Diabetes and Heart Failure: Can I help, Sweetheart?

Addressing an Unmet through “Proof of Concept“ Studies

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Professor of Cardiology
University of Dundee
In 1888 the German physician Ernst von Leyden reported the striking finding of paroxysmal nocturnal dyspnoea in patients with diabetes mellitus.

Prevalence of Diabetes in patients with Heart Failure

- Population studies
  - 12%-30% of symptomatic CHF
- Hospitalized patients
  - 30-45% of hospitalized patients

Thrainsdotter IS et al. Diabetes Care 2005
Harris MI et al. Diabetes Care 2006
Greenberg BH Am Heart J 2007
DM and HF hospitalization

• National Diabetes Audit (2011-2012) of over 2 million T2DM patients
• T2DM patients have a 74 per cent greater risk of HF hospitalization
• 28 % of HF admissions involve a patient with diabetes.

http://www.hscic.gov.uk/catalogue/PUB12421
CHF and mortality in diabetics

Bertoni AG et al. Diabetes Care 2004; 27: 699-703

5-yr survival rate
80% vs 12.5%
Research Program

- Better Understand the pathophysiology
- Define Therapeutic Strategies for these Patients

Large patient cohorts with NHS electronic record linkage

Consented bio-resource

‘Proof of concept’ Clinical trials
Why do diabetics develop heart failure?

• Risk factors for HF are common in diabetics
  • CAD, Hypertension, Obesity, Renal dysfunction, Increased arterial stiffness

• ‘Diabetic cardiomyopathy’
  • Disturbance in cardiac metabolism
  • Abnormal intracellular signalling and calcium handling
  • Neurohormonal activation
  • Advanced glycation end products

Unanswered questions?

• How important is glycaemic control?
  • Hyperglycaemia
    • Up-regulate the renin-angiotensin-aldosterone system,
    • Increase oxidative stress, promote accumulation of advanced glycation end-products (cause interstitial fibrosis)

Miki T, Yuda S, Kouzu H, Miura T. Heart Fail Rev. 2012
Impact of Glycemic Control on HF Risk:
Each 1% elevation in HbA1c leads to a 15% increase in risk of HF

Based on a single HbA1c measure
Intense Glycaemic Control may not be good in T2DM

<table>
<thead>
<tr>
<th></th>
<th>VADT</th>
<th>ACCORD</th>
<th>ADVANCE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td>Non-fatal MI</td>
<td>Non-fatal MI</td>
<td>Non-fatal MI</td>
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<tr>
<td></td>
<td>Non-fatal stroke</td>
<td>Non-fatal stroke</td>
<td>Non-fatal stroke</td>
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<tr>
<td></td>
<td>CVD death</td>
<td>CVD death</td>
<td>CVD death</td>
</tr>
<tr>
<td></td>
<td>Hospitalization for CHF</td>
<td>Revascularization</td>
<td></td>
</tr>
<tr>
<td>Hazard Ratio for</td>
<td>0.87 (0.73 – 1.04)</td>
<td>0.90 (0.78 – 1.04)</td>
<td>0.94 (0.84 – 1.06)</td>
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<tr>
<td>primary outcome</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
<td>(95% CI)</td>
</tr>
<tr>
<td>Hazard Ratio for</td>
<td>1.07 (0.80 – 1.42)</td>
<td><strong>1.22 (1.01 – 1.46)</strong>*</td>
<td>0.93 (0.83 – 1.06)</td>
</tr>
<tr>
<td>mortality</td>
<td>(95% CI)</td>
<td></td>
<td></td>
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</tbody>
</table>

*P=0.04
Record linkage in Dundee
Time updated analysis with longitudinal HbA1c and risk of incident CHF

- 8683 T2DM individuals.
- 701 (8%) developed CHF during FU (mean 5.5 yrs)
- HbA1c <6% (hazard ratio =1.60; 95% CI, 1.38-1.86; P value <0.0001)
- HbA1c >10% (hazard ratio =1.80; 95% confidence interval, 1.60-2.16; P value <0.0001)

HbA1c and Outcome in T2D and HF: Existence of a ‘Sweet’ Spot

HbA1c and Outcome in T2D and HF: Existence of a ‘Sweet’ Spot

More use of SU, insulin, TZDs

Drug

Intended or Unintended Tissue

“On-Target” Effects

“Off-Target” Effects

Intended Receptor

Unintended Receptor

Drug

metabolite

R

R
Glucose-lowering drugs or strategies and cardiovascular outcomes in patients with or at risk for type 2 diabetes: a meta-analysis of randomised controlled trials

Jacob A Udell, Matthew A Cavender, Deepak L Bhatt, Saurav Chatterjee, Michael E Farkouh, Benjamin M Scirica

Summary

Background Some glucose-lowering drugs or strategies adversely affect cardiovascular outcomes. We aimed to assess the extent to which glucose lowering by various drugs or strategies increases the risk of heart failure in patients with or at risk for type 2 diabetes, and to establish whether risk is associated with achieved differences in glycaemia or weight control.

Methods We searched Ovid Medline, the Cochrane Library, and meeting abstracts up to Feb 20, 2015, for large randomised controlled trials of glucose-lowering drugs or strategies that assessed cardiovascular outcomes. The primary endpoint was incidence of heart failure. We derived pooled risk ratios (RRs) with random-effects models.

14 trials, with mean duration 4·3 (2·3) years, comprising 95 502 patients, of whom 3907 (4%) patients developed a heart failure event
## PPAR agonists

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean</th>
<th>CI Lower</th>
<th>CI Upper</th>
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<tbody>
<tr>
<td>2005 PROactive</td>
<td>281</td>
<td>2605</td>
<td>198</td>
<td>2633</td>
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<tr>
<td>2006 ADAPT</td>
<td>22</td>
<td>1456</td>
<td>28</td>
<td>2895</td>
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<tr>
<td>2006 DREAM</td>
<td>14</td>
<td>2635</td>
<td>2</td>
<td>2634</td>
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<tr>
<td>2009 BARIT2</td>
<td>248</td>
<td>1183</td>
<td>218</td>
<td>1185</td>
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<tr>
<td>2009 RECORD</td>
<td>61</td>
<td>2220</td>
<td>29</td>
<td>2227</td>
</tr>
<tr>
<td>2014 AleCardio</td>
<td>122</td>
<td>3616</td>
<td>100</td>
<td>3610</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>13715</td>
<td>15184</td>
<td>35.9%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0.04$, $\chi^2=13.82$, df=5; $p=0.017$; $I^2=64\%$

Test for overall effect: $Z=3.29$; $p=0.0010$

## DPP-4 inhibitors

<table>
<thead>
<tr>
<th>Study</th>
<th>N</th>
<th>Mean</th>
<th>CI Lower</th>
<th>CI Upper</th>
</tr>
</thead>
<tbody>
<tr>
<td>2013 EXAMINE</td>
<td>106</td>
<td>2701</td>
<td>89</td>
<td>2679</td>
</tr>
<tr>
<td>2013 SAVOR-TIMI</td>
<td>289</td>
<td>8280</td>
<td>228</td>
<td>8212</td>
</tr>
<tr>
<td>Subtotal</td>
<td></td>
<td>10981</td>
<td>10891</td>
<td>16.8%</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2=0.00$, $\chi^2=0.15$, df=1; $p=0.70$; $I^2=0\%$

Test for overall effect: $Z=2.94$; $p=0.0033$
Thiazolidinediones

- Potent insulin sensitizer
- ‘Off Target’ Effects
  - Fluid retention and weight gain (1-3 kg)
  - Increased incidence of CHF
- ADA/ AHA consensus statement
  - Should not be used in patients with NYHA III/IV HF
“On-Target” Effects

“Off-Target” Effects
Drug metabolite

Intended or Unintended Tissue

“On-Target” Effects

“Off-Target” Effects

Intended Receptor

Unintended Receptor

Hypos, Weight gain
ACCORD: higher mortality in participants who experienced severe hypoglycaemia

The cause of the increased mortality could not be proven; severe hypoglycaemia was implicated

SH = severe hypoglycaemia
Risks and Benefits of Glucose-lowering Medications

Figure 4  Events per 1000 patient-years for representative endpoints.

FDA approval raised threshold for approval of DM drug

1. Study patients must include individuals with relatively advanced disease, elderly patients, and patients with some degree of renal impairment.

2. A minimum of 2 years’ CV safety data must be provided.

3. All phase 2 and 3 studies should include a prospective independent adjudication of CV events. Adjudicated events should include CV mortality, MI, and stroke and can include hospitalization for ACS, urgent revascularization procedures, and possibly other end points.
Diabetic cardiomyopathy

Advanced glycation endproducts

\[ \uparrow \text{Protein Kinase C} \]

Post-translational modification

\[ \uparrow \text{Insulin} \]

\[ \downarrow \text{SERCA 2a} \]

Oxidative stress

Diabetic microangiopathy

Induction of foetal gene Programme

\[ \uparrow \text{Myocardial mass} \]

\[ \uparrow \text{Myocardial fibrosis} \]

\[ \uparrow \text{Myocardial } O_2 \text{ consumption} \]

CPT-1

Promotes use of Free fatty acids

Contractile dysfunction

Myocyte apoptosis

Collagen III and collagen IV proteins were increased in the heart of insulin resistant obese mice.
High fat diet feeding induced insulin resistance in heart.

MMP9 deletion exacerbated cardiac insulin resistance in high fat-fed mice.

? Therapeutic potential for anti-fibrotic agents (tranilast, FT011)

Chronic hyaluronidase treatment improved cardiac insulin resistance in high fat-fed mice.
“Proof of Concept’ Studies of anti-fibrotic agents:
? Surrogate end points

• Plasma Biomarkers
  • Procollagen aminoterminal propeptide type I (PINP) and type III (PIIINP) levels
  • Soluble ST2
  • Galectin

• Imaging
  • Late Gadolinium enhancement
  • T1 mapping
Relationship Between Diabetes and Heart Failure
CHF: an insulin resistant state

Potential Mechanisms for development of DM in CHF

- Sympathetic activation
  - ↓ insulin sensitivity
  - ↓ insulin release
  - ↑ hepatic glucose production
  - ↑ glucagon production and lipolysis
- Decreased skeletal muscle mass (consequential sedentary lifestyle)
- Impaired endothelial function and ↓ skeletal blood flow
- Pro-inflammatory cytokines and leptin

61% of CHF patients have Insulin Resistance

Insulin resistance and outcome

- N=105 CHF pt
- FU 44 mths
- Insulin resistant patients (below median value) had worse 2 y survival
  - 61% vs 85% [Risk ratio 0.38, P=0.001]

Doehner W et al. JACC 2005;46; 1019-26
Insulin resistance and heart failure: A vicious cycle

Research Program

- Better Understand the pathophysiology
- Define Therapeutic Strategies for these Patients

Large patient cohorts with NHS electronic record linkage
Consented bio-resource
‘Proof of concept’ Clinical trials
Treatment of Diabetes in HF

Conundrum

noun (con-nun'drum)

1. a riddle whose answer is, or involves a pun
2. a question or problem having only a conjectural answer
3. an intricate and difficult problem with a whimsical solution
Thiazolidinediones

- Potent insulin sensitizer

- ‘Off Target’ Effects
  - Fluid retention and weight gain (1-3 kg)
  - Increased incidence of CHF

- ADA/ AHA consensus statement
  - Should not be used in patients with NYHA III/IV HF
Risk of cardiovascular disease and all cause mortality among patients with type 2 diabetes prescribed oral antidiabetes drugs: retrospective cohort study using UK general practice research database

Risk of a first episode of CHF with SU:

HR 1.46 (1.32 to 1.63) (P<0.001)
Sulphonylureas may not be good (when compared to metformin)

- Saskatchewan Health databases
- SU not as good as metformin

Eurich et al. Diabetes Care 2005
Metformin and safety in CHF

- Historical concern of lactic acidosis largely based on previous experience with phenformin.
- Systematic review of metformin use in T2DM with over 70,000 patient years follow-up demonstrated no cases of fatal or nonfatal lactic acidosis.
- How safe is metformin in patients with CHF?

Roussel R et al. Arch Intern Med 2010
30% lower risk of mortality in metformin users

HR, 0.67 (95% CI 0.51-0.88).

Evans J et al. Am J Cardiol 2010
Guidelines for the prevention, detection and management of chronic heart failure in Australia

Updated October 2011

- Metformin appears to be safe to use in recent analysis of patients with heart failure, except in cases of concomitant renal impairment.¹⁸³
Metformin improves cardiac function in animal models

Improvement of Cardiac Functions by Chronic Metformin Treatment Is Associated With Enhanced Cardiac Autophagy in Diabetic OVE26 Mice
Zhonglin Xie,1 Kai Lau,2,3 Bonnie Eby,2 Pedro Lozano,3,4 Chaoyong He,1 Becky Pennington,3 Hongliang Li,1 Shradha Rathi,4 Yunzhou Dong,1 Rong Tian,5 David Kem,1,3 and Ming-Hui Zou1

Metformin Prevents Progression of Heart Failure in Dogs Role of AMP-Activated Protein Kinase
Hideyuki Sasaki, MD; Hiroshi Asanuma, MD, PhD; Masashi Fujita, MD, PhD; Hiroyuki Takahama, MD, PhD; Masakatsu Wakeno, MD, PhD; Shin Ito, MD; Akiko Ogai, BS; Masanori Asakura, MD, PhD; Jiyoong Kim, MD; Tetsuo Minamino, MD, PhD; Seiji Takashima, MD, PhD; Shoji Sanada, MD, PhD; Masaru Sugimachi, MD, PhD; Kazuo Komamura, MD, PhD; Naoki Mochizuki, MD, PhD; Masafumi Kitakaze, MD, PhD

Metformin inhibits NF-κB inflammatory signalling: dissociation from effects of metformin on glucose production

Metformin prescribing is associated with a lower Neutrophil to Lymphocyte ratio (a marker of inflammation) in diabetics


<table>
<thead>
<tr>
<th>Group analysed</th>
<th>12 month geometric mean NLR metformin versus sulfonylurea % difference (95% CI)</th>
<th>12 month NLR &lt; 0 month NLR O.R., metformin versus sulfonylurea (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All subjects</td>
<td>-9% (2-15)</td>
<td>1.83 (1.22-2.75)</td>
</tr>
<tr>
<td>NLR above group median</td>
<td>-15% (5-23)</td>
<td>1.91 (1.02-3.59)</td>
</tr>
</tbody>
</table>
First ‘proof of concept’ study of metformin in CHF

The effect of metformin on insulin resistance and exercise parameters in patients with heart failure

Aaron K.F. Wong, Ruth Symon, Matlooba A. AlZadjali, Donald S.C. Ang, Simon Ogston, AnnaMaria Choy, John R. Petrie, Allan D. Struthers, and Chim C. Lang*

Centre for Cardiovascular and Lung Biology, Division of Medical Sciences, University of Dundee, Ninewells Hospital & Medical School, Dundee DD1 9SY, UK

Received 1 November 2011; revised 14 March 2012; accepted 1 June 2012; online publish-ahead-of-print 27 June 2012

See page 1197 for the editorial comment on this article (doi:10.1093/eurjhf/hfs155)
## TAYSIDE Trial

<table>
<thead>
<tr>
<th></th>
<th>Metformin</th>
<th>Placebo</th>
<th>P value</th>
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</thead>
<tbody>
<tr>
<td>Peak VO$_2$ (ml/kg/min)</td>
<td>$-0.38 \pm 1.40$</td>
<td>$3.60 \pm 3.90$</td>
<td>NS</td>
</tr>
<tr>
<td>Weight (Kg)</td>
<td>$-1.9 \pm 2.3$</td>
<td>$1.1 \pm 2.5$</td>
<td>$&lt;0.001$</td>
</tr>
<tr>
<td>VE/VCO$_2$ Slope*</td>
<td>$-7.5 \pm 21.7$</td>
<td>$-0.2 \pm 3.5$</td>
<td>0.05</td>
</tr>
<tr>
<td>Ventilatory Class*</td>
<td>$-0.33 \pm 0.96$</td>
<td>$0.10 \pm 0.31$</td>
<td>0.021</td>
</tr>
</tbody>
</table>

Wong AFK et al. Eur J Heart Fail 2012; 14: 1303-1310
Pre-Discharge or Recent Hospitalization for or with Heart Failure
National Heart Failure Audit

Diuretic Therapy

NT-proBNP >250ng/L if SR or >1,000 if AF
Exclude Severe Valve Disease
Stratify within each group below by LVEF <40%, 40-50%, >45%
Most difficult groups to recruit to take preference unless strong patient/investigator opinion

Raised Uric Acid
Allopurinol v Control

Raised HbA1c
Metformin v Control (Chim Lang)

Sinus Rhythm
Digoxin v Control (JGFC)

AF
Rate Control
(<65 v >80bpm)

HFpEF & SR
Beta-Blockers v Control

Any Patient not already treated with:

Factorial Design
• Nitrate v Control
• Hydralazine v Control

Control intervention - Vitamin C 25mg/day
Averts psychological impact of receiving nothing
Can legitimately say to patients that there might be benefit

Re-evaluate at 6 months
Continue Medications Assigned Above
Re-randomize (if willing & appropriate) Patients from any of First Five Groups to Nitrate/Hydralazine Factorial Study

Re-evaluate at 12 months
Long-Term Follow-up

Suggest an interim analysis for futility & replace/stop all interventions where a HR of <0.70 has been excluded (eg: HR 1.1 95% CI 0.80-1.4).
Is the NHS interested in certainty of small risks and benefits or can it live with a point estimate and exclusion of large benefit?
MetfoRmin and its Effects on Myocardial Dimension and Left ventricular hypertrophy in Normotensive patients with Coronary Artery Disease (MET-REMODEL)

• The hypotheses:
  • Metformin will regress LVH in normotensive patients with IHD identified to have IR
  • Recruitment to target (July 2016)


www.clinicaltrials.gov (NCT NCT02226510)
Allopurinol reduces LVH in diabetics

Szwejkowski BR et al. J Am Coll Cardiol 2013; 62: 2284-93
Newer Compounds

• Incretin based therapies
  • GLP-1 analogues
    • Awaiting large outcome trials. When given to CHF patients, they increases heart rate (not good for CHF)
  • DPP-IV inhibitors
    • ? HF risk
## Meta-analysis

**Time to 1st Occurrence of Any Hosp for HF**

### Peto odds ratio plot

<table>
<thead>
<tr>
<th>Study</th>
<th>DPP4i</th>
<th>Placebo</th>
<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>EXAMINE</td>
<td>106</td>
<td>89</td>
<td>1.19 (0.89-1.58)</td>
</tr>
<tr>
<td>SAVOR-TIMI 53</td>
<td>289</td>
<td>228</td>
<td>1.27 (1.07-1.51)</td>
</tr>
<tr>
<td>Combined</td>
<td>395</td>
<td>317</td>
<td>1.24 (1.07-1.44)</td>
</tr>
</tbody>
</table>

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Cirica BM. American Heart Association Scientific Sessions, Dallas, 2013
No signal for heart failure in TECOS

Hospitalization for Heart Failure

No. at Risk
Sitagliptin: 7332, 7189, 7036, 6917, 6780, 6619, 4728, 3515, 2175, 1324
Placebo: 7339, 7204, 7025, 6903, 6712, 6549, 4599, 3443, 2131, 1315

Hazard ratio: 1.00 (95% CI: 0.83–1.20)
P = 0.98
SGLT2 inhibitors

Site of SGLT-2 Inhibitor Effect on Glucose Reabsorption

- SGLT2
  - S1 segment of proximal tubule
  - ~90% reabsorption
- SGLT1
  - S2/S3 segment of proximal tubule
  - ~10% reabsorption
- No glucose

References:
- Tahrani AA, Barnett AH. *Diabetes Ther. 2010;1:45-56.*[^17]
Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators
EMPÄ-REG OUTCOME: cumulative incidence of death from CV causes

In patients with T2DM and at high risk of CV events, in addition to standard care

Placebo

Empagliflozin

P<0.001
Hazard ratio, 0.62 (95% CI, 0.49–0.77)

Adapted from: Zinman et al., NEJM 2015
EMPA-REG
Potential beneficial CV effects in CHF and LVH

- Weight loss
- Improve insulin sensitivity
- Diuresis (decrease pre-load)
  - Osmotic diuretic
- Lowers Blood Pressure (decrease afterload)
Cardiovascular Effects of SGLT inhibitors

- Research into the **Effect Of** SGLT2 inhibition on left ventricular **Remodelling** in patients with heart failure and diabetes **Mellitus** (REFORM)
  - LV volumes
  - Exercise capacity
- Recruitment to target (August 2016)

Research on the Effects of sodium-glucose co-transporter-2 inhibition on left ventricular remodelling in diabetic patients: A Scottish proof of concept Study (REGRESS)
Diuretic Resistance

- Can be described as a clinical state in which the diuretic response is diminished or lost before the therapeutic goal of relief from oedema has been reached\(^1\)

- Affects 20\%–30% of patients with HF\(^2\)

Renal and Cardiovascular Effects of SGLT2 inhibition in combination with loop Diuretics in diabetic patients with Chronic Heart Failure. (RECEDE-CHF) Enhance the effects of loop diuretics?

Sairaku A et al. Int J Cardiol 2015; 180:42-43
Summary
Diabetic Heart Failure

• Epidemiology
  • Diabetes and heart failure commonly co-exist
  • Lethal combination

• Pathophysiology
  • U shape relationship for glycaemic control (Development of CHF and Outcome)
  • Role of ECM remodeling in myocardial Insulin Resistance
  • Genetics of LVH/CHF in T2DM
Summary
Diabetic Heart Failure

• Diabetic drugs
  • No RCT that have adequately explored the risks and benefits
  • Problems with TZD
  • SU and insulin may not be good
  • Metformin
    • May actually be good (TAYSIDE Trial). ? IHD with LVH (MET-REMODEL)
• Incretin-based therapies. ? HF signal. No CV benefit
• SGLT inhibitors. Promising
Acknowledgements

• MD/PhD Fellows
  • Jagdeep Singh, Ify Mordi, Aaron Wong, Helen Parry, Matlooba Alzadjali, Mohanpradeep Mohan, Natalie Mordi, Fatima Baig, Daniel Levin, Benjamin Swejkowski, Maheshwar Pauriah, Adnan Nadir, TK Lim, Shaween Al Talabany

• Colleagues / collaborators
  • Allan Struthers, AnnaMaria Choy, Li Kang, Dougie Elder, Colin Palmer, Alex Doney, Graeme Houston, Jill Belch, Faisel Khan, Graham Rena, Bruce Guthrie, Jacob George, Simon Ogston, Louise Donnelly, Paul Meakin, Mike Ashford, Christian Schulze