New Concepts in Diabetes Underwriting 2017

Metropolitan Underwriting Discussion Group
Annual Meeting       January 2017

William Figura
Director of Underwriting

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Chief Medical Director

Penn Mutual Life
 Agenda
New Concepts in Diabetes Underwriting

— Diabetes epidemiology update
— New perspective: diabetes and vascular disease
— New perspective: diabetes and fatty liver
— Other “brain-changers”
  — HgbA1c levels
  — Bariatric surgery
  — Getting to the preferred diabetic – a thought experiment
While diabetes prevalence has increased in all groups, death rates continue a decades-long decline!
Diabetic mortality and cause of death: population study

40,000 diabetics
mean age = 58

Source: NEJM 2015
Diabetic mortality in insurance applicants

Diabetic Mortality vs. VBT2008

Mortality Ratio vs. Age

Source: J Ins Med (MIB) 2016
Multiple Impairment Mortality Experience Study: diabetes mellitus

<table>
<thead>
<tr>
<th>Sex</th>
<th>Rating</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>To 175%</td>
</tr>
<tr>
<td>Male</td>
<td>151%</td>
</tr>
<tr>
<td>Female</td>
<td>166%</td>
</tr>
</tbody>
</table>

Source: Multiple Medical Impairment Study 1998 (MIB, SOA, AAIM, HOLUA)
– Diabetes epidemiology update
– New perspective: diabetes and vascular disease
– New perspective: diabetes and fatty liver
– Other “brain-changers”
  – HgbA1c levels
  – Bariatric surgery
  – Getting to the preferred diabetic – a thought experiment
Case: Diabetes and vascular disease

55 year-old female
Ht: 5’8” (172 cm)  Wt: 228 lbs (103 kg)
BMI 34

➢ “Pre-diabetes”
➢ Rx: Atorvastatin; lisinopril-HCTZ
➢ Labs:
  ➢ HgbA1c – 6.4%-6.7%
  ➢ Total cholesterol 168 mg/dl (4.3 mmol/l)
  ➢ HDL cholesterol 70 mg/dl (1.8 mmol/l)
  ➢ TC/HDL ratio 2.4
  ➢ Triglycerides 100 mg/dl (1.12 mmol/l)

➢ LFTs
  ➢ AST 41 u/l  Normal to 34
  ➢ ALT 60 u/l  Normal to 44
  ➢ GGT 38 u/l  Normal to 50

➢ Abdominal ultrasound
  ➢ Diffuse fatty liver infiltration

➢ ECG
  ➢ Non-specific ST changes

➢ Exercise testing
  ➢ Negative stress echo 7 years ago
While the prevalence of serious diabetic vascular complications has declined, chronic renal disease prevalence has increased, reflecting the decrease in early cardiovascular mortality.
Carotid intimal thickness (CIMT) in diabetes

CIMT levels are increased in diabetes – a marker for increased risk of atherosclerosis
ABI results are often abnormal in diabetics

- reflect increased risk of atherosclerotic disease and peripheral vascular disease

- Arterial calcification and peripheral neuropathy in diabetics can lead to false positive ABI results
Vascular disease in diabetes

Large vessel (“macro-vascular”) disease: myocardial infarction; stroke; peripheral vascular disease

Small vessel (“micro-vascular”) disease: retinopathy; nephropathy; neuropathy

Invariably progressive???
Diabetes is a disease of the *endothelium*

A physical barrier between vessel wall and lumen

An endocrine organ that secretes a number of “mediators” that regulate:

- arterial tone
- coagulation
- platelet function

Source: Hiroshima University (Higashi) 2010
Diabetes Care (Avogaro) 2011
Endothelial cells circulate in the bloodstream in low numbers

Endothelial progenitor cells (EPCs) emerge from the bone marrow and can mature into endothelial cells

Function:
- Heal vascular injury
- Form new blood vessels

The number of EPCs are reduced and functionally impaired in diabetics with vascular disease

Source: Cardiovasc Res (Fadini) 2010
Therapies:

- GLP-1 receptor agonists:
  - Sitagliptin (Januvia/Janumet)
  - Saxagliptin (Onglyza)
- "EPC" bone-marrow-derived infusions

Challenges

- Drug side-effects
- Long-term improvement with cell therapies

Source: Diabetes Care (Avogaro) 2011; Cardiovasc Res (Fadini) 2010
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Case: Non-alcoholic steato-hepatitis (NASH)

65 year-old male   Ht: 5’10” (178 cm)   Wt: 240 lbs (110 kg)   BMI 34

- Diabetes x 15 years
- Rx: Metformin, Glipizide, Androgel
- Labs:
  - HgbA1c – 7.5%
  - Total cholesterol 162 mg/dl (4.2 mmol/l)
  - HDL cholesterol 28 mg/dl (0.72 mmol/l)
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- GGT 220 u/l  Normal to 50
Abdominal ultrasound/CT 2015 Indication: “Abdominal pain”

IMPRESSION:

1. Stable right lower lobe lung nodule.
2. Fatty liver
3. Renal cysts
4. Punctate calcifications within the pancreas which can be seen with chronic pancreatitis. No acute inflammation identified.
5. Mildly enlarged prostate gland
6. No suspicious lytic or blastic osseous lesions.
7. Gallstones

IMPRESSION: Echogenic liver, statistically a function of fatty infiltration. Other possibilities not excluded.

Clustering echogenic bili +/- tiny stones near the gallbladder neck. No compelling evidence of cholecystitis by ultrasound, however. No biliary tree dilatation.

Left-sided renal cysts, the dominant cyst slightly larger compared to CT from 2007, measuring up to 3.4 cm maximally.

Repeat CT cross-sectional imaging can be considered for further evaluation.
Fatty liver
Non-alcoholic fatty liver disease (NAFLD)

Increasingly common on liver ultrasounds and CT scans

Prevalence mirrors that of obesity and diabetes

Mortality assessment??

Thanks to Dr. Alison Moy!
Major diabetes complications

Cardiovascular disease
Eyes
Kidney
Feet
Co-morbidities

Fatty liver
Sleep apnea

http://www.idf.org/diabetesatlas
NAFLD – relationship to diabetes and more ominous liver disease

Predictors of fibrosis:
- BMI, type 2 diabetes
- Insulin resistance
- PNPLA3 genotype

Overproduction of:
- Glucose
- VLDL
- C-reactive protein, fibrinogen
- Coagulation factors
- Cholesterol

- Non-alcoholic steatohepatitis
- Cirrhosis
- Hepatocellular carcinoma
- Cholesterol gallstones
- Deep venous thromboembolism
- Type 2 diabetes
- Cardiovascular disease

Source: Lancet (Yki-Jarvinen) 2014
## Emerging Risk Factor Collaboration: Risk of Death in Diabetics vs Nondiabetics

<table>
<thead>
<tr>
<th>Death Outcome</th>
<th>Hazard Ratio (95% Confidence Intervals) Diabetes vs No Diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td>From any Cause</td>
<td>1.80 (1.71 to 1.90)</td>
</tr>
<tr>
<td>Renal Disease</td>
<td>3.02 (2.39 to 3.82)</td>
</tr>
<tr>
<td>Coronary Heart</td>
<td>2.31 (2.05 to 2.60)</td>
</tr>
<tr>
<td>Liver Disease</td>
<td>2.28 (1.90 to 2.74)</td>
</tr>
<tr>
<td>Other Vascular</td>
<td>1.73 (1.51 to 1.98)</td>
</tr>
</tbody>
</table>

Diabetes mellitus, fasting glucose, and risk of cause-specific death.


Collaborators (284)
## Distinguishing NASH from fatty liver

<table>
<thead>
<tr>
<th>Risk factor scoring to identify NASH</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>≥ 50</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td>Female</td>
</tr>
<tr>
<td><strong>AST level</strong></td>
<td>&gt;45</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td>&gt;30</td>
</tr>
<tr>
<td><strong>AST/ALT ratio</strong></td>
<td>≥ 0.8</td>
</tr>
</tbody>
</table>

**Sensitivity 74%**

**Specificity 66%**

Source: Liver International (Palekar) 2006
Assessing NASH severity – MRI/ultrasound elasticity

**Fibroscan**

**Sensitivity 62%**

**Specificity 91%**

Liver stiffness cut-offs in chronic liver diseases

<table>
<thead>
<tr>
<th>Matavir</th>
<th>F0-F1</th>
<th>F2</th>
<th>F3</th>
<th>F4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrosis</td>
<td>Mild</td>
<td>Sign</td>
<td>Severe</td>
<td>Cirrhosis</td>
</tr>
</tbody>
</table>

- LSM 2.5 – 7 kPa → Mild or absent fibrosis is likely
- LSM > 12.5 kPa → Cirrhosis is likely

NAFLD – mortality risk in diabetes

Prevalence

- 30% of the U.S. general population
- 75%-90% in obese patients
- 50%-75% in type 2 diabetics

Risks

- Mortality in diabetes – 2.2 times that of those without NAFLD
  - Major causes of death: malignancy (33%); cardiovascular disease (19%)
  - Other mortality risks: cirrhosis (2.5x general population); hepatocellular carcinoma (5%)

Source: Nat Rev Endocrin (Smith) 2011
Fibroscan: evaluation of liver fibrosis

<table>
<thead>
<tr>
<th>Test Name</th>
<th>Result</th>
<th>Flag</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALPHA 2 MACROGLOBULIN - Q</td>
<td>303 mg/dL</td>
<td>H</td>
<td>109-278</td>
</tr>
<tr>
<td>HAPTOGLOBIN - Q</td>
<td>88 mg/dL</td>
<td></td>
<td>43-212</td>
</tr>
<tr>
<td>APOLIPOPROTEIN A1 - Q</td>
<td>164 mg/dL</td>
<td></td>
<td>94-178</td>
</tr>
<tr>
<td>TOTAL BILIRUBIN - Q</td>
<td>1.1 mg/dL</td>
<td></td>
<td>0.2-1.2</td>
</tr>
<tr>
<td>GOT - Q</td>
<td>191 U/L</td>
<td>H</td>
<td>3-95</td>
</tr>
<tr>
<td>ALT - Q</td>
<td>129 U/L</td>
<td>H</td>
<td>0-46</td>
</tr>
<tr>
<td>FIBROSIS SCORE - Q</td>
<td>0.76</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIBROSIS STAGE - Q</td>
<td>F4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FIBROSIS INTERPRETATION - Q</td>
<td>(Report)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**FIBROSIS SCORE - Q**

<table>
<thead>
<tr>
<th>FIBRO Test Score</th>
<th>Metavir Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.21</td>
<td>F0</td>
<td>No fibrosis</td>
</tr>
<tr>
<td>0.22-0.81</td>
<td>F1</td>
<td>Minimal fibrosis</td>
</tr>
<tr>
<td>0.82-1.50</td>
<td>F2</td>
<td>Moderate fibrosis</td>
</tr>
<tr>
<td>1.51-4.00</td>
<td>F3</td>
<td>Advanced fibrosis</td>
</tr>
<tr>
<td>4.01-10.00</td>
<td>F4</td>
<td>Severe fibrosis</td>
</tr>
</tbody>
</table>

**NECROINFLAMMAT ACT SCORE - Q**

<table>
<thead>
<tr>
<th>NECROINFLAMMAT ACT GRADE - Q</th>
<th>A3</th>
</tr>
</thead>
<tbody>
<tr>
<td>NECROINFLAMMAT INTERP - Q</td>
<td>(Report)</td>
</tr>
</tbody>
</table>

**NECROINFLAMMAT ACT Score**

<table>
<thead>
<tr>
<th>Activity Score</th>
<th>Metavir Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00-0.17</td>
<td>A0</td>
<td>No activity</td>
</tr>
<tr>
<td>0.18-0.36</td>
<td>A1</td>
<td>Minimal activity</td>
</tr>
<tr>
<td>0.37-0.52</td>
<td>A2</td>
<td>Significant activity</td>
</tr>
<tr>
<td>0.61-1.00</td>
<td>A3</td>
<td>Severe activity</td>
</tr>
</tbody>
</table>

**REFERENCE ID - Q**

1180545

**FOOTNOTE - Q**

The validity of results is dependent on compliance with the prescriptive and analytical conditions recommended by the manufacturer. The tests have to be performed for acute hepatitis, acute pancreatitis, acute inflammation, acute hepatitis cholangitis. The advice of a specialist should be sought for interpretation in chronic hepatitis and Gilbert's syndrome. The test interpretation is not validated in liver transplant patients. Isolated extreme values of one of the
Case: Non-alcoholic steato-hepatitis (NASH)

65 year-old male  Ht: 5’10” (178 cm)  Wt: 240 lbs (110 kg)  BMI 34

- Diabetes x 15 years
- Rx: Metformin, Glipizide, Androgel
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HgbA1c levels correlate with mortality in those at risk for diabetes

- metabolic syndrome
- PCOS

What about in known diabetics??

For diabetics, the lower the HgbA1c, the better?
Current diabetes therapeutic targets

Lowering A1C below or around 7.0% shown to reduce
- Microvascular complications
- Macrovascular disease*

More or less stringent targets may be appropriate for individual patients if achieved without significant hypoglycemia or adverse events

More stringent (<6.5%)
- Short diabetes duration
- Long life expectancy
- No significant CVD/vascular complications

Less stringent (<8%)
- Severe hypoglycemia history
- Limited life expectancy
- Advanced microvascular or macrovascular complications
- Extensive comorbidities
- Long-term diabetes in whom general A1C target difficult to attain

7.0%!!

American Diabetes Association
http://www.ndei.org/dsl/mainpage.aspx

Radically different therapeutic approaches from the American and Canadian Diabetes Associations

Canadian Diabetes Association
8.5%!!
Intensive HgbA1c lowering in diabetics

Meta-analysis: All-cause Mortality

<table>
<thead>
<tr>
<th>Trials</th>
<th>Number of Events (Annual Event Rate, %)</th>
<th>Favours More Intensive</th>
<th>Favours Less Intensive</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCORD</td>
<td>257 (1.41)</td>
<td>203 (1.14)</td>
<td>–1.01</td>
<td>1.22 (1.01–1.46)</td>
</tr>
<tr>
<td>ADVANCE</td>
<td>498 (1.86)</td>
<td>533 (1.99)</td>
<td>–0.72</td>
<td>0.93 (0.83–1.06)</td>
</tr>
<tr>
<td>UKPDS</td>
<td>123 (0.13)</td>
<td>63 (0.25)</td>
<td>–0.66</td>
<td>0.96 (0.70–1.33)</td>
</tr>
<tr>
<td>VADT</td>
<td>102 (2.22)</td>
<td>95 (2.06)</td>
<td>–1.16</td>
<td>1.07 (0.81–1.42)</td>
</tr>
<tr>
<td>Overall</td>
<td>980</td>
<td>884</td>
<td>–0.88</td>
<td>1.04 (0.90–1.20) (Q=5.71, p=0.13, I²=47.6%)</td>
</tr>
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</table>

No impact on mortality!

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Can Weight-Loss Surgery Cure Diabetes?

Some people with Type 2 diabetes can put their medicine aside.

Of the types of weight-loss surgery, gastric banding typically has the most powerful effect.
52 year-old female  Ht: 5’1” (157 cm)  Wt: 210 lbs (95 kg)  BMI 40

- Application: LOV 6 months ago for “physical” – no meds
- Rx profile: no medications for past 3 years
- Labs:
  - HgbA1c 5.4%
  - Cholesterol 259 mg/dl (6.7 mmol/l)
  - HDL cholesterol 89 mg/dl (2.3 mmol/l)
  - Triglycerides 109 mg/dl (1.2 mmol/l)

PMH: “Gastric bypass” 10 years ago; “Lap band” 5 years ago

- Prior to lap-band surgery
  - Wt 228 lbs (103 kg)
  - HgbA1c 7.6%
  - Rx: Metformin
Bariatric surgery in diabetes – 2 year follow-up

Promising 2 year results suggested diabetes control or “cure”

Source: NEJM (Mingrone) 2012
At 15 years, 70% of those undergoing bariatric surgery are again diabetic.

Macrovascular complications remain somewhat less frequent in the bariatric surgery group.

Source: JAMA (Sjostrom) 2014
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Start with diabetes-rated applicant
Credit for control and other risk factors
Best case – approaching standard mortality risk
Thought experiment – find the “perfect person” and make them a diabetic!
The “best” cardiovascular risk

Under age 50
- BP 120/80
- TC/HDL 3.2
- BMI 21

Over age 60
- BP 140/80
- TC/HDL N/A
- BMI 26
Adding “best” cardiovascular risks to baseline mortality assessment

“Best risks” clearly improve baseline mortality assessment
Adding diabetes risk (+50) to “best” cardiovascular risks

Thought experiment failure – I was unable to get diabetic mortality estimate better than standard with “best risks”

Why????

- Population analyzed
- True diabetes risk!
Diabetic mortality in insurance applicants – impact of treatment

Mortality ratio for hyperglycemia

Mortality ratio for diet-controlled

Mortality ratio for oral medication

Mortality ratio for insulin use

Source: J Ins Med (MIB) 2016
Diabetes epidemiology update

New perspective: diabetes and fatty liver

New perspective: diabetes and vascular disease

Other “brain-changers”

- HgbA1c levels
- Bariatric surgery
- Calcium scans

Getting to the preferred diabetic – a thought experiment

Improving the diabetic mortality assessment – other ideas?
Moving substandard closer to standard!

– Exercise testing
– Renal function
– Coronary revascularization (CABG > Stenting)
NT-proBNP and diabetes

NT-proBNP levels predict cardiovascular events in diabetics

Data suggest that low initial NT-proBNP levels are predictive of better cardiac and mortality outcomes

Early data indicate that treatment protocols based on reducing NT-proBNP levels improved hospitalization

Too early to assess survival impact

NT-proBNP ability to predict freedom from cardiac events or death

Source: J Am Coll Cardiol (PONTIAC) 2013 
Eur Heart J (Huelsmann) 2008
Any other ideas???
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Thanks!