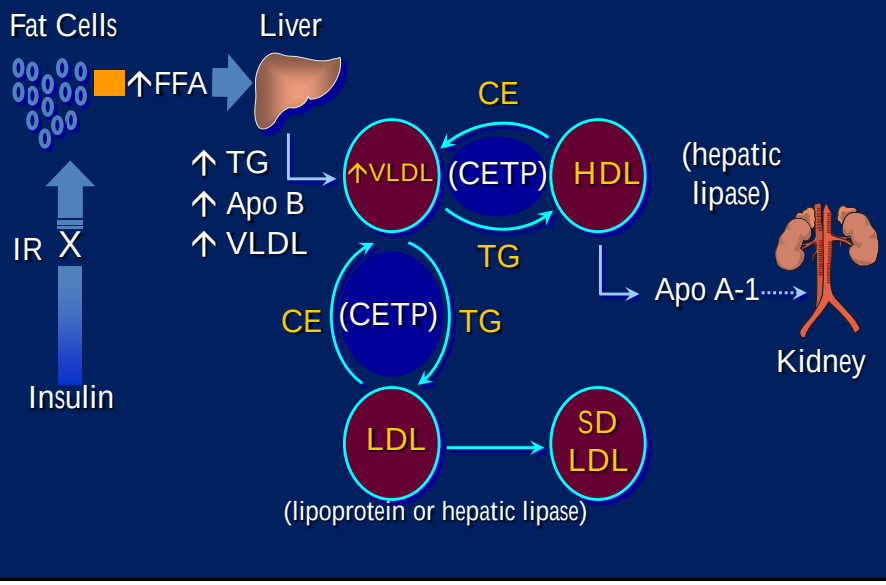
Mechanisms of DM Dyslipidemia

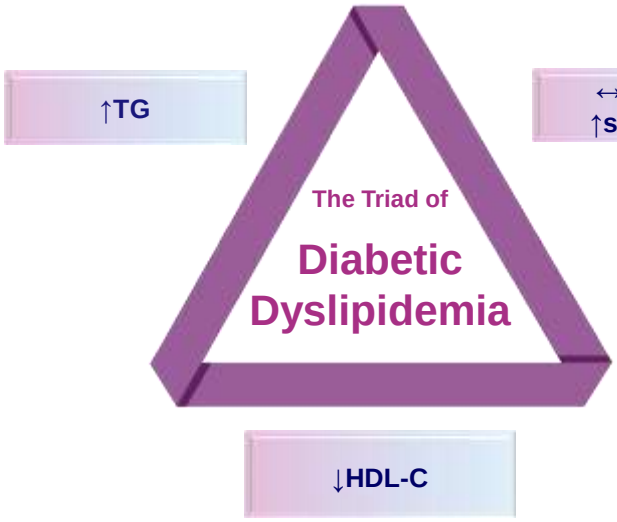


Mechanisms of DM Dyslipidemia



Mechanisms of DM Dyslipidemia



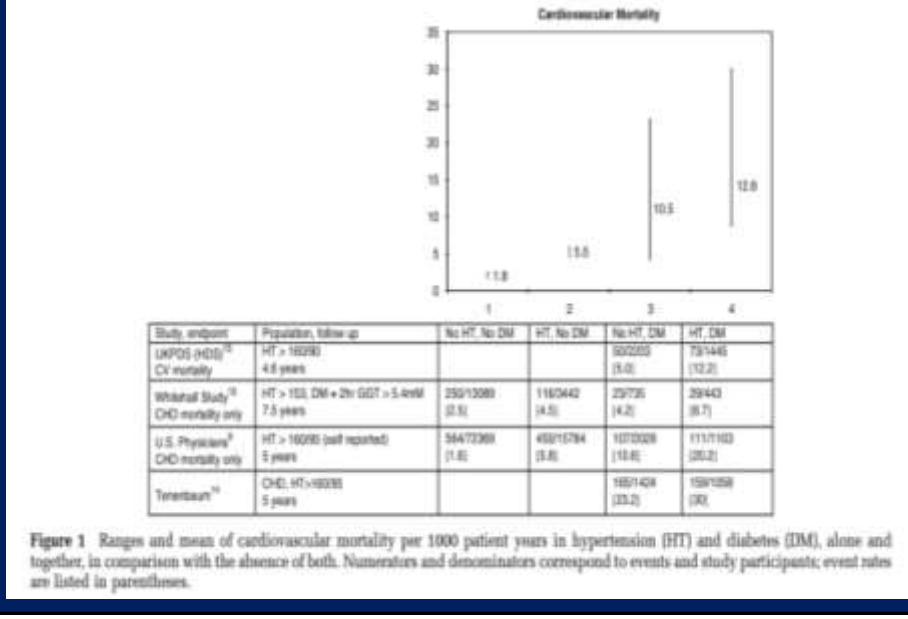


- Insulin resistance contributes to this characteristic dyslipidemia
- Propensity to develop atherosclerotic disease - much higher in these patients – also called Atherosclerotic Diabetic Dyslipidemia (ADD)
- Disturbance of lipid metabolism – early event, potentially preceding the disease by several years.
- Monitoring of the conventional (LDL-C) may be misleading in diabetic patients– requires specific monitoring

16

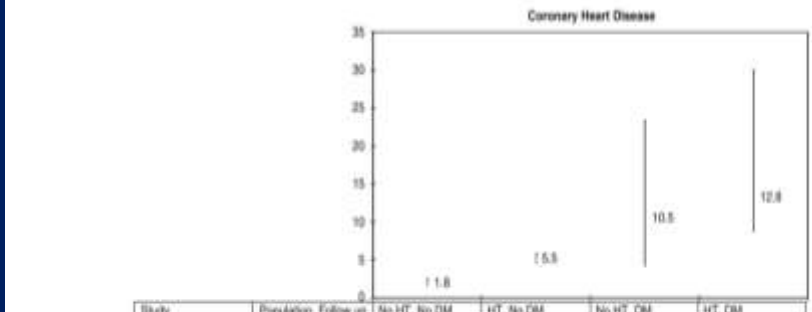
Agenda

- 1- Background for the risk.
- 2- Interacting mechanisms.
- 3- Evidence based studies.
- 4- Guidelines.



Study, endpoint	Population, follow-up	No HT, No DM	HT, No DM	No HT, DM	HT, DM
UKPDS (HDS)[13] CV mortality	HT > 160/90 4.6 years			52/2053 (5.0)	73/1445 (12.2)
Whitehall Study[15] CHD mortality only	HT > 153, DM + 2hr GGT > 5.4mM 7.5 years	250/13089 (2.5)	116/3442 (4.5)	23/735 (4.2)	29/443 (6.7)
U.S. Physicians[9] CHD mortality only	HT > 160/90 (self reported) 5 years	564/72369 (1.6)	455/15784 (3.8)	107/3028 (10.6)	111/1103 (20.2)
Terentaum[14]	CHD, HT >160/95 5 years			165/1424 (33.2)	159/1259 (30)

Figure 1 Ranges and mean of cardiovascular mortality per 1000 patient years in hypertension (HT) and diabetes (DM), alone and together, in comparison with the absence of both. Numerators and denominators correspond to events and study participants; event rates are listed in parentheses.



Study	Population, Follow up	No HT, No DM	HT, No DM	No HT, DM	HT, DM
PROCAM[15]	HT > 160/95 4 years	19/3240 (1.5)	28/1992 (3.5)	6/386 (3.8)	10/212 (12.0)
Gothenburg[7]	HT > 140 7.1 years	82/2565 (4.5)	247/4077 (8.6)	3/45 (9.4)	28/187 (21.1)
UKPDS[16]	HT>160/90 4.6 years			99/2200 (9.8)	97/1445 (14.5)
Finland[17]	HT > 140/90 21.5 years	90/21449 (2.0)	394/27414 (6.7)	39/238 (7.6)	193/674 (13.3)
UKPDS[18]	HT > 140 10 years			341 (11.3)	378 (18.5)

Figure 2 Effects of hypertension (HT) and diabetes (DM), alone and together, in comparison with the absence of both, on coronary h disease presentations. The figure summarizes ranges and mean of coronary heart disease (CHD) presentations per 1000 patient ye Numerators and denominators correspond to events and study participants, with event rates per 1000 patient years are liste parentheses.

Original Investigation

Blood Pressure Lowering in Type 2 Diabetes
A Systematic Review and Meta-analysis

Connor A. Emdin, HBSc; Kazem Rahimi, DM, MSc; Bruce Neal, PhD; Thomas Callender, MBChB; Vlado Perkovic, PhD; Anushka Patel, PhD

IMPORTANCE Lowering blood pressure (BP) is widely used to reduce vascular risk in individuals with diabetes.

OBJECTIVE To determine the associations between BP-lowering treatment and vascular disease in type 2 diabetes.

DATA SOURCES AND STUDY SELECTION We searched MEDLINE for large-scale randomized controlled trials of BP-lowering treatment including patients with diabetes, published between January 1966 and October 2014.

DATA EXTRACTION AND SYNTHESIS Two reviewers independently extracted study characteristics and vascular outcome data. Estimates were stratified by baseline BP and achieved BP, and pooled using fixed-effects meta-analysis.

MAIN OUTCOMES AND MEASURES All-cause mortality, cardiovascular events, coronary heart disease events, stroke, heart failure, retinopathy, new or worsening albuminuria, and renal failure.

Figure 1. Flowchart of Trial Identification for Meta-analysis

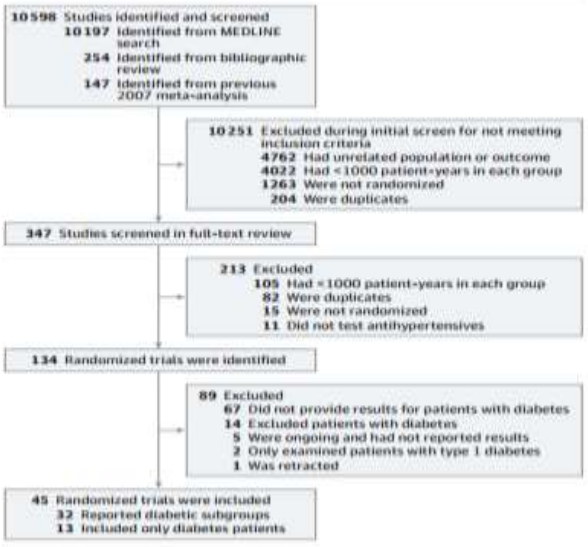


Figure 2. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes in Diabetic Patients

Outcome	No. of Studies	BP Lowering Events	BP Lowering Participants	Control Events	Control Participants	Relative Risk (95% CI)
Mortality	20	2134	27693	2319	25864	0.87 (0.79-0.96)
Cardiovascular disease	17	3230	25756	3280	24362	0.89 (0.83-0.95)
Coronary heart disease	17	1390	26150	1449	24761	0.88 (0.80-0.98)
Stroke	19	1350	27614	1475	26447	0.73 (0.64-0.83)
Heart failure	13	1235	21684	1348	20791	0.86 (0.74-1.00)
Renal failure	9	196	19835	160	18912	0.91 (0.74-1.12)
Retinopathy	7	844	9781	905	9566	0.87 (0.76-0.99)
Albuminuria	7	2799	11804	3163	12821	0.83 (0.79-0.87)

Macrovascular outcomes include cardiovascular events, coronary heart disease, stroke, and heart failure; and microvascular outcomes include renal failure, retinopathy, and albuminuria. The area of each square is proportional to the inverse variance of the estimate. Horizontal lines indicate 95% CIs of the estimate. BP indicates blood pressure.

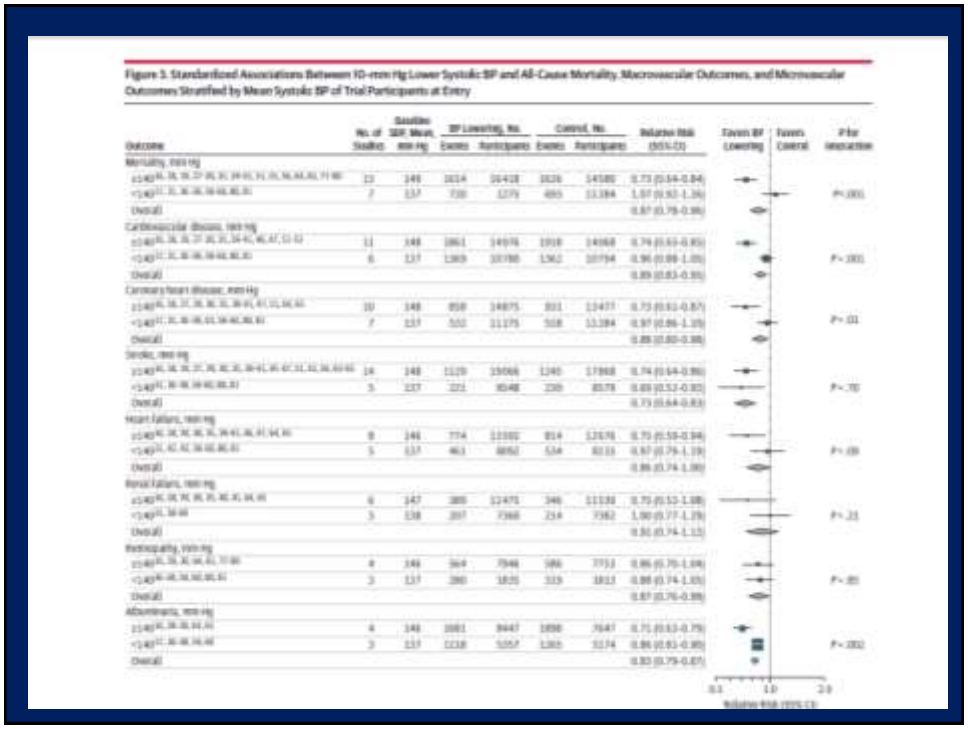
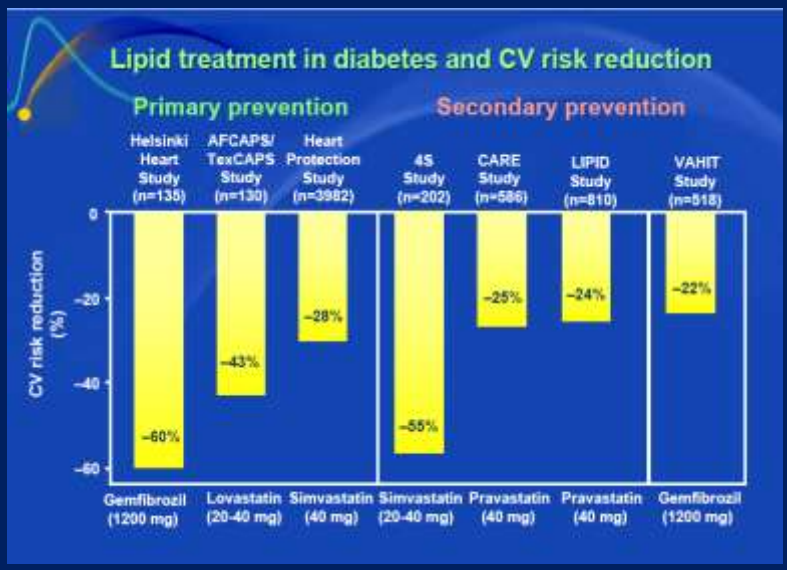


Figure 3. Standardized Associations Between 10-mm Hg Lower Systolic BP and All-Cause Mortality, Macrovascular Outcomes, and Microvascular Outcomes Stratified by Mean Systolic BP of Trial Participants at Entry

CHD Prevention Trials with Statins in Diabetic Patients Subgroup Analyses

			CHD % Risk↓	
Primary prevention			**Overall**	**Diabetes**
AFCAPS/TexCAPS	Lovastatin	155	37	43 (NS)
HPS	Simvastatin	2913	24	20 (P<0.0001)
ASCOT-LLA	Atorvastatin	2532	36	16 (NS)
Secondary prevention				
CARE	Pravastatin	586	23	25 (P=0.05)
4S	Simvastatin	202	32	55 (P=0.002)
LIPID	Pravastatin	782	24	19 (NS)
4S reanalysis	Simvastatin	483	32	42 (P=0.001)
HPS	Simvastatin	3050	24	18.4 (P<0.0001)
Primary/Secondary				
ALLHAT	Pravastatin	3648	9	11 (=NS)



Agenda

- 1- Background for the risk.
- 2- Interacting mechanisms.
- 3- Evidence based studies.
- 4- Guidelines.

TABLE I. Hypertension Thresholds, Goals, and Agents in Diabetics

Guideline	Year Published	Threshold for Treatment	Goal Blood Pressure	First-Line Agents
JNC 7[4]	2004	≥130/80	<130/80	ACE inhibitor, ARB, BB, CCB
JNC 8[5]	2014	≥140/90	<140/90	Nonblacks: thiazide-type diuretic, ACE inhibitor, ARB, or CCB Blacks: thiazide-type diuretic or CCB
ASH/ISH[6]	2014	≥140/90	<140/90	Diabetics: ACE inhibitor or ARB Blacks: thiazide-type diuretic or CCB
ESH/ESC[8]	2013	≥140/85	<140/85	ACE inhibitor or ARB
CHEP[10]	2014	≥130/80	<130/80	ACE inhibitor, ARB, CCB, thiazide-type diuretic
ADA[7]	2013	≥140/80	<140/80	ACE inhibitor or ARB
WHO/ISH[9]	2003	≥130/80	<130/80	ACE inhibitor or ARB

Abbreviations: ACE, angiotensin-converting inhibitor; ADA, American Diabetes Association; ARB, angiotensin receptor blocker; ASH, American Society of Hypertension; BB, β-blocker; CCB, calcium channel blocker; CHEP, Canadian Hypertension Education Program; ESH/ESC, European Society of Hypertension/European Society of Cardiology; ISH, International Society of Hypertension; JNC 7, Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; JNC 8, Eighth Report of the Joint National Committee; WHO, World Health Organization.

ADA 2017

BLOOD PRESSURE CONTROL Recommendations

- **Screening and Diagnosis :**

Blood pressure should be measured at every routine visit. Patients found to have elevated blood pressure should have blood pressure confirmed on a separate day. (B)

- **Goals :**

1- Most patients with diabetes and hypertension should be treated to a systolic blood pressure goal of ,140 mmHg and a diastolic blood pressure goal of ,90 mmHg.(A).

2- Lower systolic and diastolic blood pressure targets, such as 130/80 mmHg, may be appropriate for individuals at high risk of cardiovascular disease, if they can be achieved without undue treatment burden. (C)

ADA 2017

- Treatment :
- Patients with confirmed office-based blood pressure 140/90 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of pharmacologic therapy to achieve blood pressure goals. (A).

- Patients with confirmed office-based blood pressure 160/100 mmHg should, in addition to lifestyle therapy, have prompt initiation and timely titration of two drugs or a single pill combination of drugs demonstrated to reduce cardiovascular events in patients with diabetes. (A)

- Treatment for hypertension should include drug classes demonstrated to reduce cardiovascular events in patients with diabetes (ACE inhibitors, angiotensin receptor blockers, thiazide-like diuretics, or dihydropyridine calcium channel blockers). Multipledrug therapy is generally required to achieve blood pressure targets (but not a combination of ACE inhibitors and angiotensin receptor blockers). (A)
- An ACE inhibitor or angiotensin receptor blocker, at the maximum tolerated dose indicated for blood pressure treatment, is the recommended first-line treatment for hypertension in patients with diabetes and urinary albumin–to– creatinine ratio 300 mg/g creatinine (A) or 30–299 mg/g creatinine (B). If one class is not tolerated, the other should be substituted. (B).
- For patients with blood pressure 120/80 mmHg, lifestyle intervention consists of weight loss if overweight or obese; a Dietary Approaches to Stop Hypertension– style dietary pattern including reducing sodium and increasing potassium intake; moderation of alcohol intake; and increased physical activity. (B)

American Heart Association guidelines 2013

The expert panel identified 4 groups that would benefit from statin therapy:

1) Individuals with clinical ASCVD
2) Individuals with LDL >190 mg/dl
3) Individuals with Diabetes mellitus, 40-75 yrs with LDL 70-189 mg/dl and without clinical ASCVD
4) Individuals without clinical ASCVD or Diabetes mellitus with LDL 70-189 mg/dl and estimated 10-year ASCVD risk >7.5%

ADA 2017 (Cholest. Management)

- **Diagnosis and follow up :**
- **Obtain a lipid profile at the time of diabetes diagnosis, at an initial medical evaluation, and every 5 years thereafter, or more frequently if indicated. (E)**
- **Obtain a lipid profile at initiation of statin therapy and periodically thereafter as it may help to monitor the response to therapy and inform adherence. (E)**
- **Treatement :**
- **Lifestyle modification focusing on weight loss (if indicated); the reduction of saturated fat, trans fat, and cholesterol intake; increase of dietary v-3 fatty acids, viscous fiber, and plant stanols/sterols intake; and increased physical activity should be recommended to improve the lipid profile in patients with diabetes. (A)**
- **Intensify lifestyle therapy and optimize glycemic control for patients with elevated triglyceride levels (150 mg/dL [1.7 mmol/L]) and/or low HDL cholesterol (,40 mg/dL [1.0 mmol/L] for men, ,50 mg/dL [1.3 mmol/L] for women). (C)**

- 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)
- For patients of all ages with diabetes and atherosclerotic cardiovascular disease, high-intensity statin therapy should be added to lifestyle therapy. (A)
- For patients with diabetes aged 40 years with additional atherosclerotic cardiovascular disease risk factors, consider using moderate intensity or high-intensity statin and lifestyle therapy. (C)
- For patients with diabetes aged 40–75 years without additional atherosclerotic cardiovascular disease risk factors, consider using moderate-intensity statin and lifestyle therapy. A c For patients with diabetes aged 40–75 years with additional atherosclerotic cardiovascular disease risk factors, consider using high-intensity statin and lifestyle therapy. (B)

Take Home Message

- 1- HTN and HC may carry higher risk for CV events than hyperglycemia itself in diabetics.
- 2- Underlying pathological mechanisms may explain higher incidence of HTN and special pattern of dyslipidemia in diabetics.
- 3- Evidence based data confirm importance and outlined the benefits of controlling BP and CH in diabetics .
- 4- Screening is crucial for HTN and HC in diabetics

- 5- Special drug therapy for hypertension may have an edge in diabetics, specially with proteinuria. (ACE/ ARB)
- 6- Fixed dose combination is liberally advocated for treatment starting from stage 2.
- 7- ADA 2017 recommendation, started to re-issue target 130/80 and life style for 120/80.

- 8- ESC/ESA still recommend LDL goal of 100mg/dl and optionally 70 mg/dl.
- 9- American guidelines put DM is one of 4 groups allocated for statins irrespective of LDL level.
- 10- ADA 2017 advocated statins for all diabetics, those with CVD or multiple risk factors will receive high intensity,
- Those with no other risk factors moderate intensity statains.


Thank You!