The Epidemic of Obesity, Diabetes, and the Metabolic Syndrome

Holly Novak, MD, FACC

Obesity Trends* Among US Adults – BRFSS, 1985

BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.


Obesity Trends* Among US Adults – BRFSS, 1986

BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.

Obesity Trends* Among US Adults – BRFSS, 1987

*BMI ≥ 30, or ≈ 30 lbs overweight for 5'4" woman.


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Obesity Trends* Among US Adults – BRFSS, 1988

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Obesity Trends* Among US Adults – BRFSS, 1989

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Obesity Trends* Among US Adults – BRFSS, 1990

*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.


Adapted with permission from Mokdad AH et al. JAMA. 2001;286:1195-1200.

Obesity Trends* Among US Adults – BRFSS, 1991

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Adapted with permission from Mokdad AH et al. JAMA. 2001;286:1195-1200.

Obesity Trends* Among US Adults – BRFSS, 1992

*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.


Adapted with permission from Mokdad AH et al. JAMA. 2001;286:1195-1200.
Obesity Trends* Among US Adults – BRFSS, 1993

*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.

Obesity Trends* Among US Adults – BRFSS, 1994

*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.

Obesity Trends* Among US Adults – BRFSS, 1995

*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.
Obesity Trends* Among US Adults – BRFSS, 1996

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Obesity Trends* Among US Adults – BRFSS, 1997

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*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.

Obesity Trends* Among US Adults – BRFSS, 2001


*BMI ≥ 30, or ≈ 30 lbs overweight for 5’4” woman.
**Obesity Trends** Among US Adults – BRFSS, 2002

*BMI ≥30, or ≈30 lbs overweight for 5'4” woman.

**Diabetes Can Appear Right Under Your Nose**

Midwest Heart Foundation.
**Diabetes Mellitus: ↑ Prevalence in the US**


<table>
<thead>
<tr>
<th>Year</th>
<th>Diagnosed diabetes (in millions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1958</td>
<td>0</td>
</tr>
<tr>
<td>1963</td>
<td>1</td>
</tr>
<tr>
<td>1968</td>
<td>2</td>
</tr>
<tr>
<td>1979</td>
<td>3</td>
</tr>
<tr>
<td>1984</td>
<td>4</td>
</tr>
<tr>
<td>1989</td>
<td>5</td>
</tr>
<tr>
<td>1994</td>
<td>6</td>
</tr>
</tbody>
</table>

5x increase

**Diabetes: Atherosclerotic Complications**

- Responsible for 80% of diabetic mortality
- 75% cases due to coronary artery disease (CAD)
- Results in >75% of all hospitalizations for diabetic complications
- 50% of type 2 diabetes patients have preexisting CAD
- 1/3 of patients presenting with myocardial infarction have undiagnosed diabetes mellitus

Lewis GF. Can J Cardiol. 1995;11(suppl C):24C-28C.
Midwest Heart Foundation.

**Type 2 Diabetes and CHD 7-Year Incidence of Fatal/Nonfatal MI (East West Study)**

CHD=coronary heart disease; MI=myocardial infarction; DM=diabetes mellitus.
Post-MI Survival (5 Year): Diabetic Patients vs Nondiabetic Patients


![Graph showing survival rates for diabetic and nondiabetic patients over 5 years after MI.]

1-Year Mortality in Diabetic and Nondiabetic Subjects After a First MI


Midwest Heart Foundation.

Age-Adjusted CVD Death Rates (MRFIT)

CVD=cardiovascular disease; MRFIT=Multiple Risk Factor Intervention Trial.

DSW1  What is Midwest Heart Foundation. If it's a reference, it seems incomplete.
wordsetc@chesco.com, 8/11/2005
Proteinuria Predicts Stroke and CHD Events in Type 2 Diabetes

- A: U-Prot <150 mg/L
- B: U-Prot 150–300 mg/L
- C: U-Prot >300 mg/L

Survival curves for CV mortality:
- Overall: P<0.001

LDL-C as a Predictor of CAD in Diabetic Patients

- LDL=C hazard ratio
- LDL=C quartile mean:
  - 70
  - 98
  - 118
  - 151

LDL=C: low-density lipoprotein cholesterol. CAD: coronary artery disease.

HOT Trial: Effect of BP Control on CV Event Rate

- Major CV events per 1000 patient-years

BP: blood pressure.
The Effect of ASA on CV Risk in Patients With Diabetes

![Graph showing the effect of ASA on CV risk in patients with diabetes. The graph indicates a 17% reduction with ASA compared to placebo, with a p-value of <0.002.]


“Ticking Clock” Hypothesis

![Diagram illustrating the progression from NGT to IGT, then to Microvascular Disease and Hyperglycemia.]


Nurses’ Health Study: Elevated Risk of CVD Prior to Clinical Diagnosis of Type 2 Diabetes

![Bar chart showing the relative risk of CVD in nondiabetic throughout the study, prior to diagnosis of diabetes, after diagnosis of diabetes, and diabetic at baseline.]

Relative risk

1.00  2.82  3.71  5.02

Clinical Identification of the Metabolic Syndrome (NCEP)*

- Abdominal obesity (waist circumference)
  - Men >40 in (>102 cm)
  - Women >35 in (>88 cm)
- Triglycerides ≥150 mg/dL
- High-density lipoprotein (HDL)
  - Men <40 mg/dL
  - Women <50 mg/dL
- Blood pressure ≥130/≥85 mm Hg
- Fasting glucose ≥100 mg/dL

*Diagnosis is established when ≥3 of these risk factors are present.


Metabolic Syndrome and Mortality

Kuopio Ischaemic Heart Disease Risk Factor Study.
Adapted with permission from Lakka H-M et al. JAMA. 2002;288:2709.

Hazard Ratio* for CVD Mortality with the Metabolic Syndrome (Orange=Women; Blue=Men)

<table>
<thead>
<tr>
<th>No MetSyn</th>
<th>MetSyn</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Diabetes</td>
<td>1.0</td>
</tr>
<tr>
<td></td>
<td>1.0</td>
</tr>
<tr>
<td>Diabetes</td>
<td>3.53 (0.75, 16.7)</td>
</tr>
<tr>
<td></td>
<td>2.34 (0.70, 7.82)</td>
</tr>
</tbody>
</table>

San Antonio Heart Study.
*Adjusted for age and ethnicity.
1.0=no cardiovascular disease at baseline; MetSyn=metabolic syndrome (as defined by NCEP); Hunt KJ, et al. Circulation. 2004;110:1231-1237.
As defined by NCEP criteria. Adapted with permission from Lorenzo C et al. Diabetes Care. 2003;26:3153-3159.

Incident Diabetes After Stratification by IGT and the Metabolic Syndrome*

P = 0.018
P < 0.0001

No
Yes
NGT
IGT
MetS

Approaches to Therapy: Metabolic Syndrome/Diabetes – The Basis for the Project

• Behavioral therapy
  — Weight loss and increased physical activity
• Treat existing risk factors
  — For nondiabetic patients with MetS, management should be intensified over and above global risk, but not to the level of a CHD risk equivalent
• Use of insulin-sensitizing therapies in nondiabetic patients with MetS
  — No clinical trials support use in patients with MetS alone
  — Some clinical trial support use for MetS patients with IGT
    • DPP, STOP-NIDDM, TRIPOD

OGTT=oral glucose tolerance test.

The Epidemic – Key Takeaway Points

• The prevalence of obesity, metabolic syndrome, and diabetes continues to increase
• Diabetes is a major US health problem associated with atherosclerotic disease
• Renal function, LDL-C levels, and blood pressure are all predictive of CV risk in diabetic patients
• An increased risk of macrovascular complications precedes the development of hyperglycemia
• The metabolic syndrome increases risk for CVD mortality and is an independent predictor of diabetes

LDL-C=low-density lipoprotein cholesterol.
Diabetes Education Initiative: A Collaboration for Intervention

The American College of Cardiology Foundation in Collaboration With the Midwest Heart Foundation

Diabetes and Cardiovascular Health: Reducing the Risk

Holly Novak, MD, FACC

Statins

Should every patient get one?
4S Study—Lowering Total Cholesterol Reduces Mortality in Patients With and Without Diabetes

![Graph showing mortality comparison between Simvastatin and Placebo with and without diabetes.](image)


Heart Protection Study – Primary Prevention of CV Events in Patients With Diabetes and Without High LDL-C

- Diabetic patients in the Heart Protection Study
  - 5963 high-risk patients >40 years
    - Mean baseline LDL-C = 124 mg/dL
  - Simvastatin 40 mg vs placebo
  - 5-Year follow-up
  - 22% Reduction in major CV events (P<0.0001)
    - 27% reduction in 2462 patients with LDL-C <116 mg/dL
    - 33% reduction in 2912 patients without CVD

DSW3  Is red font deliberate?
wordsetc@chesco.com, 8/11/2005
**Statin Therapy – Number Needed to Treat**

- Diabetic patients – NNT
  - Without CAD 14
  - With CAD 4

CAD = coronary artery disease.

*Based on the HPS and 4S studies.


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**Primary Prevention of CV Events in Patients With Diabetes and Without High LDL-C**

- Diabetic patients in CARDS
  - 2838 Diabetic patients without CVD
    - Mean baseline LDL-C = 116 mg/dL
    - At least 1 additional CV risk factor
    - Atorvastatin 10 mg vs placebo, 3.9-year follow-up
    - 37% Decrease in major CV events (P=0.001)

- ASCOT-LLA
  - 2532 Diabetic patients with no CHD
    - Mean baseline LDL-C = 128 mg/dL
    - At least 2 additional CV risk factors
    - Atorvastatin 10 mg vs placebo, 3.3-year follow-up
    - 23% Decrease in major CV events or procedures (P=0.036)

In diabetics without CAD, data support statin therapy regardless of LDL-C level

CARDS = Collaborative Atorvastatin Diabetes Study.

ASCOT-LLA = Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm.


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**TNT: Low LDL-C Benefits Patients With Diabetes and CHD**

- Post hoc analysis:
  - 1501 subjects with CHD
  - Mean baseline LDL-C <100 mg/dL
- Atorvastatin 80 mg vs atorvastatin 10 mg, 4.9 year follow-up
  - Atorvastatin 80 mg: LDL=77 mg/dL
  - Atorvastatin 10 mg: LDL=99 mg/dL
- 25% reduction in risk of major CV events with atorvastatin 80 mg, compared to the 10-mg group (P=0.026)

Lowering LDL levels below suggested guidelines continues to benefit high-risk patients

Shepherd J on behalf of the TNT Diabetes Subcommittee and the TNT Steering Committee. Presented at the Annual Meeting of the American Diabetes Association; June 13, 2005; San Diego, California.

ACEIs/ARBs

Should every patient get one?

ACE Inhibitors Reduce CV and Renal Risk in Patients With Diabetes

• UKPDS
  — Tight blood pressure control reduced micro- and macrovascular risk
• UKPDS, FACET, CAPPP, ABCD meta-analysis
  — ACEIs reduce risk of CV and renal disease more effectively than other antihypertensive agents
• MICRO-HOPE
  — ACEIs reduce CV risk in patients who are normotensive at baseline

Steno 2: Key Takeaway

- Compared to conventional treatment, aggressive management of risk factors results in significant decreases in CV risk

Treat to Goal!
### Scientific Statements: Diabetes, CV Disease, and Hypertension

<table>
<thead>
<tr>
<th>• AHA Scientific Statement on Diabetes and CVD</th>
</tr>
</thead>
<tbody>
<tr>
<td>— BP goal in hypertension: &lt;130/85 mm Hg</td>
</tr>
<tr>
<td>— ACE inhibitors favored as antihypertensive agents</td>
</tr>
<tr>
<td>• ACE inhibitors probably slow progression of nephropathy, even in normotensive patients</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• JNC VII Report on Diabetic Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Combinations of 2 or more drugs to achieve BP goal (130/80 mm Hg)</td>
</tr>
<tr>
<td>— Thiazide-diuretics, β-blockers, ACEIs, ARBs, CCBs reduce CVD and stroke incidence</td>
</tr>
<tr>
<td>— ACEIs/ARBs reduce progression of diabetic nephropathy and reduce albuminuria</td>
</tr>
<tr>
<td>— ARBs reduce progression of macroalbuminuria</td>
</tr>
</tbody>
</table>


### ADA 2002 Clinical Practice Guidelines

<table>
<thead>
<tr>
<th>• Treatment of hypertension in patients with diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Initial drug therapy: ACEI, ARBs, β-blockers, diuretics</td>
</tr>
<tr>
<td>— If &gt;55 yrs, without hypertension but with another CV risk factor, consider an ACE inhibitor</td>
</tr>
<tr>
<td>— Treat to target of &lt;130 mm Hg systolic</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>• With diabetic nephropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Hypertensive type 2 diabetic patients – ARBs are the drugs of choice</td>
</tr>
<tr>
<td>— Type 1 diabetic patients – ACE inhibitors are preferred</td>
</tr>
<tr>
<td>— Combination of ACEI and ARBs will decrease albuminuria more than either agent alone</td>
</tr>
<tr>
<td>— If ACEI or ARBs are used, monitor serum potassium for development of hyperkalemia</td>
</tr>
</tbody>
</table>

**American Diabetes Association.** *Diabetes Care.* 2002;25(suppl 1):S71-S73, S85-S89

### Recommendation

<table>
<thead>
<tr>
<th>• ACEIs and ARBs in DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>— Recommend the use of an ACEI and/or ARB in all type 2 DM patients with at least 1 additional CV risk factor, and/or microalbuminuria</td>
</tr>
<tr>
<td>— Consider the use of ACEI and/or ARB in all other patients with type 2 DM</td>
</tr>
</tbody>
</table>
β-Blockers

Should every patient get one? Does it matter which one you use?

β-Blockers in Diabetes: UKPDS

• UKPDS (1998)
  — Captopril vs atenolol
  — 9-year follow-up
  — Similar decreases in BP
  — Similar decreases in diabetic complications

UKPDS=UK Prospective Diabetes Study.

β-Blockers in Diabetes: Gemini

• Study Design
  — Carvedilol vs metoprolol
  — 1235 diabetic patients with hypertension and receiving RAS blockers
  — 35 week follow up

• Results*
  — Similar decreases in BP
  — Carvedilol had no effect on A1C; metoprolol ↑ A1C
  — Carvedilol ↓ albumin/creatinine ratio, compared to metoprolol (16%, P=0.003)

Effect of Antihypertensive Medication on Renal Function in Hypertensive Patients With Type 2 Diabetes

- 52 Patients with NIDDM, nephropathy, and hypertension
- Annual decline in creatinine clearance (mL/min/1.73m²) with each medication
  - ACE inhibitor 1.0
  - Non-DCCP 1.4
  - β-Blocker 3.5*

*P=0.001 vs ACE I; P=0.004 vs Non-DCCP.

Recommendation

- β-blockers in DM
  - Recommend the use of β-blocker in all type 2 DM patients with heart failure, CAD and/or history of MI
  - Consider the use of β-blocker in all other patients with type 2 DM

Remember the ABCs for Diabetes Care

- “A” aspirin/A1C (goal ≤ 6.5%)
- “B” blood pressure control (goal <130/80)
- “C” cholesterol (LDL <100, non-HDL <130)
- “D” diet
- “E” exercise

*Treat to Goal!*

LDL=low density lipoprotein; HDL=high density lipoprotein.
Diabetes and Heart Failure

Epidemiology of Diabetic Heart Failure

- Framingham Study (risk of HF in diabetic patients)
  - 2x diabetic males
  - 5x diabetic females
  - 4x young diabetic males
  - 8x young diabetic females
- US HMO prevalence study
  - With diabetes, HF developed at a rate of 3.3% per year
- Each 1% elevation in hemoglobin A1C leads to a 15% increase in frequency of HF

Framingham Heart Study 30-Year Follow-up of CVD Events in Patients With Diabetes

(Ages 35–64)

<table>
<thead>
<tr>
<th>Risk ratio</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total CVD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CHD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermittent claudication</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

P<0.001 for all values, except stroke (P<0.05).
("Figure 2.5" from HYPERGLYCEMIA, DIABETES AND VASCULAR DISEASE, edited by Neil Ruderman et al, copyright © 1992 by American Physiological Society. Used by permission of Oxford University Press, Inc.)
**Insulin Resistance in CHF**

![Graph showing insulin resistance comparison between normal and CHF conditions.]

*\( \text{P}=0.01; \text{P}=0.007. \)


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**Therapies Demonstrated to Reduce Mortality in HF**

- ACEI (ARB)
- \( \beta \)-blockers
- Aldosterone antagonists
- Hydralazine-isosorbide dinitrate
- ICD
  - LVEF \( \leq \) 35, Class I, II, or III
  - Cardiac resynchronization
    - LVEF \( \leq \) 35%, QRS \( \geq \) 130 ms, Class III or IV

*R* by NY Heart Association criteria.

ACEI=angiotensin converting enzyme inhibitor; ARB=angiotensin receptor blocker; ICD=implantable cardioverter defibrillator; LVEF=left ventricular ejection fraction.


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**Aldosterone Blockade in HF**

**RALES: Randomized Aldactone Evaluation Study**

![Graph showing the probability of survival over follow-up months for spironolactone and placebo.]

RR 0.70 (0.60–0.82)

*\( \text{P}=0.001. \)

NYHA=New York Heart Association

1663 patients NYHA II, III, and IV, average age 65 and LVEF \( \leq \) 0.35, on ACEI, loop diuretic, ± digoxin randomized to spironolactone 25 mg PO qd vs placebo.

**Conclusions**

- Diabetic patients are at elevated risk for HF
- Combined neurohormonal blockade with the use of ACEI, aldosterone antagonists, and β-blockers is essential in the treatment of the type 2 diabetic patient with HF
- β-blockers and ACEI are useful in type 2 diabetic patients across the CVD continuum: before a CV event, for secondary prevention, and as soon as possible in HF

**Simple Steps to Reduce CV Events in Patients With Type 2 Diabetes**

- ASA in all patients
- Statin in all patients
- ACE/ARB in all patients with additional risk factor; consider in all patients
- β-Blocker in all patients with CAD/CHF or history of MI; consider in all patients
- Diet and exercise therapy
- Encourage smoking cessation
- Glucose management for small-vessel disease