Personalising Treatment in Diabetes

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Diabetes is highly heterogeneous

ALL ARE DIFFERENT – PHENOTYPICALLY/BIOLOGICALLY

Yet we treat them all the same!
### The ADA/EASD consensus guidelines

**Table 1: Treatment Algorithm**

<table>
<thead>
<tr>
<th>Metformin</th>
<th>Sulfonylurea</th>
<th>Thiazolidinedione</th>
<th>DPP-4 Inhibitor</th>
<th>GLP-1 receptor agonist</th>
<th>Insulin (usually basal)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high</td>
<td>high</td>
<td>high</td>
<td>intermediate</td>
<td>high</td>
<td>highest</td>
</tr>
<tr>
<td>moderate</td>
<td>moderate</td>
<td>low risk</td>
<td>low risk</td>
<td>low risk</td>
<td>high risk</td>
</tr>
<tr>
<td>risk</td>
<td>gain</td>
<td>weight neutral</td>
<td>weight gain</td>
<td>weight loss</td>
<td>weight gain</td>
</tr>
<tr>
<td>hypoglycaemia</td>
<td>low</td>
<td>hypoglycaemia</td>
<td>variable</td>
<td>hypoglycaemia</td>
<td>variable</td>
</tr>
</tbody>
</table>

If needed to reach individualised HbA1c target after \(\sim 3\) months, proceed to two-drug combination (order not meant to denote any specific preference):

1. **Metformin**
2. **Sulfonylurea**
3. **Thiazolidinedione**
4. **DPP-4 Inhibitor**
5. **GLP-1 receptor agonist**
6. **Insulin (usually basal)**

If needed to reach individualised HbA1c target after \(\sim 3\) months, proceed to three-drug combination (order not meant to denote any specific preference):

1. **Metformin**
2. **Sulfonylurea**
3. **Thiazolidinedione**
4. **DPP-4 Inhibitor**
5. **GLP-1 receptor agonist**
6. **Insulin (usually basal)**

**Then add any other**

### ADA/EASD joint position statement
“Choice is based on patient and drug characteristics”

THERE IS VIRTUALLY NO PUBLISHED DATA TO GUIDE THIS DECISION!!
The ‘Anti-Precision’ Argument

Why bother trying to target a drug to an individual? Why not just try and see if it works?

• SIGN guidelines
  – Stop drug if HbA1c does not improve by 0.5% (5mmol/mol)

• NICE guidelines
  – GLP-1RA - stop if HbA1c reduction not greater than 0.5%
HbA1c can vary widely even within blocks of treatment

One person:

(mean) SD is 7mmol/mol
so SD of estimates of falls ~10mmol/mol

mean treatment effect sizes are 10 mmol/mol
Given the variation in HbA1c we can only be confident that an individual has responded or not responded ~25% of the time.

Distributions for baseline HbA1c ~8

Black: observed
Red: if differences all due to chance

Only extreme values (■) cannot be due to chance, ~25% of total over all baseline levels.

We can predict which drug should be better for a particular subgroup of people based upon their characteristics, but we cannot say if were right (after we start the drug)!
An individualized approach: predicting who will respond to what drug best with least side effects

Person with Diabetes
Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR
Age, Sex, BMI, Waist
Fasting insulin
Lipids
+/- Genotype (or WGS)
+/- Biomarker panel

Sitagliptin
Likelihood of response 88%
Likelihood of ADR 2%

Pioglitazone
Likelihood of response 50%
Likelihood of ADR 10%

SU
Likelihood of response 20%
Likelihood of ADR 1%
MASTERMIND
MRC APBI STRatification Extreme Response Mechansim IN Diabetes

Andrew Hattersley & Ewan Pearson

What patient characteristics determine response to treatment in Type 2 diabetes?

CPRD/ADOPT
Bev Shields
Mike Wheedon
Lauren Rogers
John Dennis

GoDARTS
Louise Donnelly
Mike Lonergan

UKPDS
Rury Holman
Orunsola Agbaje
Response to TZD and SU influenced by **SEX** and **OBESITY**

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Dennis et al. manuscript under review
An individualized approach: predicting who will respond to what drug best with least side effects

Person with Diabetes
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RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
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Slim Males -- SU; Obese Females - Pio
An individualized approach: predicting who will respond to what drug best with least side effects

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Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR

Age, Sex, BMI, Waist
Fasting insulin
Lipids
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What about genotype?
A subtype of sulphonylurea sensitivity in Type 2 diabetes

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Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR
Age, Sex, BMI, Waist
Fasting insulin
Lipids
+/- Genotype (or WGS)
+/- Biomarker panel

Sitagliptin
Likelihood of response 50%
Likelihood of ADR 2%

Pioglitazone
Likelihood of response 50%
Likelihood of ADR 1%

SU
Likelihood of response 99%
Likelihood of ADR 20%

Figures are illustrative only!
Change in FPG mmol/l

Pearson et al. Lancet 2003

p<0.0001
Phenotypically Type 2DM

Yet SU sensitive

Changed from Metformin and Rosiglitazone to Gliclazide 80mg od

HbA1c from 8% to 7.2%
Insulin Cessation in HNF1A MODY

Median time on insulin 20 years prior to transfer to SU

Shepherd Diabetes Care 2003
Ah – but MODY is rare – what about genetic impact on drug response in ‘type 2 diabetes’?

Person with Diabetes
Treated with Metformin
HbA1c 7.5% (58mmol/mol)

RESPONSE PREDICTION CALCULATOR

- Age, Sex, BMI, Waist
- Fasting insulin
- Lipids
- +/- Genotype (or WGS)
- +/- Biomarker panel

METFORMIN
THIAZOLIDINEDIONES
SULPHONYLUREAS
GLP-1 R Agonists
Insights from genetic studies of metformin action

The value of EMR linked to bioresources

A Role for Genome Wide Association Studies
A National Diabetes System for Scotland

Total Scottish Population 5.3M

People with diabetes: 268,154 All patients nationally are registered onto a single register; the SCI-DC register

SCI-DC used in all hospitals

Nightly capture of data from all 1200 primary care practices across Scotland
SCI-DC: harnessing data from multiple Sources
Data from Cradle to Grave

Scottish Birth Record SBR

BIRTH

Immunisation

GP consultations

Dental SMR13

Out patients SMR00

Mental Health SMR04

Hospital Admissions SMR01

DEATH

Prescribing

A&E

Screening

Imaging

Cancer registry

Cancer registrations SMR06

Very little migration out of Scotland (or even out of region)
40,000 people in Tayside are in a bioresource

10% of the population

GoDARTS
18,000 patients with T2DM and controls

All prescription encashment for 30 years

GWAS
152,000

Consent for:

Access to medical records

Collection of leftover blood

Linkage of genetic information to medical record for clinical use

Roll out to everyone with Diabetes in Scotland via Retinal Screening Service now starting
Glycaemic Response to Metformin

Considerable variation in how well metformin works

Is this intrinsic to individual biology or metabolism

Or does this reflect:

Adherence to medication?
Lifestyle change?
Stage of disease?

Data from DARTS, Tayside, Scotland

Baseline Hba1c 8-9%
Mean reduction = 1.315
Std. Dev. = 1.05189
N = 290
Heritability – what component of variation in metformin response is genetic?

**Twin Studies**
- MZ: Share 100% Variants
- DZ: Share 50% Variants

**GWAS Studies**
- Variants shared in the population
Metformin response is highly heritable

Glycaemic response to Metformin is, at least in part, a feature of the biology of the individual

Zhou, Pearson Lancet Diabetes & Endocrinology 2014
Genome wide association study of glycaemic response to Metformin makes no assumption about mechanism

Combined analysis (incl UKPDS) (n=4200)  
OR 1.34  P=1.9*10^-9

Zhou, Bellenguez... ...Palmer, Donnelly, Pearson  Nat Genetics Feb 2011
Logistic Regression Results at ATM Region

rs11212617
p = 1.1 x 10^{-7}

Zhou, Bellenguez ..., Palmer, Donnelly, Pearson

Nat Genetics Feb 2011
NPAT/ATM

• ATM (a PI 3-kinase) main function is in controlling cell cycle progression after DNA damage

• Recessive mutations cause Ataxia Telangiectasia
  – Cerebellar ataxia
  – Malignancies - lymphoproliferative
  – Premature ageing
  – INSULIN RESISTANCE ++ and less commonly diabetes

• NPAT activates ATM, and is involved in cell cycle control
Follow up work

MRC funding (£0.5M) to Calum Sutherland (with Rory McCrimmon, Mike Ashford, Colin Palmer)

Role of NPAT on weight and glucose response to Metformin

Wellcome Investigator

Patients with Ataxia Telangiectasia

Diabetes, Insulin Resistance, Fatty Liver, Cancer

Dual labelled MMTs, fat turnover, liver imaging, iPSCs
Other genes involved?

Genome wide association study of glycaemic response to Metformin makes no assumption about mechanism
**SLC2A2 (Glut2)**

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>Baseline Adjusted</th>
<th>Baseline Non-Adjusted</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Beta</td>
<td>SE</td>
</tr>
<tr>
<td>GoDARTS GWAS Discovery*</td>
<td>1478</td>
<td>0.127</td>
<td>0.038</td>
</tr>
<tr>
<td>GoDARTS Internal Replication*</td>
<td>1625</td>
<td>0.1</td>
<td>0.038</td>
</tr>
<tr>
<td>UKPDS Replication</td>
<td>1223</td>
<td>0.136</td>
<td>0.061</td>
</tr>
<tr>
<td>Meta-Analysis</td>
<td>4326</td>
<td>0.117</td>
<td>0.025</td>
</tr>
</tbody>
</table>

Beta is reduction in HbA1c from baseline per C allele at rs8192675
Robust evidence that variation in Glut 2 alters response to metformin

0.15% greater reduction in HbA1c Per minor allele at rs8192675 in SLC2A2 (GLUT2)
What’s the effect size?

• Effect is greater in the obese
  – CC at rs8192675 4mmol/mol greater reduction in HbA1c than TT
  – Dose difference of 550mg metformin between these genotype groups
  – About half the effect seen for starting a new diabetes drug e.g. DPP-4 inhibitor
Clinically important genetic effects on metformin treatment?

GI intolerance with Metformin

~20% of patients treated with Metformin have GI side effects with metformin treatment

~5-10% cannot tolerate metformin at all

Why?

Can we find a way to avoid intolerance in these individuals?
Metformin and the gut enterocytes

Metformin

PMAT, OCTN1
[Metformin]

Gut Lumen

Apical

[Metformin]

Basolateral

Blood

OCT3, OCT1

Metformin

Metformin

Metformin

Metformin

OCT1
# OCT1 transport

## Genetic variation
- R61C
- C88R
- G401S
- M420del
- G465R

8% of us carry two loss of function variants

## OCT1 Interacting Drugs
- TCA
- PPI
- VERAPAMIL
- DILTIAZEM
- DISOPYRAMIDE
- QUINIDINE
- PRAZOSIN
- DOXAZOSIN
- SPIRONOLACTONE
- TRIMETHOPRIM
- ROSIGLITAZONE
- REPAGLINIDE
Side effects

**Association of Organic Cation Transporter 1 With Intolerance to Metformin in Type 2 Diabetes: A GoDARTS Study**

*Diabetes 2015;64:1786–1793 | DOI: 10.2337/db14-1388*

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**Table 2—Logistic regression model of metformin intolerance**

<table>
<thead>
<tr>
<th></th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.10 (1.08–1.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Sex (females vs. males)</td>
<td>1.85 (1.33–2.57)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Weight</td>
<td>0.99 (0.98–1.00)</td>
<td>0.064</td>
</tr>
<tr>
<td>Use of OCT1-inhibiting drugs</td>
<td>1.64 (1.20–2.25)</td>
<td>0.002</td>
</tr>
<tr>
<td>Two reduced-function OCT1 alleles</td>
<td>2.41 (1.48–3.93)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Logistic regression analysis included 205 intolerant and 1,650 tolerant patients.

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Combined effect of OCT1 genotype and drug on metformin intolerance
Validation in a Recruit by Genotype clinical trial

Randomised, placebo-controlled matched cross-over design.
THIAZOLIDINEDIONES

Work best in obese females

Work best in insulin resistant (with fatty liver)

What about genotype?

Both Rosi and Pio are metabolised by CYP2C8
Variants in CYP2C8 increase metabolism

Both are transported by SLCO1B1
Variants in SLCO1B1 reduce transport
Glycaemic response to ROSIGLITAZONE

Patients with reduced transport and normal metabolism by CYP2C8 respond very well.

Patients with normal transport and increased metabolism by CYP2C8 respond poorly.

Dawed et al. Diabetes Care 2016
Weight gain with ROSIGLITAZONE

The genetically poor responders gain little weight.

The genetically good responders gain weight (4kg).

<table>
<thead>
<tr>
<th>CYP2C8</th>
<th>W/W</th>
<th>W/W</th>
<th>W/V</th>
<th>V/V</th>
</tr>
</thead>
<tbody>
<tr>
<td>SLCO1B1</td>
<td>W/V</td>
<td>W/W</td>
<td>W/W</td>
<td>W/W</td>
</tr>
</tbody>
</table>

Dawed et al. Diabetes Care 2016
Pharmacogenetic effect of CYP2C8 is seen for Rosiglitazone not Pioglitazone

Pioglitazone metabolites are active
Rosiglitazone metabolites are inactive

Dawed et al. Diabetes Care 2016
SULPHONYLUREAS

Slim Men

Genotype?

- CYP2C9 *2*2 or *2*3 or *3*3

6% of population

3.44 times more likely to achieve an A1c <7%

Zhou et al. CPT 2009

Genotype?

T2D risk variants in TCF7L2 halve the likelihood of achieving treatment target

Pearson et al. Diabetes 2007
Personalizing treatment in T2DM

**Metformin**
- Best in slim people
- Better with reduced GLUT2 transport
- Side effects in those with reduced OCT1 transport

**TZDs**
- Best in obese women
- Response and weight gain with Rosiglitazone altered by CYP2C8 and SLCO1B1 activity

**Sulphonylureas**
- Best in slim men
- 3.44 times better in those who metabolise SU slowly (CYP2C9)
- Better with KCNJ11/ABCC8 mutation
- Worse in those with TCF7L2 risk variants
- EXCELLENT in those with HNF1A/4A/ABCC8

**GLP-1RA**