There is great interest in real world evidence to determine if trial evidence can be translated into routine care. Efficacy trials test whether interventions work under highly controlled and optimal conditions with tight inclusion and exclusion criteria with often homogeneous populations, while effectiveness studies determine if the interventions work in a much broader population in the real world setting. Efficacy trials therefore ask the question “can this intervention work in ideal setting” while effectiveness ask the question “does this work in the real world setting”. Real world studies complement randomised controlled trials and are becoming important for prescribers, payers, regulatory authorities and patients. However, gaps in translation of evidence into real world practice are well documented although it is often assumed that effectiveness studies will follow efficacy trials. A number of factors are responsible for the efficacy-effectiveness gap. These include differences in populations who are in efficacy studies who are highly selected and often motivated with less co-morbidities. Efficacy to effectiveness in pharmaco-epidemiological research include variability of drug response, inadequate follow-up of safety signals, therapeutic inertia and poor adherence. Poor results in public health translational research include poor attention to reach, adoption, implementation and maintenance (RE-AIM Framework) in the real world setting. Methodologies for reducing the efficacy to effectiveness gap are improving and include use of pragmatic trials and use of RE-AIM framework to translate research into the real world practice.
Gap between Efficacy to Effectiveness: Re-evaluation of Population Level Interventions and Pharmaco-Effectiveness

Kamlesh Khunti
University of Leicester, UK
Presenter Disclosure

• **Consultant:** Amgen, AstraZeneca, BMS, Boehringer Ingelheim, Janssen, Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi and Servier.

• **Research Support:** AstraZeneca, Boehringer Ingelheim, Lilly, MSD, Novartis, Janssen, Novo Nordisk, Roche and Sanofi

• **Speaker’s Bureau:** AstraZeneca, Berlin-Chemie AG / Menarini Group, Boehringer Ingelheim, Janssen, Lilly, MSD, Napp, Novartis, Novo Nordisk, Roche and Sanofi

Outline

• Evidence Continuum: RCT to RWE
• Efficacy to Effectiveness Gap
• Efficacy to Effectiveness
  – Pharmaco-Effectiveness
  – Population Level Interventions
• Methods to improve efficacy to effectiveness gap
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What are we measuring, moving beyond clinical trials

In RCT:
  • **Efficacy** is the extent to which an intervention does more good than harm under ideal circumstances

In RWE:
  • **Effectiveness** is the extent to which an intervention does more good than harm when provided under the usual circumstances of healthcare practice
**RCT vs Real-world data**

"Data that are **collected** outside the controlled constraints of conventional randomised clinical trials to evaluate what is happening in normal clinical practice"¹

Ever-increasing role in decisions that affect patients’ access to therapies²


**Real-world evidence outcomes**

- Treatment adherence or persistence
- Financial burden on patients and healthcare systems
- Psychosocial factors
- Quality of life measures
- Healthcare utilization
- Patient-reported outcomes
- Clinical outcomes

**In large populations such as**
- patients with Type 2 diabetes
- patients using basal-bolus insulin

**In subpopulations of interest such as**
- patients at high risk of hypo
- patients with renal impairment
- patients with different ethnicity
What does real-world evidence (RWE) mean?

RWE is the use of real-world data (RWD) and analytics to discover, develop, deliver and provide new insights on healthcare interventions.

Availability of RWD and use of appropriate analytical methods create a big opportunity to accelerate/increase patient access to innovative medicines.

RWE differs from the traditional randomized controlled trial (RCT) approach because it uses primary and secondary data from the real world instead of data generated from a standard, randomized patient base.

RWE does not replace results from RCTs, but is complementary because it offers a broader range of data to generate the evidence necessary for medical and healthcare decision-makers.

RCTs and RWE form a continuum of evidence.

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Efficacy to Effectiveness Gap

• Implementation of pharmaceutical or public health interventions do not *(always)* perform as well in clinical practice as they do in clinical trials

Reasons for efficacy to effectiveness gap

• Population differences (co-morbidities, motivation, homogeneous populations)
• Biological differences (variability of drug response, off label prescribing, genetic)
• Behavioural differences (therapeutic inertia, adherence)
• Failure to follow-up minor safety signals

Khunti K et al. Diabetes Obesity Metabolism 2017:20:427-437
Khunti K et al. Diabetes Care 2017:40:1588–96
RCT vs RW populations

- RCTs are typically highly selective, often excluding:
  - Elderly patients (aged 65 and older)
  - Patients with comorbidities
  - Patients taking other drugs

- Patients seen in real-world practice may be:
  - Mostly older than 65 years
  - Suffering from several diseases
  - Taking multiple drugs
  - “Diverse and complex”

**How can I be sure that RCT results are applicable to my patients?**
**Does your drug work in the real world?**

Comorbidities of top 10 common conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage with comorbid condition</th>
<th>Percentage who only have the condition*</th>
<th>Mean No of conditions in people aged 65 years with condition</th>
<th>Mean No of conditions in people aged 65 years with comorbid condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease</td>
<td>21.9</td>
<td>8.8</td>
<td>3.4</td>
<td>4.4</td>
</tr>
<tr>
<td>Hypertension</td>
<td>17.6</td>
<td>5.5</td>
<td>3.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Heart failure</td>
<td>21.6</td>
<td>2.8</td>
<td>5.6</td>
<td>6.0</td>
</tr>
<tr>
<td>Stroke and transient ischaemic attack</td>
<td>6.0</td>
<td>6.0</td>
<td>4.8</td>
<td>5.6</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21.6</td>
<td>6.5</td>
<td>3.9</td>
<td>5.6</td>
</tr>
<tr>
<td>Diabetes</td>
<td>19.9</td>
<td>9.2</td>
<td>3.9</td>
<td>4.7</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>14.3</td>
<td>14.3</td>
<td>4.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Painful condition</td>
<td>17.6</td>
<td>17.6</td>
<td>4.3</td>
<td>5.3</td>
</tr>
<tr>
<td>Depression</td>
<td>12.7</td>
<td>12.7</td>
<td>3.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Dementia</td>
<td>25.4</td>
<td>25.4</td>
<td>2.6</td>
<td>4.9</td>
</tr>
</tbody>
</table>

* Percentage who do not have one of 39 other conditions in the full count

BP, blood pressure; CVD, cardiovascular disease; RCT, randomized controlled trial

The majority of patients are not represented in RCTs

How many real-world patients with T2DM would be eligible for landmark diabetes RCTs?

Total Scottish Care Information – Diabetes Collaboration population
N = 180,590 patients with T2DM (100%)

Royal College of General Practitioners Database
n = 60,327 patients with T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Approval</th>
<th>Eligible</th>
<th>Treated with SGLT-2 inhibitor %</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCORD</td>
<td>11.4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>35.7%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PROactive</td>
<td>3.5%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RECORD</td>
<td>9.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>18.3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>EMPA-REG</td>
<td>15.7%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Eligibility for EMPA-REG OUTCOME

- Diabetes Collaborative Registry\(^1\):
  - In a large US-based outpatient registry, ~1 in 4 patients with T2D met the main eligibility criteria for EMPA-REG OUTCOME

- Royal College of General Practitioners Research and Surveillance Centre database\(^2\):
  - 16% of patients with T2D from the UK-eMR database met the inclusion criteria for EMPA-REG OUTCOME

CV, cardiovascular; eMR, electronic medical record; T2D, type 2 diabetes

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Real-world effects of liraglutide on HbA1c and body weight

![Graph showing mean change from baseline in HbA1c and body weight across different BMI categories.](image)

Confirmation of findings from RCTs in the real-world setting

Data are unadjusted incidence rates. CV, cardiovascular; CVD, cardiovascular disease; T1D, type 1 diabetes; T2D, type 2 diabetes.


SGLT2 inhibitor CVOTs

<table>
<thead>
<tr>
<th>Drug</th>
<th>EMPA-REG OUTCOME</th>
<th>CANVAS Program</th>
<th>DECLARE-TIMI 58</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doses analysed</td>
<td>Empagliflozin</td>
<td>Canagliflozin</td>
<td>Dapagliflozin</td>
</tr>
<tr>
<td>10 mg, 25 mg (once daily)</td>
<td>100 mg, 300 mg (once daily)</td>
<td>10 mg (once daily)</td>
<td></td>
</tr>
<tr>
<td>Median follow-up time, years</td>
<td>3-1</td>
<td>2-4</td>
<td>4-2</td>
</tr>
<tr>
<td>Trial participants</td>
<td>7020</td>
<td>10142</td>
<td>17160</td>
</tr>
<tr>
<td>Age, mean</td>
<td>63.1</td>
<td>63.3</td>
<td>63.9</td>
</tr>
<tr>
<td>Women</td>
<td>2004 (28.5%)</td>
<td>3633 (35.8%)</td>
<td>6422 (37.4%)</td>
</tr>
<tr>
<td>Patients with established atherosclerotic cardiovascular disease</td>
<td>7020 (100%)</td>
<td>6656 (65.6%)</td>
<td>6974 (40.6%)</td>
</tr>
<tr>
<td>Patients with a history of heart failure</td>
<td>706 (10.1%)</td>
<td>1461 (14.4%)</td>
<td>1724 (10.0%)</td>
</tr>
<tr>
<td>Patients with eGFR &lt;60 ml/min per 1.73 m²</td>
<td>1819 (25.9%)</td>
<td>2039 (20.1%)</td>
<td>1265 (7.4%)</td>
</tr>
</tbody>
</table>

Data are n (%) unless otherwise specified. The CANVAS Program consisted of two trials, CANVAS and CANVAS-R, but are presented combined. eGFR-estimated glomerular filtration rate.

Table: Randomised controlled phase 3/4 clinical trials of sodium-glucose cotransporter-2 inhibitors
Meta-analysis of CVOTs: CV deaths/HHF by presence of ASCVD

Baseline characteristics for the full propensity matched cohort

<table>
<thead>
<tr>
<th>SGLT2 inhibitor</th>
<th>Other glucose-lowering drug</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean (SD)</td>
<td>N=154,528</td>
</tr>
<tr>
<td>Women (%)</td>
<td>56.9 (10.0)</td>
</tr>
<tr>
<td>Established cardiovascular disease* (%)</td>
<td>20,044 (13.0)</td>
</tr>
<tr>
<td>Acute myocardial infarction (%)</td>
<td>3,793 (2.5)</td>
</tr>
<tr>
<td>Unstable angina (%)</td>
<td>2,529 (1.6)</td>
</tr>
<tr>
<td>Heart failure (%)</td>
<td>4,714 (3.1)</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>5,632 (3.6)</td>
</tr>
<tr>
<td>Stroke (%)</td>
<td>6,337 (4.1)</td>
</tr>
<tr>
<td>Peripheral arterial disease (%)</td>
<td>5,239 (3.4)</td>
</tr>
<tr>
<td>Frailty† (%)</td>
<td>11,982 (7.8)</td>
</tr>
<tr>
<td>Microvascular disease (%)</td>
<td>42,217 (27.3)</td>
</tr>
<tr>
<td>Chronic kidney disease (%)</td>
<td>3,920 (2.5)</td>
</tr>
</tbody>
</table>

*Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularisation or occlusive peripheral artery disease; †in UK CPRD/THIN, frailty defined as ≥1 hospitalisation within 1 year prior to on on index date; in other databases defined as ≥1 hospital stay of ≥3 days within 1 year prior to the index date

CVD-REAL: The risk of HHF and all-cause mortality is reduced with SGLT2 inhibitors compared with other AHAs

<table>
<thead>
<tr>
<th>Country</th>
<th>N</th>
<th>No. of events</th>
<th>HHF (primary outcome)</th>
<th>All-cause mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>US</td>
<td>233,798</td>
<td>298</td>
<td>0.55 (0.44, 0.69)</td>
<td>0.38 (0.29, 0.50)</td>
</tr>
<tr>
<td></td>
<td>143,264</td>
<td>250</td>
<td>0.62 (0.49, 0.79)</td>
<td>0.55 (0.44, 0.68)</td>
</tr>
<tr>
<td>Norway</td>
<td>25,050</td>
<td>278</td>
<td>0.77 (0.59, 1.01)</td>
<td>0.46 (0.37, 0.57)</td>
</tr>
<tr>
<td>Denmark</td>
<td>18,468</td>
<td>167</td>
<td>0.61 (0.45, 0.82)</td>
<td>0.47 (0.37, 0.60)</td>
</tr>
<tr>
<td>Sweden</td>
<td>18,378</td>
<td>191</td>
<td>0.36 (0.12, 1.13)</td>
<td>0.73 (0.47, 1.15)</td>
</tr>
<tr>
<td>UK</td>
<td>10,462</td>
<td>16</td>
<td>0.14 (0.03, 0.68)</td>
<td>–</td>
</tr>
<tr>
<td>Germany*</td>
<td>2,900</td>
<td>11</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Total</td>
<td>309,056</td>
<td>961</td>
<td>0.61 (0.51, 0.73)</td>
<td>0.49 (0.41, 0.57)</td>
</tr>
</tbody>
</table>

*Death data were not available for Germany.

AHA: anti-hyperglycaemic agent; HR: hazard ratio.

HHF, P<0.001 for SGLT2 inhibitors vs. other AHAs; heterogeneity P value: 0.17

All-cause mortality P<0.001 for SGLT2 inhibitors vs. other AHAs; heterogeneity P value: 0.09

**Sodium-glucose co-transporter-2 inhibitors in patients with and without cardiovascular disease**

<table>
<thead>
<tr>
<th>Condition</th>
<th>With prior cardiovascular disease*</th>
<th>Without prior cardiovascular disease*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.56 [0.44, 0.70]</td>
<td>0.56 [0.50, 0.63]</td>
</tr>
<tr>
<td>Heart failure</td>
<td>0.72 [0.63, 0.82]</td>
<td>0.61 [0.48, 0.78]</td>
</tr>
<tr>
<td>Heart failure + death</td>
<td>0.63 [0.57, 0.70]</td>
<td>0.56 [0.50, 0.62]</td>
</tr>
</tbody>
</table>

*Diagnosis of AMI, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization (CABG of PCI) or occlusive peripheral artery disease prior to index drug initiation. Pooled adjusted hazard ratios from meta-analyses for death, heart failure, and heart failure or death in patients with and without cardiovascular disease at initiation of the index drug in the intention-to-treat cohort. AMI = acute myocardial infarction; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention.

Safety signals worse in RW implementation

Licensed 2006- as adjunct to diet and exercise for treatment for obese people

Safety signals in trials- depression, suicidal and aggressive behaviour- considered not to outweigh benefits

RWE- weight benefits lower and risk of adverse mental health effects higher especially in people with co-mobidities

Therapeutic Inertia in T2DM over the lifecourse

81,573 people in the UK

Time to treatment intensification from first HbA1c ≥ 7.5% (58 mmol/mol) by number of OADs and type of intensification

Data for a subgroup of more than 55,000 participants with HbA1c ≥ 7.5% (58 mmol/mol) having any intensification to their treatment at end of follow-up within a retrospective cohort of over 80,000 people

HbA1c, glycated hemoglobin; OAD, oral antidiabetes drug

Titration is not optimal, patients remain at low basal insulin dose

SOLVE:1-2 24-week observational study of once-daily (QD) insulin detemir in patients with T2DM receiving OADs

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EU5 and US real-world data in 40627 patients with type 2 diabetes initiating basal insulin 2008–2012

---

Adherence: Effectiveness gap between trials and the real world

GLP-1 RA Adherence Rate in Real World = 29%

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Prevention of diabetes

Some translational studies demonstrate improvements to risk factors or lifestyle factors

Lack of evidence in prevention of diabetes in real world setting

Results of Real World studies

- Some translational studies demonstrate improvements to risk factors or lifestyle factors
- Lack of evidence in prevention of diabetes in real world setting
DPP Case Study: Impact of Loss at Each RE-AIM Concept

Example of Translation of Interventions into Practice

<table>
<thead>
<tr>
<th>Dissemination Step</th>
<th>RE-AIM Concept</th>
<th>% Impact</th>
</tr>
</thead>
<tbody>
<tr>
<td>50% of settings use intervention</td>
<td>Adoption</td>
<td>50.0%</td>
</tr>
<tr>
<td>50% of staff take part</td>
<td>Adoption</td>
<td>25.0%</td>
</tr>
<tr>
<td>50% of patients identified, accept</td>
<td>Reach</td>
<td>12.5%</td>
</tr>
<tr>
<td>50% follow regimen correctly</td>
<td>Implementation</td>
<td>6.2%</td>
</tr>
<tr>
<td>50% benefit from the intervention</td>
<td>Effectiveness</td>
<td>3.2%</td>
</tr>
<tr>
<td>50% continue to benefit after six months</td>
<td>Maintenance</td>
<td>1.6%</td>
</tr>
</tbody>
</table>

www.re-aim.org Slide taken from ACCORDS, University of Colorado

DPP Recruitment Strategy

1.9 million factsheets
4.6 million brochures
30,000 to 480,000 mailings per clinic

Annually
Screening
OGTT
Start run in
End run in
Randomised

158,777
30,985
4,715
4,080
3,819

Trial 3,234
Recruitment in Finnish DPS

The DPS is a multicentre study with five participating centres in Finland, located in Helsinki, Kuopio, Oulu, Tampere and Turku. Each centre has recruited over 100 subjects. Altogether 523 subjects have been randomised. The recruitment started after a pilot study in 1993 and was completed in May 1998. The study subjects were recruited through various methods, e.g. from epidemiological surveys and by opportunistic population screenings with special emphasis on the high-risk groups such as obese subjects and first-degree relatives of Type II diabetic patients. Subjects were also recruited through advertising in local newspapers.

Challenges

Perceived Need for Lifestyle Counselling in Individuals at High Risk of Type 2 Diabetes (FIND2D n = 10,104)
Difficulties of recruiting to a large-scale physical activity behavioral intervention randomised controlled trial

70388 Postal Invitations

282 (0.4%) Consented & randomised

Adherence

Prevention Self management education programmes

- 30% attend all sessions
- Median is 2-3 out of 5 sessions

Pharmacotherapy: NHS Health Checks

- 64% of those at high CVD risk accepted statins
- Adherence 74% at 12 months
- Simple interventions such as text messaging can improve adherence

3. Wald DS et al. PLOS One 2014; DOI: 10.1371/journal.pone.0114268
Prevention in the real-world setting

- Systematic review of 63 studies
- RRR incidence of diabetes 0.71 (95% CI: 0.58–0.88)
- Every additional session participants received was associated with 18% lower odds of developing diabetes

Prevention of T2DM in high risk groups: Engagement and retention

Adjusted for age, sex, deprivation, smoking, BMI

Progression to diabetes at 3 years

Structured 6 hour education programme with annual refresher course

Engagers- attended initial session
Retainers- attended all session

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Why Don’t We See More Translation of Health Promotion Research to Practice?

“Moderating factors that limit robustness across settings, populations, and intervention staff need to be addressed in efficacy studies, as well as in effectiveness trials.

Greater attention needs to be paid to documenting intervention reach, adoption, implementation, and maintenance.”

Glasgow RE et al. AJPH 2003;93:1261-67
The RE-AIM Framework and External Validity Reporting
www.re-aim.org

Focus on enhancing:

**Reach** – Participation rates and representativeness
**Effectiveness** – Breadth (quality of life), including negative or unintended effects
**Adoption** - Setting and staff participation rate and representativeness
**Implementation** – Consistency, adaptation and costs to deliver the program
**Maintenance** – Extent to which program and effects are sustained


Pragmatic-Explanatory Continuum Indicator Summary (PRECIS)

More Pragmatic
Less Pragmatic

Thorpe KE J Clin Epidemiol 2009
Summary and conclusions

• Well-designed real-world studies complement RCTs
• A number of reasons for efficacy to effectiveness gap
• Need to be aware of types of real world data
• Choose appropriate data and methodology to answer the question
• Methodologies for RWE are improving and should reduce E2E gap

Thank you

www.leicesterdidabetescentre.org.uk
www.facebook.com/LeicesterDiabetesCentre
@kamleshkhunti
@LDC_Tweets