What is new in the year 2022/2023 Internal Medicine updates
Metformin: A Game-Changer in Cancer Treatment?
(Report From a 2023 meta analysis)

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Outline

• Introduction
• Cancer In Ethiopia
• Type 2 DM and Cancer
• Clinical Evidence for the Potential Anti-Cancer Effects of Metformin
• Meta analysis report
• Conclusion
• Future directions
Introduction

- Cancer death accounts for 21% of all cases in both men and women in the USA, and cancer is the second leading cause of death worldwide. (1)
- Lung, prostate cancer, and colorectal cancer (CRC) account for the largest percentages in men. While for women mostly include breast cancer (BC), lung cancer, and CRC. (2)
- In Ethiopia country's annual cancer incidence is estimated to be around 60,960 cases, with an annual mortality of over 44,000.
- Breast cancer is the most common cancer in Ethiopia, accounting for 30.2% of all cases, followed by cervical (13.4%) and colorectal cancers (3)
Cancer In Ethiopia

![Cancer Incidence and Mortality in Ethiopia](chart.png)
Type 2 DM and Cancer

• Several studies indicate that people with diabetes (mainly type 2, T2DM) are also at substantially higher risk of cancer of the pancreas, liver, endometrium, breast, colon, rectum and urinary bladder compared to individuals without this chronic disease (1).

• However, the incidence of other types of cancer (e.g., lung, kidney, non-Hodgkin lymphomas) does not seem to be strongly associated with diabetes or the evidence is inconclusive (2).

• Interestingly enough, it has been suggested that diabetes is associated with a lower risk for prostate cancer
Risk factors

• There is a general agreement that T2DM and cancer share several common potential risk factors (e.g., aging, sex, obesity, physical inactivity, diet, alcohol, and smoking).

• In T2DM, insulin resistance and hyperinsulinemia (either endogenous due to insulin resistance or induced by administration of exogenous insulin formulations) are considered to be independent risk factors for cancer development (1,2).

• In addition, hyperglycemia-related oxidative stress, accumulation of advanced glycation end products as well as low-grade inflammation may also enhance the risk of malignant transformation.
In 2005, a landmark study published
11,876 had been newly diagnosed with type 2 diabetes
1993-2001, Of these, 923 developed cancer
Mean age was 73
Mean duration of diabetes was 8.5 (6.4) years.
More than a third (336; 36.4%) of the cases had been given at least one prescription for metformin in the year before their index date compared with 732 (39.7%) of the controls.
The unadjusted odds ratio was 0.86 (95% confidence interval 0.73 to 1.02). The unadjusted odds ratio for any exposure to metformin since 1993 was 0.79 (0.67 to 0.93).
Taking metformin may be associated with reduced risk of cancer in patients with type 2 diabetes, and a biologically plausible mechanism exists (4)
Metformin

• Metformin is the first-line drug for type 2 diabetes (T2D) patients, which induces a hypoglycemic effect by targeting and activating the enzyme AMP-activated protein kinase (AMPK) and inhibiting hepatic glucose production

• The activation of the AMPK-pathway may reduce the activity of insulin in promoting tumor progression and can inhibit the mammalian target of rapamycin (mTOR), which is closely connected to tumor cell proliferation. (4)

• The current proposed anticancer molecular action of metformin is mainly associated with the inhibition of the mammalian target of rapamycin complex 1 (mTORC1).
• it is believed that **systemic effect of metformin manifested by the reduction of circulating level of insulin and insulin-like growth factor 1 (IGF-1)** might be associated with anticancer action.

• **Insulin/IGF-1** is involved not only in regulation of glucose uptake but also in carcinogenesis through up regulation of insulin/IGF receptor signaling pathway.

• The excessive food consumption (insulin) leads to increased liver production of IGF-1 that binds to IGF-1 receptor and insulin receptor.
Mechanism of action
What is the potential impact of Metformin on cancer treatment and how can it revolutionize the way we approach cancer therapy?
Background

• Efficacy of metformin therapy in patients with cancer: a meta-analysis of 22 randomised controlled trials
• To investigate whether metformin monotherapy or adjunctive therapy improves the prognosis in patients with any type of cancer compared to non-metformin users (age ≥18).
Methodology

• This prospective study was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis

A. Inclusion criteria

1. RCTs if metformin was one of the randomized therapies
2. investigation of the efficacy of metformin monotherapy or as an adjunctive therapy comparing the treatment group with a control group (placebo or no treatment)
3. Investigation of adults (age ≥ 18 years) with any type of cancer
4. Presence of reported results on progression-free survival (PFS) and/or overall survival (OS)
B. Exclusion criteria

- Retrospective studies
- Observational studies
- Post hoc analyses of RCTs
- Synchronously used other antidiabetic drugs; or
- had no available results related to survival.
C. Data collection

- Data on the study designs, patient characteristics, interventions, and outcomes were collected from the included studies into a standard sheet by two independent researchers.

D. Risk of bias assessment

- The risk of bias in each trial was evaluated using the Cochrane Risk of Bias Assessment Tool (version 2).
- It was scored every trial as low risk, with some concerns, or high risk based on the following criteria: (1) randomization process, (2) deviations from intended interventions, (3) missing outcome data, (4) measurement of the outcome, and (5) selection of the reported result.
E. Subgroup analyses

- several subgroup analyses to evaluate the interactions according to the maintenance dose ([500, 1000), [1000, 1500), [1500, 2000), [2000, 2500) mg),
- diabetes exclusion (yes or no),
- risk of bias (low risk, some concerns, high risk),
- chemotherapy,
- radiotherapy (yes or no),
- targeted therapy (yes or no).
- subgroup analyses of the cancer type based on the systems that they originated from (reproductive, respiratory, or digestive system cancers).
Statistical analysis

Primary endpoints

- **PFS and OS of cancer**
- Statistical analyses based on the intention-to-treat results using the meta package in R (version 4.1.3).
- HRs and their 95% confidence intervals (CI) were used to assess outcomes, and $P < 0.05$ was considered statistically significant.
- Heterogeneity was estimated with the $I^2$ test. The assumption of heterogeneity was deemed valid for $I^2 > 25\%$ and $P < 0.10$ as in a previous study.
- If heterogeneity was not significant, we used fixed effects models to pool outcomes.
- When heterogeneity was significant, we used random-effects models. Metaregression and sensitivity analyses were performed to investigate potential sources of heterogeneity.
Results

• 22 eligible trials (5943 participants) in the final meta-analysis
• All the studies were RCTs published between 2015 and 2022
• The mean age 58.6 and 58.9
• The female proportion in the metformin and control groups was 64% and 65%, respectively.
• All studies administered antitumor therapies to the patients, including chemotherapy, radiotherapy, targeted therapy, hormone therapy, and immunotherapy.
Records identified through database searching (n=8419): Pubmed (n=2414) Embase (n=4623) Cochrane (n=1382)

Records from other sources (n=85): ClinicalTrials.gov (n=54) ICTRP (n=31)

Records screened after duplicates removed (n=6185)

Records remained after screening by title and abstract (n=369)

Full text articles excluded (n=348): 238 No survival data 50 Not a randomised controlled trial 36 No published results 24 Duplicate article of a trial

Studies included in qualitative synthesis (n=22)

Studies included in quantitative synthesis (meta-analysis) (n=22)

Fig. 1 Search and selection of eligible studies for inclusion
Results

- Both PFS (HR 0.97, 95% CI 0.82–1.15, I² = 50%) and OS (HR 0.99, 95% CI 0.86–1.13, I² = 33%) showed no significant difference between the metformin and control groups for patients with cancers
However

• Subgroup analyses indicated that metformin use resulted in marginally significant improvement in PFS for patients with reproductive system cancers (HR 0.86, 95% CI 0.74–1.00).
• For digestive system cancers, metformin use showed significantly worse PFS (HR 1.45, 95% CI 1.03–2.04) (Fig. 3).
• The difference between subgroups based on cancer type was statistically significant in PFS ($p = 0.04$) but not in OS.
## PFS

<table>
<thead>
<tr>
<th>Study</th>
<th>Maintenance Dose (mg/day)</th>
<th>Median Follow-up (months)</th>
<th>Hazard Ratio Random, 95% CI</th>
<th>Hazard Ratio Random, 95% CI</th>
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</thead>
<tbody>
<tr>
<td>Zheng–2019</td>
<td>850</td>
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<tr>
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<td>1.01 (0.71–1.43)</td>
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<tr>
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<td>1.20 (0.69–2.08)</td>
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</tr>
<tr>
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<td>39</td>
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<tr>
<td>El-Haggar–2016</td>
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</tr>
<tr>
<td>Alghandour–2021</td>
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<td>22</td>
<td>0.53 (0.31–0.92)</td>
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</tr>
<tr>
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<tr>
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<td>86</td>
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<tr>
<td>Pimentel–2019</td>
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<tr>
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<tr>
<td>Nanni–2019</td>
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<td>0.81 (0.50–1.31)</td>
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<td>19.15</td>
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<tr>
<td>Kordes–2015</td>
<td>2000</td>
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<td>1.18 (0.77–1.81)</td>
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<tr>
<td>Skinner–2021</td>
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<td>1.20 (0.81–1.78)</td>
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<tr>
<td>Reni–2016</td>
<td>2000</td>
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<tr>
<td>Tsakiridis–2021</td>
<td>2000</td>
<td>Not given</td>
<td>2.42 (1.14–5.12)</td>
<td></td>
</tr>
</tbody>
</table>

**Total**

Heterogeneity: $\chi^2 = 38.35$ (P = .005), l = 50%
Test for overall effect: $z = -0.30$ (P = .76)
### OS

<table>
<thead>
<tr>
<th>Study</th>
<th>Maintenance Dose (mg/day)</th>
<th>Median Followup (months)</th>
<th>Hazard Ratio Random, 95% CI</th>
<th>Hazard Ratio Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
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</tr>
<tr>
<td>Arrieta–2019</td>
<td>1000</td>
<td>16.9</td>
<td>0.52 (0.30–0.90)</td>
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</tr>
<tr>
<td>Shorbagy–2020</td>
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<td>0.95 (0.48–1.87)</td>
<td></td>
</tr>
<tr>
<td>Lee–2021</td>
<td>1000</td>
<td>32.4</td>
<td>0.95 (0.68–1.33)</td>
<td></td>
</tr>
<tr>
<td>Zhao–2017</td>
<td>1000</td>
<td>22.3</td>
<td>1.10 (0.50–2.41)</td>
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</tr>
<tr>
<td>Liubota–2018</td>
<td>1500</td>
<td>39</td>
<td>0.87 (0.55–1.37)</td>
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<td>Alghandour–2021</td>
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<tr>
<td>Bae–Jump–2020</td>
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<td>28</td>
<td>0.89 (0.68–1.16)</td>
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<tr>
<td>Martin–2021</td>
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<td>86</td>
<td>1.00 (0.65–1.53)</td>
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<tr>
<td>Goodwin–2022</td>
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<td>Pimentel–2019</td>
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<td>Marrone–2018</td>
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<tr>
<td>Skinner–2021</td>
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<td>Kordes–2015</td>
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<td>1.06 (0.73–1.55)</td>
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<td>Nanni–2019</td>
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<td>1.56 (0.87–2.80)</td>
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<tr>
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<td>3.80 (1.49–9.71)</td>
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<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td><strong>0.99 (0.86–1.13)</strong></td>
<td></td>
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</tbody>
</table>

Heterogeneity: $\chi^2_{16} = 26.71$ (P = 0.08), $I^2 = 33\%$

Test for overall effect: $z = -0.14$ (P = 0.89)

*96.2 and 94.1 for patients with ER/PgR+ and ER/PgR- breast cancers, respectively

**Fig. 2** Forest plot of PFS and OS of trials evaluating metformin use
<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Trials</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio (95%CI)</th>
<th>Hazard Ratio (95%CI)</th>
<th>P value for Subgroup Difference</th>
<th>Heterogeneity within Subgroup</th>
<th>I² (%)</th>
<th>p value</th>
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<tbody>
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<td>Overall</td>
<td>20</td>
<td>2264 (100.0)</td>
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<td>0.97 (0.82-1.15)</td>
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<td>Maintenance dose</td>
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<tr>
<td>[2000,2500]</td>
<td>8</td>
<td>800 (55.3)</td>
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<td>1.15 (0.96-1.38)</td>
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<td>[1500,2000]</td>
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<td>976 (63.1)</td>
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<td>0.85 (0.72-1.01)</td>
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<td>[1000,1500]</td>
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<td>444 (19.6)</td>
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<td>44 (1.9)</td>
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<td>Reproductive system cancers</td>
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<td>1252 (55.3)</td>
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<td>751 (32.2)</td>
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<td>Low risk</td>
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<td>1783 (78.8)</td>
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<td>1698 (75.0)</td>
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<td>0.97 (0.79-1.2)</td>
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<td>0.01</td>
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</table>

Fig. 3 Subgroup analyses for PFS
There was no clear evidence of between-subgroup differences based on maintenance dose, diabetes exclusion, median followup, risk of bias, and combined antitumoral therapies, neither in PFS nor in OS.
Proposed mechanism and evidence

• The effect of metformin in the prevention of reproductive system cancer progression may be related to its impact on the gonadal hormone levels.

• Metformin was reported to be effective in preventing hormone-related tumor progression, including breast prostate, ovarian, and endometrial cancers.

• Previous studies have reported that progestin can activate the PI3K/Akt pathway without progesterone receptor (PgR) mediation and metformin suppresses both estrogen receptor (ER)/PgR signaling and PI3K/AKT/mTOR signaling to inhibit estradiol and progesterone-associated abnormal cell proliferation and hormone therapy resistance.
Conclusion

• Metformin treatment not associated with cancer-related mortality in adults compared with placebo or no treatment

• Beneficial effects in PFS observed in patients with reproductive system cancers, but worse PFS observed in patients with digestive system cancers
Implications

- Metformin may **have potential as an adjunctive therapy for certain types of cancer**
- Further research needed to identify optimal dosing, timing, and patient selection criteria
- Metformin's safety profile and low cost make it an attractive option for cancer therapy
Future Directions

• **Larger, well-designed RCTs** needed to confirm findings and identify optimal treatment protocols

• **Biomarker studies** to identify patient populations most likely to benefit from metformin therapy

• Mechanistic studies to elucidate the anticancer effects of metformin and identify potential drug targets for combination therapy
References


• Thank you
Use of Aspirin in the cancer patient (Trial Update)

Dr Yonas Dandena
Department of Clinical Oncology
Addis Ababa University
August 4, 2023
Hall marks of cancer
Aspirin and cancer risk: a quantitative review to 2011

C. Bosetti, V. Rosato, S. Gallus, J. Cuzick, C. La Vecchia

meta-analysis of all observational studies on aspirin and 12 selected cancer sites published up to September 2011.
Result

- Regular aspirin is associated with a statistically significant reduced risk of colorectal cancer \([\text{summary relative risk (RR) from random effects models} = 0.73, \text{95\% confidence interval (CI)} = 0.67–0.79]\), and of other digestive tract cancers.

- Modest inverse associations were also observed for breast \([\text{RR} = 0.90, \text{95\% CI} = 0.85–0.95]\) and prostate cancer \([\text{RR} = 0.90, \text{95\% CI} = 0.85–0.96]\).

- No meaningful overall associations were observed for cancers of the pancreas, endometrium, ovary, bladder, and kidney.
<table>
<thead>
<tr>
<th>Study</th>
<th>Site</th>
<th>Cases users/total</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Farrow–1998</td>
<td>EA</td>
<td>50/293</td>
<td>0.37 (0.24, 0.58)</td>
</tr>
<tr>
<td>Farrow–1998</td>
<td>GCA</td>
<td>56/261</td>
<td>0.80 (0.54, 1.19)</td>
</tr>
<tr>
<td>Akre–2001</td>
<td>GCA</td>
<td>25/90</td>
<td>0.70 (0.40, 1.20)</td>
</tr>
<tr>
<td>Anderson–2006</td>
<td>EA</td>
<td>59/227</td>
<td>0.57 (0.36, 0.93)</td>
</tr>
<tr>
<td>Jayaprakash–2006</td>
<td>EA</td>
<td>34/87</td>
<td>0.50 (0.29, 0.87)</td>
</tr>
<tr>
<td>Ranka–2006</td>
<td>EA</td>
<td>62/318</td>
<td>0.35 (0.24, 0.51)</td>
</tr>
<tr>
<td>Fortuny–2007</td>
<td>EA</td>
<td>34/163</td>
<td>0.45 (0.30, 0.69)</td>
</tr>
<tr>
<td>Fortuny–2007</td>
<td>GCA</td>
<td>29/176</td>
<td>0.29 (0.18, 0.47)</td>
</tr>
<tr>
<td>Duan–2008</td>
<td>EA</td>
<td>51/220</td>
<td>0.88 (0.63, 1.23)</td>
</tr>
<tr>
<td>Duan–2008</td>
<td>GCA</td>
<td>75/277</td>
<td>1.11 (0.83, 1.49)</td>
</tr>
<tr>
<td>Sadeghi–2008</td>
<td>EA</td>
<td>52/367</td>
<td>0.48 (0.32, 0.73)</td>
</tr>
<tr>
<td>Sadeghi–2008</td>
<td>EA/GCA</td>
<td>70/426</td>
<td>0.70 (0.49, 1.01)</td>
</tr>
<tr>
<td>Figueroa–2009</td>
<td>EA</td>
<td>49/170</td>
<td>0.67 (0.44, 1.02)</td>
</tr>
<tr>
<td>Figueroa–2009</td>
<td>GCA</td>
<td>46/147</td>
<td>1.02 (0.67, 1.55)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>0.60 (0.48, 0.75)</td>
</tr>
<tr>
<td><strong>Cohort studies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abnet–2009</td>
<td>EA</td>
<td>176/228</td>
<td>0.91 (0.59, 1.40)</td>
</tr>
<tr>
<td>Abnet–2009</td>
<td>GCA</td>
<td>130/178</td>
<td>0.71 (0.43, 1.18)</td>
</tr>
<tr>
<td>Epplin–2009</td>
<td>GCA</td>
<td>40/93</td>
<td>1.01 (0.66, 1.57)</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td></td>
<td>0.88 (0.68, 1.15)</td>
</tr>
</tbody>
</table>

**Overall**                        |      |                  | 0.64 (0.52, 0.78) |
Randomised Vascular Trials

- A major part of the evidence base relating to aspirin & cancer has emerged from RCT’s of aspirin in vascular diseases (Rothwell, Lancet 2010, 2011, 2012)

- 51 randomised trials with ~77,000 participants

- Decreased cancer incidence HR 0.81 (0.7-0.93) with rx > 5yrs & reduced cancer deaths by ~ 15%

Cancer with no metastasis at presentation in which metastasis developed on follow-up
AspECT Trial: Esomeprazole and Aspirin in Barrett’s Oesophagus

Event Free Survival:

Combination of high dose PPI & aspirin vs low-dose PPI & no aspirin

Time Ratio = 1.59 [95% CI 1.14-2.23], p=0.0068

Only 28/2557 (1%) participants reported study-treatment-related serious adverse events

Jankowski July 2018, The Lancet
Rationale for the Add-Aspirin Trial

• In vitro, epidemiological and randomized data suggest a possible therapeutic role for aspirin particularly in the adjuvant treatment of several of the most common cancers
• Low cost, generic drug, available worldwide, generally safe with known side effects
• Readily accessible in lower resource settings (unlike many new agents or complex regimens) and therefore the potential for huge global impact
### Adjuvant Setting: Non-Randomised Data for the Use of Aspirin

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Study/Year</th>
<th>No of cases</th>
<th>Result (in favour of aspirin)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colorectal</strong></td>
<td>Bains 2015</td>
<td>25644</td>
<td>CRC-specific mortality: HR 0.53 (0.50-0.57) All-cause mortality: HR 0.71 (0.68-0.75)</td>
</tr>
<tr>
<td></td>
<td>McCowan 2013</td>
<td>2990</td>
<td>CRC-specific mortality: HR 0.58 (0.45-0.75) All-cause mortality: HR 0.67 (0.57-0.79)</td>
</tr>
<tr>
<td><strong>Breast</strong></td>
<td>Holmes 2010</td>
<td>4164</td>
<td>BC mortality: RR=0.36 (0.24 – 0.65) Overall Survival: RR=0.54 (0.41 - 0.70)</td>
</tr>
<tr>
<td></td>
<td>Fraser 2014</td>
<td>4627</td>
<td>All-cause mortality: HR=0.53 (0.45 – 0.63) BC mortality: HR=0.42 (0.31 – 0.55)</td>
</tr>
<tr>
<td><strong>Gastro-oesophageal</strong></td>
<td>Liu 2009</td>
<td>1716</td>
<td>5 year Overall survival Aspirin 51.2%, placebo 41%, no tablet 42.3%</td>
</tr>
<tr>
<td></td>
<td>Staalduinen 2016</td>
<td>560</td>
<td>OS adjusted RR=0.42 (0.30-0.57)</td>
</tr>
<tr>
<td></td>
<td>Frouws 2017</td>
<td>1696</td>
<td>OG-specific survival: HR 0.45 in oesophageal HR 0.87 in gastric cancer</td>
</tr>
<tr>
<td><strong>Prostate</strong></td>
<td>Zaorsky 2012</td>
<td>2051</td>
<td>Reduced interval to biochemical failure Aspirin non-use OR=2.05 (1.33 – 3.17)</td>
</tr>
<tr>
<td></td>
<td>Choe 2012</td>
<td>5955</td>
<td>PC mortality: HR=0.43 (0.21 – 0.87)</td>
</tr>
<tr>
<td></td>
<td>Jacobs 2014</td>
<td>8427</td>
<td>PC mortality: HR=0.60 (0.37 – 0.97)</td>
</tr>
</tbody>
</table>
Aspirin increases bleeding risk, however this increase is small

<table>
<thead>
<tr>
<th>Bleeding site</th>
<th>Estimated risk in control group</th>
<th>Estimated risk on aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serious bleeding** gastrointestinal or other extracranial site</td>
<td>0.07% per year</td>
<td>0.1% per year</td>
</tr>
<tr>
<td>Intracranial bleed</td>
<td>0.03% per year</td>
<td>0.04% per year</td>
</tr>
</tbody>
</table>

Antithrombotic Trialists’ Collaboration (ATTC) meta-analysis ~95,000 participants, (mean age 56 years, 46% men)

**Serious bleeding = hospital admission or blood transfusion
Phase 3 randomized controlled trial

The effect of daily aspirin on recurrence and survival after radical cancer therapy in four tumour cohorts: *gastro-oesophageal, colorectal, breast, and prostate cancer.*

Aspirin 100 mg daily for 8 weeks) precedes double-blind randomisation (for participants aged under 75 years, aspirin 300 mg, aspirin 100 mg, or matched placebo in a 1:1:1 ratio; for patients aged 75 years or older, aspirin 100 mg or matched placebo in a 2:1 ratio).
• 3494 participants
• 115 in the gastro-oesophageal cancer cohort, 950 in the colorectal cancer cohort, 1675 in the breast cancer cohort, and 754 in the prostate cancer cohort
• 2719 (85%) of 3194 participants who had finished the run-in period proceeded to randomisation
1. primary endpoint of the trial
   • Disease-free survival - defined as the time from randomization to the first occurrence of cancer recurrence
   • second primary cancer
   • or death from any cause.
2. Secondary End Point evaluating the effect of aspirin on overall survival, time to distant metastasis, and quality of life.
FOUR PARALLEL COHORTS WITHIN AN OVER-ARCHING PROTOCOL
Participants will have undergone primary treatment with curative intent

<table>
<thead>
<tr>
<th>BREAST</th>
<th>COLORECTAL</th>
<th>GASTRO-OESOPHAGEAL</th>
<th>PROSTATE</th>
</tr>
</thead>
</table>

REGISTRATION AND RUN-IN PERIOD
Participants take 100mg aspirin for 8 weeks to assess adherence and tolerability

RANDOMISATION
Performed separately within each tumour cohort, double-blind

<table>
<thead>
<tr>
<th>100mg ASPIRIN</th>
<th>300mg ASPIRIN</th>
<th>PLACEBO</th>
</tr>
</thead>
</table>

FOLLOW-UP (≥ 5 years)
Active follow-up, aligned with standard care, and long-term passive follow-up (UK)

- Breast primary outcome: Invasive Disease-free survival, n=3100
- Colorectal primary outcome: Disease-free survival, n=2600
- Gastro-oesophageal primary outcome: Overall survival, n=2100
- Prostate primary outcome: Biochemical recurrence-free survival, n=2120
Adherence and Toxicity

(Data from the run-in period, n=2253, all tumour groups)

- Adherence generally very good across all tumour groups – 2148/2253 (95%) taking 6-7 tablets per week

- 85% proceeded to randomisation - very similar across all cohorts and close to what was expected (90%)

- Reasons for not proceeding often multi-factorial – main reasons minor toxicity and participant choice

- Only 0.7% (15/2253) experienced toxicity requiring discontinuation during the run-in
Add-Aspirin Run-In Toxicity

- Most common grade 1-2 toxicities were dyspepsia and bruising
- 13/2253 (0.6%) participants had grade 3 toxicities, between 0.5% and 1.0% in individual tumour groups

<table>
<thead>
<tr>
<th></th>
<th>Breast</th>
<th>Colorectal</th>
<th>OG</th>
<th>Prostate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants with run-in data available</td>
<td>1113</td>
<td>602</td>
<td>75</td>
<td>463</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>138 (12%)</td>
<td>51 (8%)</td>
<td>10 (13%)</td>
<td>47 (10%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0 (0%)</td>
<td>2 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Bruising</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>133 (12%)</td>
<td>53 (9%)</td>
<td>2 (3%)</td>
<td>23 (5%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Lower GI bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>4 (0%)</td>
<td>6 (1%)</td>
<td>1 (1%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>1 (0%)</td>
</tr>
<tr>
<td>Upper GI bleed</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Grade 1-2</td>
<td>0 (0%)</td>
<td>1 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>
Conclusion

• Overall, the results of these trials suggest that aspirin may have potential as a cancer treatment or preventative measure in certain patients.
• However, the decision to use aspirin as part of cancer treatment should be made on a case-by-case basis in consultation with a healthcare provider.
The year in review: 2022-2023
Critical Care

Dr. Amsalu Bitew
(Internist, PCCM physician & assistant professor of medicine/AAU)
Major practice changing studies

1. Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension
2. Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation
Early Restrictive or Liberal Fluid Management for Sepsis-Induced Hypotension

The National Heart, Lung, and Blood Institute Prevention and Early Treatment of Acute Lung Injury Clinical Trials Network*
the Crystalloid Liberal or Vasopressors Early Resuscitation in Sepsis (CLOVERS) trial

• Multicenter, randomized, unblinded superiority trial
• 1563 patients at 60 U.S. centers were enrolled (782 patients were assigned to the restrictive fluid group and 781 to the liberal fluid group)
• The restrictive group received 1.3 liters while the liberal group received 3.4 liters in the first 24 hours after randomization
The main findings

• There was no significant difference in the primary outcome of 90-day mortality in the restrictive vs liberal group (14% vs 14.9%).

• There were no differences in secondary outcomes and no differential benefit in prespecified subgroup analyses.
Conclusion

• In patients with sepsis-induced hypotension, there was no significant difference in outcomes with either a restrictive or liberal fluid strategy.
Take away

• Further studies are recommended including beyond 24 hours duration
• Until further results are available there should be no dispute in restrictive Vs liberal fluid resuscitation of sepsis induced hypotension.
Original Article

Oxygen-Saturation Targets for Critically Ill Adults Receiving Mechanical Ventilation

Matthew W. Semler, M.D., Jonathan D. Casey, M.D.,
Margaret A. Hays, R.N., Joanna L. Stollings, Pharm.D., Kevin G. Buell, M.B., B.S.,
John H. Brems, M.D., Edward T. Qian, M.D., Kevin P. Seitz, M.D., Li Wang, M.S.,
Christopher J. Lindsell, Ph.D., Robert E. Freundlich, M.D.,
Jonathan P. Wanderer, M.D., Jin H. Han, M.D., Gordon R. Bernard, M.D.,
Wesley H. Self, M.D., M.P.H., and Todd W. Rice, M.D., for the PILOT
Investigators and the Pragmatic Critical Care Research Group*

N Engl J Med 387;19  NEJM.org  November 10, 2022
the Pragmatic Investigation of Optimal Oxygen Targets (PILOT) trial.

- Pragmatic, **unblinded**, cluster randomized, cluster-crossover trial
- The trial enrolled 2,541 patients receiving invasive ventilation at single center in the US.
- 22 clusters were randomized to pulse oximetry readings of either low (between 88-92%), intermediate (92-96%) or high (96-100%) target ranges.
The main findings

• No significant difference in the primary outcome of ventilator-free days was seen between any of these groups.
Proportion of Patients Alive and Not Receiving Invasive Mechanical Ventilation

P = 0.81 for the comparison of ventilator-free days
Conclusion

• Among critically ill adults receiving invasive mechanical ventilation, the number of ventilator-free days did not differ among groups in which a lower Spo2 target (90%), an intermediate Spo2 target (94%), or a higher Spo2 target (98%) was used.
• SPO2 greater than or equal to 88% might be used as a target for mechanically ventilated critically ill patients
A New Global Definition of Acute Respiratory Distress Syndrome

M.A. Matthay, Y. Arabi, A.C. Arroliga, G.R. Bernard, A.D. Bersten, L.J. Brochard, C.S. Calfee, A. Combes, B. Daniel, N.D. Ferguson, M.N. Gong. Show All...

• Rationale. Since the 2012 Berlin Definition of ARDS, several developments support the need for a revised Global Definition of ARDS

• Methods- A consensus conference including 32 critical care ARDS experts (clinicians and investigators); six virtual meetings & input from members of several global critical care societies
The main findings

New Global Definition of ARDS

- Intubation not required
- High flow nasal oxygen (HFNO) ≥ 30 L/min or NIV/CPAP ≥ 5 cm H₂O end-expiratory pressure

Hypoxemia levels of:
- \( \frac{PaO_2}{FiO_2} \leq 300 \text{ mmHg} \)
  or \( \frac{SpO_2}{FiO_2} \leq 315 \text{ mmHg} \) with \( \text{SPO}_2 \leq 97\%

- Bilateral opacities confirmed by one of the following: chest radiograph, computed tomography, or ultrasound with a well-trained operator

- In resource limited settings the following are not required: PEEP, oxygen flow, or specific respiratory support devices
Conclusion

• Acutely ill patients being treated with HFNO ≥30 L/min can be diagnosed with ARDS and represent a new category of non-intubated ARDS.

• Pulse oximetry can be used instead of arterial blood gases for the diagnosis of ARDS.

• Bilateral opacities should be retained as a required criterion, and ultrasound is an acceptable imaging modality.
Conclusion

• Patients in resource-variable settings will no longer be excluded from the definition of ARDS and will be included in epidemiology, clinical research, and clinical trials.

• The recommendations identify areas for future research, including prospective assessments of feasibility, reliability, and prognostic validity and the relationship of biological categories of ARDS to the Global Definition.
The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition

Thank you
The year in review: 2022-2023
Endocrinology- Diabetes

Limi Basha (Consultant Internist, Endocrinologist)
August 5, 2023
Outline of presentation

• Brief summary of practice changing studies in endocrinology and metabolism.

• Summary of major guideline changes in the year 2022/ 23
PREVENTION – Type 1 DM

Over the last nearly 2 decades, different approaches have been tried for the prevention, delay, and possible delay of Type 1 diabetes at different stages of development.
A phase 2, randomized, placebo-controlled, double-blind trial of teplizumab (an Fc receptor–nonbinding anti-CD3 monoclonal antibody)

76 relatives of patients with type 1 diabetes [high risk for development of clinical disease- stage 2]

single 14-day course of teplizumab or placebo , 32 : 44

Follow-up for progression to clinical type 1 diabetes was performed with the use of oral glucose-tolerance tests at 6-month intervals.

N Engl J Med 2019; 381:603-613
Results … T1 dm Trialnet study group

• The median delay in the diagnosis of diabetes was 2 years.

• At the conclusion of the trial, the percentage of diabetes-free persons in the teplizumab group (57%) was double that in the placebo group (28%).

• The safety analysis revealed expected adverse events of rash and transient lymphopenia among both children and adults.
PREVENTION .. Type 1 DM

Teplizumab improves and stabilizes beta cell function in antibody positive high-risk individuals

• **Aim**: analysis of the effect of a single 14 day course of Teplizumab treatment on metabolic function and immune cells among non-diabetic relatives at high risk for Type 1 DM

• An **extended followup of 923 days** of a previous report of teplizumab treatment.
Figure 1. Teplizumab Treatment is Associated with a Sustained Effect on Type 1 Diabetes Progression Over 923 Days of Follow-up.
Type 1 DM … prevention

• **Results**
  - The median times to diagnosis were 59.6 and 27.1 months for teplizumab- and placebo-treated participants, respectively (HR = 0.457, \( P = 0.01 \)) ➔ A median delay of 32.5 months
  - Teplizumab treatment improved beta cell function, reflected by average on-study C-peptide AUC (1.94 vs 1.72 pmol/ml; \( p=0.006 \)).
  - Drug treatment reversed a decline in insulin secretion prior to enrollment
  - Increases in CD8+ T cells

• **Conclusion**: Teplizumab treatment of non-diabetic relatives at high-risk for T1D showed improvement in metabolic responses and delay of diabetes.
TEPLIZUMAB

- FDA approved to delay the onset of Stage 3 T1D in adults and pediatric patients aged 8 years of age and older with Stage 2 T1D [on 17 November 2022]
• Does this translate to a change in clinical practice?

• Implications for the relevance and logistics of screening for type 1 diabetes.

• An entry for the development of additional prevention therapies.
Updates in management of Type 1 Diabetes
Insulin ICODEC

• Insulin icodec is a novel basal insulin analogue

• Icodec has strong and reversible albumin-binding properties along with reduced insulin receptor binding affinity, thus inactive circulating albumin-bound depot from which icodec is slowly and consistently released.

• It is suitable for once-weekly dosing with a mean half-life of 196 hours (nearly 7 days)
ONWARDS program

- A phase 3a clinical development program, ONWARDS, evaluated the efficacy and safety of once-weekly insulin icodec across diverse populations and comparator treatments available T2D and T1D.

- Three trials involved participants with type 2 diabetes who had not previously received insulin: ONWARDS 1, 3, and 5.

- ONWARDS 2 and 4 involved participants who had previously received insulin.

- ONWARDS 6 involved participants with type 1 diabetes.
<table>
<thead>
<tr>
<th>Key trial details</th>
<th>ONWARDS 1</th>
<th>ONWARDS 3</th>
<th>ONWARDS 5</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Trial design</strong></td>
<td>Randomized open label</td>
<td>Randomized double-blind</td>
<td>Randomized open label real-world elements</td>
</tr>
<tr>
<td><strong>Estimated sample size required, N</strong></td>
<td>970</td>
<td>580</td>
<td>1096</td>
</tr>
<tr>
<td><strong>Study start date</strong></td>
<td>November 2020</td>
<td>March 2021</td>
<td>March 2021</td>
</tr>
<tr>
<td><strong>Trial duration</strong></td>
<td>78 wk (52-wk main phase + 26-wk extension phase) + 5-wk follow-up period</td>
<td>26 wk + 5-wk follow-up period</td>
<td>52 wk + 5-wk follow-up period</td>
</tr>
<tr>
<td><strong>Interventions</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Icodec arm</strong></td>
<td>Once-weekly icodec + non-insulin glucose-lowering agents</td>
<td>Once-weekly icodec + non-insulin glucose-lowering agents + once-daily placebo</td>
<td>Once-weekly icodec (with digital titration solution) ± non-insulin glucose-lowering agents</td>
</tr>
<tr>
<td><strong>Comparator arm</strong></td>
<td>Once-daily glargine U100 + non-insulin glucose-lowering agents</td>
<td>Once-daily degludec + non-insulin glucose-lowering agents + once-weekly placebo</td>
<td>Once-daily basal insulin analogues (degludec, glargine U100 or U300) + non-insulin glucose-lowering agents</td>
</tr>
<tr>
<td><strong>Key inclusion criteria</strong></td>
<td>T2D diagnosed ≥180 d prior to screening</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td>Male or female age ≥ 18 y at the time of signing informed consent</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Screening HbA1c</strong></td>
<td>7.0%-11% (53.0-96.7 mmol/mol)</td>
<td>&gt;7.0% (53 mmol/mol)</td>
<td></td>
</tr>
<tr>
<td><strong>BMI, kg/m²</strong></td>
<td>≤40.0</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Trial design</td>
<td>ONWARDS 1</td>
<td>ONWARDS 3</td>
<td>ONWARDS 5</td>
</tr>
<tr>
<td>--------------------------------------</td>
<td>-----------</td>
<td>-----------</td>
<td>-----------</td>
</tr>
<tr>
<td>Estimated sample size required, N</td>
<td>970</td>
<td>580</td>
<td>1096</td>
</tr>
<tr>
<td>Study start date</td>
<td>November 2020</td>
<td>March 2021</td>
<td>March 2021</td>
</tr>
<tr>
<td>Trial duration</td>
<td>78 wk (52-wk main phase + 26-wk extension phase) + 5-wk follow-up period</td>
<td>26 wk + 5-wk follow-up period</td>
<td>52 wk + 5-wk follow-up period</td>
</tr>
</tbody>
</table>

**Interventions**

**Insulin arm**
- Once-weekly icodextr + non-insulin glucose-lowering agents

**Comparator arm**
- Once-daily glargine U100 + non-insulin glucose-lowering agents

**Key inclusion criteria**

**Diagnosis**
- T2D diagnosed ≤180 d prior to screening

**Demographics**
- Male or female age ≥ 18 y at the time of signing informed consent

**Screening HbA1c**
- 7.0% 11% (53.0-67.7 mmol/mol)
- >7.0% (53 mmol/mol)
- 7.0% 10.0% (53.0-65.8 mmol/mol)
- >10% (85.5 mmol/mol)

**BMI, kg/m²**
- ≤40.0
- N/A
- ≤40.0
- N/A

**Prior insulin treatment**
- Insulin-naïve
- Short-term insulin treatment periods for a maximum of 14 d prior to the day of screening or prior insulin treatment for gestational diabetes is permitted
- Insulin treatment >90 d prior to the day of screening
- Daily basal insulin: NPH insulin, degludec, detemir, glargine U100 or U300
- N/A
ONWARDS 1, the longest trial in the ONWARDS development program for insulin icodec.

492 patients each, with mean diabetes duration of 11 yrs.

ONWARDS 1 … cond

- **Primary outcome**
  - The difference between icodec and glargine U100 in the change in the A1C from baseline to week 52

- **Key secondary end point**
  - The percentage of time spent in the target glycemic range of 70 to 180 mg per in weeks 48 to 52
ONWARS 1 results

Noninferiority (P<0.001) and superiority (P = 0.02) of icodoc

Translated to 1 hr and 1 min more time spent in TIR at wk 48-52 and a 1 hr and 4 min at wk 74-78 for icodc
ONWARDS 1…cond

CONCLUSIONS

Glycemic control was significantly better with once-weekly insulin icodex than with once-daily insulin glargine U100.
• A phase 3a, double-blind 26-week efficacy and safety treat-to-target trial
• 1:1, Icodec vs Degludec

• 588 insulin-naïve people with type 2 diabetes.
ONWARDS 3 .. Results

- **Primary outcomes**
  - Mean HbA1c level at 26 weeks decreased more in the icodec group (-1.57% compared with -1.36% for insulin degludec (estimated treatment difference: -0.21%) confirming **noninferiority (P < .001) and superiority (P = .002)** [95%CI, -0.3 to -0.1] percentage points)

- **Safety outcomes**
  - Combined level 2 or 3 hypoglycemia rates were numerically higher in the icodec group than the degludec group from week 0 to 31 (0.31 vs 0.15 events per patient-year exposure; P = .11) and statistically higher in the icodec group from week 0 to 26 (0.35 vs 0.12 events per PYE; P = .01).

**CONCLUSIONS AND RELEVANCE** Among people with insulin-naive type 2 diabetes, once-weekly icodec demonstrated superior HbA1c reduction to once-daily degludec after 26 weeks of treatment, with no difference in weight change and a higher rate of combined level 2 or 3 hypoglycemic events in the context of less than 1 event per patient-year exposure in both groups.
Aimed to assess the efficacy and safety of once-weekly icodec versus once-daily insulin degludec (degludec) in basal insulin-treated type 2 diabetes.

A 26-week trial

Once-weekly icodec Vs once-daily degludec

The primary outcome was change from baseline to week 26 in HbA1c
ONWARDS 2..results

• **Primary outcome**
  HbA\(_1c\) was reduced to a greater extent with icodec than degludec.
  Estimated treatment difference (ETD) of −0.22 percentage points (95% CI −0.37 to −0.08), demonstrating non-inferiority (p<0.0001) and superiority (p=0.0028).

• **Safety outcomes**
  Overall rates of combined level 2 or level 3 hypoglycaemia were less than one event per patient-year of exposure for both groups (0.73 [icodec] vs 0.27 [degludec]).

*Interpretation* Among adults with basal insulin-treated type 2 diabetes, treatment with once-weekly icodec versus once-daily degludec demonstrated non-inferiority and statistical superiority in HbA\(_1c\) reduction after 26 weeks, associated with modest weight gain. Overall rates of hypoglycaemia were low, with numerically but not statistically significantly higher event rates of level 2 or level 3 hypoglycaemia with icodec versus degludec.
Switching to once-weekly insulin icodec versus once-daily insulin glargine U100 in individuals with basal-bolus insulin-treated type 2 diabetes (ONWARDS 4): a phase 3a, randomised, open-label, multicentre, treat-to-target, non-inferiority trial

Prof Chantal Mathieu, MD • Björg Ásbjörnsdóttir, MD • Harpreet S Bajaj, MD • Wendy Lane, MD • Ana Laura S A Matos, PhD • Prof Sreenivasa Murthy, MD • et al. Show all authors

Published: May 05, 2023 • DOI: https://doi.org/10.1016/S0140-6736(23)00520-2 • Check for updates

- 582 participants, 1:1 to icodect treatment & glargine U100
- Participants had a mean duration of type 2 diabetes of 17·1 years, and on a basal-bolus regimen
ONWARDS 4… Results

• **Primary outcome**
  - At week 26, estimated mean change in HbA$_{1c}$ was $-1.16$ percentage points in the icodoc group (baseline 8.29%) and $-1.18$ percentage points in the glargine U100 group (baseline 8.31%), **showing non-inferiority for icodoc versus glargine U100** (estimated treatment difference 0.02 percentage points [95% CI $-0.11$ to $0.15$], $p<0.0001$).

• **Safety outcomes**
  - A post-hoc analysis of insulin dose by bodyweight from week 24 to week 26 also showed:
    - A lower estimated mean total weekly insulin dose with icodoc
    - The mean weekly bolus insulin dose by bodyweight was also lower in the icodoc group than in the glargine U100 group.

**Interpretation** In people with long-standing type 2 diabetes on a basal-bolus regimen, once-weekly icodoc showed similar improvements in glycaemic control, with fewer basal insulin injections, lower bolus insulin dose, and with no increase in hypoglycaemic rates compared with once-daily glargine U100. Key strengths of this trial include the use of masked continuous glucose monitoring; the high trial completion rate; and the inclusion of a large, diverse, and multinational population. Limitations include the relatively short trial duration and the open-label design.
## Summary

<table>
<thead>
<tr>
<th>Trial duration (weeks)</th>
<th>Baseline HbA1C (%)</th>
<th>HbA1C Non-inferiority confirmed</th>
<th>HbA1C Superiority confirmed</th>
<th>Estimated change from baseline in HbA1C (%)</th>
<th>Estimated rate of level 2 or 3 hypoglycaemia (event per PYE)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ONWARDS 1</strong>&lt;br&gt;BASAL INITIATION</td>
<td>52&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.5</td>
<td>✓</td>
<td>✓</td>
<td>-1.55&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ONWARDS 3</strong>&lt;br&gt;DOUBLE-BLIND, DOUBLE-DUMMY</td>
<td>26</td>
<td>8.5</td>
<td>✓</td>
<td>✓</td>
<td>-1.57&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ONWARDS 5</strong>&lt;br&gt;ICODEC + TITRATION APP</td>
<td>52</td>
<td>8.9</td>
<td>✓</td>
<td>✓</td>
<td>-1.68&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ONWARDS 2</strong>&lt;br&gt;BASAL SWITCH</td>
<td>26</td>
<td>8.1</td>
<td>✓</td>
<td>✓</td>
<td>-0.93&lt;sup&gt;∗&lt;/sup&gt;</td>
</tr>
<tr>
<td><strong>ONWARDS 4</strong>&lt;br&gt;BASAL/BOLUS SWITCH</td>
<td>26</td>
<td>8.3</td>
<td>✓</td>
<td>✓</td>
<td>-1.16</td>
</tr>
<tr>
<td><strong>ONWARDS 6</strong>&lt;br&gt;BASAL/BOLUS SWITCH</td>
<td>26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.6</td>
<td>✓</td>
<td>✓</td>
<td>-0.71</td>
</tr>
</tbody>
</table>

### Notes:
- HbA1C values are reported in %.
- The estimated rate of hypoglycaemia is given in events per patient-year (PYE).
- Significance markers: ∗ denotes statistical significance at the 0.05 level.
Take away

• Insulin icodec offers similar or better glycaemic efficacy compared with daily basal insulin in type 2 diabetes, with good tolerability and encouraging safety results related to hypoglycaemia.
➢ Will it change practice?
Trends over the last 2 decades in the treatment of patients with type 2 diabetes

- **before 2000**
  - Glucose lowering to keep target A1c

- **2008**
  - FDA requirement on CV safety for glucose lowering drugs

- **2015**
  - First appearance of CV beneficial antidiabetic drugs

- **2020s**
  - Complication centric CV and renal benefit focused diabetes treatment
Updates in pharmacologic management of Diabetes

- Current theme is an emphasis on a complication-centric approach, beyond glucose levels.
SURPASS trials

TIRZEPATIDE T2D SURPASSED EXPECTATIONS
HELPED UP TO 97% AND 62% OF PATIENTS REACH HBA1C BELOW 7.0% AND 5.7%, RESPECTIVELY

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Active</th>
<th>T2P</th>
<th>T2P</th>
<th>T2P</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURPASS-1</td>
<td>Placebo (40 weeks)</td>
<td>20%</td>
<td>92%*</td>
<td>98%*</td>
<td>97%*</td>
</tr>
<tr>
<td>SURPASS-2</td>
<td>Semaglutide 1mg (43 weeks)</td>
<td>81%</td>
<td>45%</td>
<td>69%*</td>
<td>80%</td>
</tr>
<tr>
<td>SURPASS-3</td>
<td>Insulin degludec (52 weeks)</td>
<td>41%</td>
<td>99%*</td>
<td>97%*</td>
<td>96%*</td>
</tr>
<tr>
<td>SURPASS-4</td>
<td>Insulin glargine (52 weeks)</td>
<td>81%</td>
<td>98%</td>
<td>97%*</td>
<td>96%*</td>
</tr>
<tr>
<td>SURPASS-5</td>
<td>Add on to insulin glargine (40 weeks)</td>
<td>34%</td>
<td>95%*</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*Denotes statistical significance to comparator; * denotes not controlled for type I error.
T2P = tirzepatide; Results presented using the efficacy armament, which represents efficacy prior to discontinuation of study drug or initiating rescue therapy for persistent severe hyperglycemia.
### Results of analysis for change in body weight (tirzepatide vs placebo)

<table>
<thead>
<tr>
<th></th>
<th>Tirzepatide 5 mg vs placebo</th>
<th>Tirzepatide 10 mg vs placebo</th>
<th>Tirzepatide 15 mg vs placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td>-4.40</td>
<td>5.18</td>
<td>48</td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td>-6.30</td>
<td>6.37</td>
<td>121</td>
</tr>
<tr>
<td>SURPASS-5 [19]</td>
<td>-7.90</td>
<td>6.31</td>
<td>116</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 70%$, $\tau^2 = 2.11$, $p = 0.04$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td>-8.30</td>
<td>6.07</td>
<td>44</td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td>-7.10</td>
<td>5.57</td>
<td>118</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>-8.43</td>
<td>6.77</td>
<td>281</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 68%$, $\tau^2 = 1.33$, $p = 0.05$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>N</td>
</tr>
<tr>
<td>Frias et al (2018) [23]</td>
<td>-10.90</td>
<td>5.86</td>
<td>35</td>
</tr>
<tr>
<td>Frias et al (2020) [18]</td>
<td>-5.10</td>
<td>3.84</td>
<td>49</td>
</tr>
<tr>
<td>SURPASS-1 [22]</td>
<td>-8.80</td>
<td>10.33</td>
<td>116</td>
</tr>
<tr>
<td>SURPASS-5 [19]</td>
<td>-12.60</td>
<td>14.21</td>
<td>120</td>
</tr>
<tr>
<td>Random-effects model</td>
<td>-9.36</td>
<td>6.20</td>
<td>320</td>
</tr>
<tr>
<td>Heterogeneity: $I^2 = 91%$, $\tau^2 = 9.50$, $p &lt; 0.01$</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Favours tirzepatide**

**Favours placebo**
In conclusion, treatment with once weekly tirzepatide at the doses of 5mg, 10mg and 15mg, with controlled treatment exposure of up to 104 weeks, was not associated with increased risk for cardiovascular events in people with T2D across a spectrum of T2D duration and cardiovascular risk levels.
SURMOUNT 1 trial

• A phase 3 double-blind, randomized, controlled trial, with adults with a BMI of 30 or more, or 27 or more and at least one weight-related complication, excluding diabetes.

• Aim: To assess the efficacy and safety of tirzepatide in adults with obesity or overweight who did not have diabetes.

• Coprimary end points were the percentage change in body weight from baseline to week 72 and a weight reduction of 5% or more at week 72.
SURMOUNT 1 …cond
The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition
Efficacy for glucose lowering

Very High:
- Dulaglutide
- Semaglutide

Combination

Injectable

GLP-1 RA (not listed above)
- SGLT2i

Efficacy for weight loss

Very High:
- Semaglutide
- Tirzepatide

High:
- Dulaglutide, Liraglutide

Intermediate:
- GLP-1RA (not listed above), SGLT2i

Neutral:
- DPP-4i, Metformin
Weight management

- Complication-centric staging of ABCD vs prior BMI based
- Newer staging of ABCD (Adiposity-based chronic disease)
  - Stage 1, 2, and 3
- The revised ABCD staging incorporates weight bias/stigma and mental health as key components of ABCD that should be addressed in addition to the cardiometabolic and biomechanical complications which can be improved by treatment of obesity.

S.L. Samson, P. Vellanki, L. Blonde et al. Endocrine Practice 29 (2023) 305e340
Cardiovascular risk reduction in diabetes

- Control of hypertension
- Lipid goal achievement
- Aspirin use
- Avoidance of smoking
- Anti hyperglycemic with CV risk reduction
Cv risk reduction .. Blood pressure control

• Definition of Hypertension in diabetics

Hypertension management

2022
• BP target < 130/80 mmHg if 10 year ASCVD > 15% 
• OTHERS < 140/90 mmHg

2023
• Target < 130/80 mmHg

10.4 People with diabetes and hypertension qualify for antihypertensive drug therapy when the blood pressure is persistently elevated ≥130/80 mmHg. The on-treatment target blood pressure goal is <130/80 mmHg, if it can be safely attained.

Standards of care in diabetes, Diabetes care 2023, 46, Sup 1
Cv risk reduction – Lipid lowering

• The increased prevalence of lipid abnormalities among type 2 diabetic individuals contributes to their high risk of ASCVD.

• In addition to lifestyle modifications, lipid lowering using statin therapy has demonstrable benefit in ASCVD outcomes across many subgroups.

• Strongest evidences for cases in age 40 – 75 years
Efficacy of cholesterol-lowering therapy in 18,686 people with diabetes in 14 randomised trials of statins: a meta-analysis

Cholesterol Treatment Trialists’ (CTT) Collaborators*

Figure 3: Proportional effects on major vascular events per mmol/L reduction in LDL cholesterol in participants with and without diabetes by history of vascular disease.
• The main report of the Cholesterol Treatment Trialists’ (CTT) Collaboration showed that statin therapy safely reduces the 5-year incidence of major coronary events, coronary revascularisation, and stroke by about a fifth per mmol/L reduction in LDL cholesterol,
  – Irrespective of initial lipid profile or other baseline characteristics.
  – Larger reductions in LDL cholesterol were associated with greater proportional reductions in major vascular events.

Lancet, 2008 Jan 12;371(9607):117-25
## Lipid management – statins for primary prevention

<table>
<thead>
<tr>
<th>Age</th>
<th>CV risk factors</th>
<th>Treatment</th>
<th>LDL Goal</th>
</tr>
</thead>
<tbody>
<tr>
<td>40 - 75</td>
<td>nil</td>
<td>Moderate intensity statin</td>
<td>LDL &lt; 100 mg/dl</td>
</tr>
<tr>
<td>40 - 75</td>
<td>1 or more</td>
<td>High intensity statin</td>
<td>LDL &lt; 70, Reduce LDL 50% from base line</td>
</tr>
<tr>
<td>20 - 39</td>
<td>+</td>
<td>Reasonable to initiate statin</td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>Nil</td>
<td>Reasonable to initiate moderate intensity statin</td>
<td></td>
</tr>
<tr>
<td>&gt; 75</td>
<td>+</td>
<td>Continue statin therapy</td>
<td></td>
</tr>
</tbody>
</table>
2018 Guideline on the Management of Blood Cholesterol

Primary Prevention:
Assess ASCVD Risk in Each Age Group
Emphasize Adherence to Healthy Lifestyle

LDL-C ≥190 mg/dL (≥4.9 mmol/L)
No risk assessment; High-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Moderate-intensity statin
(Class I)

Diabetes mellitus and age 40-75 y
Risk assessment to consider high-intensity statin
(Class IIa)

Age >75 y
Clinical assessment, Risk discussion

In patients 40 to 75 years of age with diabetes mellitus and LDL-C ≥70 mg/dL (≥1.8 mmol/L), start moderate-intensity statin therapy without calculating 10-year ASCVD risk.
Lipid management- secondary prevention

10.26 For people with diabetes and atherosclerotic cardiovascular disease, treatment with high-intensity statin therapy is recommended to target an LDL cholesterol reduction of ≥50% from baseline and an LDL cholesterol goal of <55 mg/dL. Addition of ezetimibe or a PCSK9 inhibitor with proven benefit in this population is recommended if this goal is not achieved on maximum tolerated statin therapy. B
Managing risk of comorbidities and complications

• CVD, Heart failure and risk management
Expanding indications for SGLT2i use

- Established facts for SGLT2i till this year
  - An effective oral hypoglycemic agent.
  - Decreased CKD progression in patients with type 2 diabetes.
  - Mortality benefit and decreased hospitalization and cardiovascular events in patients with or without T2DM.
  [Patients with HF with preserved EF MAY BENEFIT]
Randomized, double blind, event driven

5988 adults with New York Heart Association functional class II–IV chronic heart failure and a left ventricular ejection fraction >40%

The primary outcome of a composite of cardiovascular death or hospitalization for heart failure.
EMPEROR-PRESERVED…Results
## EMPEROR-PRESERVED...Results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Empagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>435/2997</td>
<td>311/2991</td>
<td>0.79 (0.69–0.90)</td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>239/1466</td>
<td>291/1472</td>
<td>0.79 (0.67–0.94)</td>
</tr>
<tr>
<td>No</td>
<td>176/1311</td>
<td>220/1319</td>
<td>0.78 (0.64–0.95)</td>
</tr>
<tr>
<td>LVEF at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>145/995</td>
<td>193/988</td>
<td>0.71 (0.57–0.88)</td>
</tr>
<tr>
<td>≥50% to &lt;60%</td>
<td>138/1028</td>
<td>173/1030</td>
<td>0.80 (0.64–0.99)</td>
</tr>
<tr>
<td>≥60%</td>
<td>152/974</td>
<td>145/973</td>
<td>0.87 (0.69–1.10)</td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;70 yr</td>
<td>114/1066</td>
<td>152/1084</td>
<td>0.88 (0.79–1.11)</td>
</tr>
<tr>
<td>≥70 yr</td>
<td>281/1931</td>
<td>359/1907</td>
<td>0.75 (0.64–0.87)</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

In patients with heart failure and a preserved ejection fraction, the SGLT2 inhibitor empagliflozin lowered the risk of a composite of cardiovascular death or hospitalization for heart failure, mainly owing to a reduction in hospitalizations for heart failure.
A phase 3, randomized, double blind, event driven trial (Dapagliflozin 10mg to placebo)

- 6263 patients with heart failure and EF > 40%

- **The primary outcome**: A composite of worsening heart failure or cardiovascular death.

- **Secondary outcomes**: Total number of worsening heart failure events and cardiovascular deaths, the change from baseline in the total symptom score on the Kansas City Cardiomyopathy Questionnaire (KCCQ)
DELIVER …Results

- Secondary outcomes

<table>
<thead>
<tr>
<th>Variable</th>
<th>Dapagliflozin (N=1131)</th>
<th>Placebo (N=3112)</th>
<th>Hazard or Rate Ratio or Win Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total no. of worsening heart failure events and cardiovascular deaths;‡</td>
<td>815 (7.2)</td>
<td>1077 (13.3)</td>
<td>0.77 (0.67–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in KCCQ total symptom score at mo 8§</td>
<td>—</td>
<td>—</td>
<td>1.11 (1.03–1.21)</td>
<td>0.009</td>
</tr>
<tr>
<td>Mean change in KCCQ total symptom score at mo 8 among survivors</td>
<td>—</td>
<td>—</td>
<td>2.4 (2.5–3.4)</td>
<td>NA</td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>497 (13.9)</td>
<td>526 (16.8)</td>
<td>0.94 (0.83–1.07)</td>
<td>NA</td>
</tr>
</tbody>
</table>
DELIVER ...results

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Dapagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA class at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>131/2314</td>
<td>411/2396</td>
<td>0.81 (0.70–0.94)</td>
</tr>
<tr>
<td>III or IV</td>
<td>181/817</td>
<td>158/732</td>
<td>0.80 (0.65–0.98)</td>
</tr>
<tr>
<td>LVEF at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤49%</td>
<td>207/1067</td>
<td>229/1049</td>
<td>0.87 (0.72–1.04)</td>
</tr>
<tr>
<td>50–59%</td>
<td>174/1133</td>
<td>211/1123</td>
<td>0.79 (0.65–0.97)</td>
</tr>
<tr>
<td>≥60%</td>
<td>131/931</td>
<td>170/960</td>
<td>0.78 (0.62–0.98)</td>
</tr>
<tr>
<td>NT-proBNP at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤1011 pg/ml</td>
<td>173/1555</td>
<td>208/1578</td>
<td>0.84 (0.64–1.02)</td>
</tr>
<tr>
<td>&gt;1011 pg/ml</td>
<td>339/1576</td>
<td>402/1553</td>
<td>0.79 (0.69–0.92)</td>
</tr>
<tr>
<td>Enrollment during or within 30 days after</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>hospitalization for heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>419/2803</td>
<td>457/2806</td>
<td>0.82 (0.72–0.94)</td>
</tr>
<tr>
<td>Yes</td>
<td>93/323</td>
<td>113/326</td>
<td>0.87 (0.60–1.13)</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus at enrollment</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>242/1730</td>
<td>293/1727</td>
<td>0.86 (0.64–0.96)</td>
</tr>
<tr>
<td>Yes</td>
<td>270/1401</td>
<td>317/1405</td>
<td>0.83 (0.70–0.97)</td>
</tr>
<tr>
<td>Previous LVEF ≤40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>420/2559</td>
<td>491/253</td>
<td>0.84 (0.73–0.95)</td>
</tr>
<tr>
<td>Yes</td>
<td>92/572</td>
<td>119/579</td>
<td>0.74 (0.56–0.97)</td>
</tr>
</tbody>
</table>

**CONCLUSIONS**

The SGLT2 inhibitor dapagliflozin reduced the risk of worsening heart failure or cardiovascular death among patients with heart failure and a mildly reduced or preserved ejection fraction, with no excess of adverse events.
Take away from EMPEROR-PRESERVED, DELIVER trials

• Use of an SGLT2 inhibitor is an essential therapy in patients with heart failure, regardless of the presence or absence of type 2 diabetes mellitus or status of left ventricular ejection fraction.
• Any practice changes?
10.42a In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium-glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to reduce risk of worsening heart failure and cardiovascular death. A

10.42b In people with type 2 diabetes and established heart failure with either preserved or reduced ejection fraction, a sodium-glucose cotransporter 2 inhibitor with proven benefit in this patient population is recommended to improve symptoms, physical limitations, and quality of life. A
The year in review: 2022-2023
Nephrology

Wubshet Jote (MD)
Major practice changing studies

1. Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease

The NEW ENGLAND JOURNAL of MEDICINE

Renin–Angiotensin System Inhibition in Advanced Chronic Kidney Disease

Sunil Bhandari, Ph.D., Samir Mehta, M.Sc., Arif Khwaja, Ph.D., John G.F. Cleland, M.D., Natalie Ives, M.Sc., Elizabeth Brettell, B.Sc., Marie Chadburn, Ph.D., and Paul Cockwell, Ph.D., for the STOP ACEi Trial Investigators*
Study design

- Open label randomized controlled trial

Sample size

- 411 patients
- 3 years of follow up
- Primary outcome - eGFR at 3 years.

Intention to treat analysis
The main findings

Does the discontinuation of RAS inhibitors improve eGFR in patients with advanced CKD?

<table>
<thead>
<tr>
<th>1° Outcome</th>
<th>2° Outcome</th>
<th>MACE</th>
</tr>
</thead>
<tbody>
<tr>
<td>eGFR (by MDRD*)</td>
<td>(ESKD or RRT)</td>
<td></td>
</tr>
<tr>
<td>13.3±0.6 mL/min/1.73m²</td>
<td>56% (115/205)</td>
<td>43% (88/205)</td>
</tr>
</tbody>
</table>

**Open-Label Randomized Control Trial**

<table>
<thead>
<tr>
<th>39 Centers United Kingdom</th>
</tr>
</thead>
<tbody>
<tr>
<td>411 Adults Stage 4 or 5 CKD (eGFR &lt; 30 mL/min/1.73m²)</td>
</tr>
<tr>
<td>&gt; 2 mL/min/1.73m² per year eGFR decline over 2 year</td>
</tr>
</tbody>
</table>

- **Continue RAS inhibitor n=205**
- **Discontinue RAS inhibitor n=206**

**Conclusion:** Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of eGFR decline.

*Modification of Diet in Renal Disease
Reference: STOP ACE; trial investigators, Renin-Angiotensin System Inhibition in Advanced Chronic Kidney Disease.
Visual Abstract by: Dana Larsen, MD @dana_m_larsen

The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition
Estimated Glomerular Filtration Rate at 3 Yr

Least Squares Mean Estimated GFR (ml/min/1.73 m²)

Months

Continuation group

Discontinuation group

Baseline empirical mean value

The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition
Renal-Replacement Therapy or End-Stage Kidney Disease

Discontinuation group
68% (95% CI, 61–75)

Continuation group
63% (95% CI, 55–70)

Serious Adverse Events

<table>
<thead>
<tr>
<th>Variable</th>
<th>Discontinuation Group</th>
<th>Continuation Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients — no./total no. (%)</td>
<td>107/206 (52)</td>
<td>101/205 (49)</td>
</tr>
<tr>
<td>No. of events</td>
<td>237</td>
<td>253</td>
</tr>
<tr>
<td>No. of cardiovascular events</td>
<td>108</td>
<td>88</td>
</tr>
</tbody>
</table>
Conclusion

• Among patients with advanced and progressive chronic kidney disease, the discontinuation of RAS inhibitors was not associated with a significant between-group difference in the long-term rate of decrease in the eGFR.
Drawbacks of the Study

• Under representation of non-white racial & ethnic groups
• Open-label trail
• Few patients with nephrotic syndrome
Take away

KEEP CALM AND CARRY ON INHIBITING RAS
Sepsis-associated acute kidney injury consensus report of the 28th Acute Disease Quality Initiative workgroup

https://doi.org/10.1038/s41581-023-00683-3
Nature Nephrology Review, June 2023
Consensus Statement 1

• Definition SA-AKI and sepsis-induced AKI
  – No universally accepted definition currently

  – **SA-AKI** - presence of both consensus sepsis criteria (as defined by Sepsis-3 recommendations) and AKI criteria (as defined by KDIGO) when AKI occurs within 7 days from diagnosis of sepsis

  – **Sepsis-induced AKI** - subphenotype of SA-AKI in which sepsis is the predominant driver of tissue damage
Consensus Statement 2

• Pathophysiology

  – SA-AKI is a heterogeneous syndrome as multiple mechanisms contribute to injury with varying intensity between and within patients across the course of sepsis.

  – Integrating mechanism-specific biomarkers with clinical information will enable the identification of specific endotypes of SA-AKI

  – Identifying distinct endotypes of SA-AKI might provide crucial prognostic information, help to define treatment responsiveness and enrich clinical trial populations
Sepsis leads to PAMPs and DAMPs, which in conjunction with background susceptibility, can trigger various pathways including:

- Immunomodulation
- Inflammation
- Complement activation
- RAAS dysfunction
- Mitochondrial dysfunction
- Metabolic reprogramming
- Microcirculatory dysfunction
- Macrocirculation alteration

These pathways can lead to sepsis-associated AKI and sepsis-induced AKI. Subphenotypes such as (e.g., KDIGO 1/EM or BM) can lead to tissue tolerance and adaptive repair or maladaptive repair. Sepsis therapies may include nephrotoxic drugs and fluid therapy.

The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition

ESIM - Ethiopian Society of Internal Medicine
Consensus Statement 3

• Fluid management

– In patients with SA-AKI, hemodynamic management should be similar to that recommended by the Surviving Sepsis Guidelines.
Consensus Statement 4

• Extracorporeal therapies for SA-AKI
  
  – Extracorporeal blood purification (EBP) techniques can be used to remove pathogens, microbial toxins, inflammatory mediators and toxic metabolites from the blood as well as replenish solutes
    • AN69, plasmasulfone…
  
  – Emergent indications for initiating kidney replacement therapy do not differ between SA-AKI and other types of acute kidney injury
<table>
<thead>
<tr>
<th>Technology</th>
<th>Indication</th>
<th>Modality</th>
<th>Target of removal</th>
<th>Mass separation mechanism</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAES-PVP high-flux</td>
<td>KRT, hyperinflammation</td>
<td>HD, HFI, HDF</td>
<td>Fluids, electrolytes, middle molecules</td>
<td>Convection, diffusion</td>
<td>CRRT for kidney support</td>
</tr>
<tr>
<td>AN69-PEI-heparin</td>
<td>KRT, hyperinflammation, Gram-negative sepsis or endotoxaemia</td>
<td>HD, HFI, HDF</td>
<td>Fluids, electrolytes, middle molecules, endotoxin</td>
<td>Adsorption, convection, diffusion</td>
<td>CRRT for kidney and immunomodulatory support</td>
</tr>
<tr>
<td>AN69-ST, PMMA</td>
<td>KRT, hyperinflammation</td>
<td>HD, HFI, HDF</td>
<td>Fluids, electrolytes, middle molecules</td>
<td>Adsorption, convection, diffusion</td>
<td>CRRT for kidney and immunomodulatory support</td>
</tr>
<tr>
<td>PAES-PVP MCO and HCO</td>
<td>KRT, hyperinflammation</td>
<td>HD</td>
<td>Fluids, electrolytes, middle molecules</td>
<td>Diffusion</td>
<td>CRRT for kidney and immunomodulatory support</td>
</tr>
<tr>
<td>Plasmasulfone, polypropylene (for membrane plasmapheresis)</td>
<td>Hyperinflammation</td>
<td>Centrifugation or HF</td>
<td>Fluids, electrolytes, middle molecules, endotoxin</td>
<td>Convection (membrane); gravity sedimentation (centrifuge)</td>
<td>Immunomodulatory support</td>
</tr>
<tr>
<td>Heparin covalently bound to polyethylene</td>
<td>Viraemia, bacteraemia, fungaemia</td>
<td>Haemoadsorption</td>
<td>Bacteria, fungi, viruses</td>
<td>Adsorption</td>
<td>Selective immunomodulatory support</td>
</tr>
<tr>
<td>Porous polymer beads polystyrene divinylbenzene</td>
<td>Hyperinflammation</td>
<td>Haemopadsorption</td>
<td>Protein-bound compounds, middle molecules</td>
<td>Adsorption</td>
<td>Non-selective immunomodulatory support</td>
</tr>
<tr>
<td>PMX covalently bound to polypropylene-polystyrene fibre</td>
<td>Gram-negative sepsis or endotoxaemia</td>
<td>Haemoadsorption</td>
<td>Endotoxin</td>
<td>Adsorption</td>
<td>Selective immunomodulatory support</td>
</tr>
</tbody>
</table>
Conclusion

• SA-AKI
  – Heterogenous mechanism
  – Use of specific therapies might be influenced by the endotype and specific biomarkers soon.
Evidence based guidelines updates

Executive summary of the KDIGO 2022 Clinical Practice Guideline for Diabetes Management in Chronic Kidney Disease: an update based on rapidly emerging new evidence

Peter Rosling¹,², M. Luiza Caramoro³, Juliana C.N. Chan⁴,⁵, Hiddo J.L. Heerspink⁶, Clint Hurst⁷, Kamlesh Khunti⁸, Adrian Liew⁹, Erin D. Michos¹⁰, Sankar D. Navaneethan¹¹,¹², Wasiu A. Olowu¹³, Tami Sadusky¹⁴, Nikhil Tandon¹⁵, Katherine R. Tuttle¹⁶, Christoph Wanner¹⁷, Katy G. Wilkens¹⁸, Sophia Zoungas¹⁹, Jonathan C. Craig²⁰,²¹, David J. Tunnicliffe²¹,²², Marcello A. Tonelli²³, Michael Cheung²⁴, Amy Earley²⁴ and Ian H. de Boer²⁵

Kidney International (2022) 102, 990–999; https://doi.org/10.1016/j.kint.2022.06.013
June, 2022
KDIGO 2022 guideline on diabetes in CKD

• Focused update of the KDIGO 2020 guideline

  1. Comprehensive care in patients with diabetes and CKD
  2. Glucose-lowering therapies in patients with type 2 diabetes (T2D) and CKD

- Motivated by the wealth of high-quality new evidence that has quickly become available.
KDIGO 2022 guideline on diabetes in CKD

• Comprehensive Care
• Glucose lowering therapies
  – SGLT2i
    • Initiating an SGLT2i for patients with T2D and CKD who have an eGFR ≥20 ml/min per 1.73 m² (1A)
    • Emphasizes use regardless of glycemia and use with or without RASi or metformin.
    • Insufficient data to make a recommendation for people with T1D and CKD, kidney transplant recipients, or patients treated with dialysis.
KDIGO 2022 guideline on diabetes in CKD

- **GLP-1 receptor agonists**
  - Preferred glucose-lowering drug for people with T2D and CKD who were not attaining glycemic goals despite use of SGLT2i and metformin (or who were unable to use SGLT2i and/or metformin) (1B)

- **Non-steroidal mineralocorticoid antagonists**
  - T2D, an eGFR ≥25 ml/min per 1.73 m², normal serum potassium concentration, and albuminuria (≥30 mg/g) despite a maximum tolerated dose of RAS inhibitor (RASi) (2A).
Take home message from this guideline

Lifestyle:
- Healthy diet
- Physical activity
- Smoking cessation
- Weight management

First-line drug therapy:
- SGLT2i (initiate eGFR ≥20: continue until dialysis or transplant)
- Metformin (if eGFR ≥30)
- RAS inhibitor at maximum tolerated dose (if HTN*)
- Moderate-or high-intensity statin

Additional risk-based therapy:
- GLP-1 RA if needed to achieve individualized glycemic target
- Nonsteroidal MRA if ACR ≥30 mg/g [≥3 mg/mmol] and normal potassium
- Dihydropyridine CCB and/or diuretic* if needed to achieve individualized BP target
- Antiplatelet agent for clinical ASCVD
- Ezetimib, PCSK9, or icosapent ethyl if indicated based on ASCVD risk and lipids

Data points:
- Regular risk factor reassessment (every 3-6 months)

Legend:
- T2D only
- All patients (T1D and T2D)
The year in review: 2022-2023
Hematology

Helen Hilawi,
MD, internist, Hematologist
SPHMMC
August 2023
• Venous thromboembolism treatment in cancer patients, DOACs or LMWH?

• Thrombophilia workup 2023
Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin and Recurrent VTE in Patients With Cancer: A Randomized Clinical Trial

Deborah Schrag, MD, MPH; Hajime Uno, PhD; Rachel Rosovsky, MD; Cynthia Rutherford, MD; Kristen Sanfilippo, MD, MPH; John L. Villano, MD, PhD; Monica Drescher, MD; Nagesh Jayaram, MD; Chris Holmes, MD; Lawrence Feldman, MD; Ottavia Zattra, MD; Haley Farrar-Muir, MA; Christine Cronin, BS; Ethan Basch, MD, MSc; Anna Weiss, MD; Jean M. Connors, MD; for the CANVAS Investigators

Published online June 2, 2023.

NCT02744092
International clinical practice guidelines have progressively endorsed DOACs as an alternative to LMWHs for the initial and long-term treatment of cancer-associated thrombosis.
Cont…

- American Society of Clinical Oncology guideline (ASCO) 2023
- American Society of Hematology guideline (ASH) 2021
- National Comprehensive Cancer Network (NCCN) 2022
- International Initiative on Thrombosis in Cancer (ITAC) 2022
- International Society of Thrombosis and Hemostasis (ISTH) 2019
• Several randomized controlled trials have recently reported additional results on the safety and efficacy of DOACs in the setting of cancer.
DOACs or VKAs or LMWH - What is the optimal regimen for cancer-associated venous thromboembolism? A systematic review and meta-analysis

Naser Yamani, Samuel Unzek, Talal Almas, Adeena Musheer, Arooba Ejaz, Anousheh Awais Paracha, Izza Shahid and Farouk Mookadam

Published online 2022 Jun 9. doi: 10.1016/j.amsu.2022.103925
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1124</td>
<td>523</td>
<td>336</td>
<td>979</td>
<td>406</td>
<td>1046</td>
<td>287</td>
<td>1155</td>
</tr>
<tr>
<td>Trial type</td>
<td>subgroup analysis of patients with cancer enrolled in the EINSTEIN-DVT and EINSTEIN-PEopen-label, phase 3, randomized controlled trials</td>
<td>subgroup analysis of patients with cancer on VTE treatment enrolled in the AMPLIFY was a randomized, double-blind trial</td>
<td>post-hoc analysis of CA-VTE patients enrolled in the RECOVER and RECOVER II; both studies were randomized, double-blind, double-dummy trials</td>
<td>post-hoc analysis of patients with cancer enrolled in Hokusai-VTE trial; Hokusai-VTE was a multicenter randomized, double-blind, double-dummy trial</td>
<td>randomized, open-label, multicenter pilot trial</td>
<td>randomized, open-label trial</td>
<td>randomized, open-label, investigator-initiated trial</td>
</tr>
<tr>
<td>-----------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Randomization sequence</td>
<td>computerized voice-response system</td>
<td>interactive voice-response system</td>
<td>interactive voice-response system</td>
<td>interactive, web-based system</td>
<td>interactive, web-based system</td>
<td>interactive, web-based system</td>
<td>interactive, web-based system</td>
</tr>
<tr>
<td>Definition of primary efficacy outcome</td>
<td>recurrent venous thromboembolism</td>
<td>recurrent venous thromboembolism</td>
<td>recurrent venous thromboembolism</td>
<td>recurrent venous thromboembolism</td>
<td>recurrent venous thromboembolism</td>
<td>recurrent venous thromboembolism</td>
<td>any thromboembolic recurrence, including venous thromboembolism, DVT, PE</td>
</tr>
<tr>
<td>Active or history of cancer</td>
<td>Either active cancer or history of cancer</td>
<td>Either active cancer or history of cancer</td>
<td>Active cancer</td>
<td>Either active cancer or history of cancer</td>
<td>Active cancer</td>
<td>Either active cancer or history of cancer</td>
<td>Active cancer</td>
</tr>
<tr>
<td>Follow-up</td>
<td>12 months</td>
<td>6 months</td>
<td>6 months</td>
<td>3–12 months</td>
<td>12 months</td>
<td>12 months</td>
<td>6 months</td>
</tr>
</tbody>
</table>
Direct oral anticoagulants significantly reduced VTE Recurrence in cancer patients when compared to patients treated with LMWH or VKAs. (Hazard ratio [HR] 0.62, 95% confidence interval [CI] 0.46 – 0.83; P = 0.002; I² = 26%)

### 1.6.1 DOAC vs LMWH in active CA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raskob, 2016</td>
<td>-0.0305</td>
<td>0.1684</td>
<td>28.9%</td>
<td>0.97 [0.70, 1.34]</td>
<td>2018</td>
</tr>
<tr>
<td>Young, 2018</td>
<td>-0.844</td>
<td>0.4167</td>
<td>9.9%</td>
<td>0.33 [0.10, 0.97]</td>
<td>2018</td>
</tr>
<tr>
<td>McBane, 2019</td>
<td>-3.126</td>
<td>1.0358</td>
<td>2.0%</td>
<td>0.10 [0.01, 0.75]</td>
<td>2019</td>
</tr>
<tr>
<td>Agnelli, 2020</td>
<td>-0.462</td>
<td>0.2715</td>
<td>17.5%</td>
<td>0.63 [0.37, 1.07]</td>
<td>2020</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>56.3%</strong></td>
<td></td>
<td></td>
<td><strong>0.61 [0.35, 1.06]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.18; Chi² = 8.35, df = 3 (P = 0.04); I² = 84%

Test for overall effect: Z = 1.76 (P = 0.08)

### 1.6.2 DOAC vs VKAs in active CA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prins, 2014</td>
<td>-0.478</td>
<td>0.5524</td>
<td>6.3%</td>
<td>0.62 [0.21, 1.83]</td>
<td>2014</td>
</tr>
<tr>
<td>Agnelli, 2015</td>
<td>-0.5465</td>
<td>0.7128</td>
<td>4.1%</td>
<td>0.50 [0.14, 2.34]</td>
<td>2015</td>
</tr>
<tr>
<td>Schulman, 2015</td>
<td>-0.462</td>
<td>0.5854</td>
<td>5.7%</td>
<td>0.53 [0.20, 1.38]</td>
<td>2015</td>
</tr>
<tr>
<td>Raskob, 2016</td>
<td>-0.973</td>
<td>0.63</td>
<td>5.0%</td>
<td>0.59 [0.16, 1.89]</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>21.2%</strong></td>
<td></td>
<td></td>
<td><strong>0.60 [0.33, 1.09]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.03, df = 3 (P = 1.00); I² = 0%

Test for overall effect: Z = 1.68 (P = 0.09)

### 1.6.3 DOAC vs VKAs in history of CA

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Weight</th>
<th>Hazard Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prins, 2014</td>
<td>-0.022</td>
<td>0.6392</td>
<td>4.9%</td>
<td>0.98 [0.28, 3.43]</td>
<td>2014</td>
</tr>
<tr>
<td>Agnelli, 2015</td>
<td>-1.727</td>
<td>0.7611</td>
<td>3.6%</td>
<td>0.18 [0.04, 0.78]</td>
<td>2015</td>
</tr>
<tr>
<td>Raskob, 2016</td>
<td>-0.6349</td>
<td>0.3256</td>
<td>14.0%</td>
<td>0.53 [0.20, 1.38]</td>
<td>2016</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>22.5%</strong></td>
<td></td>
<td></td>
<td><strong>0.50 [0.24, 1.05]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.15; Chi² = 2.97, df = 2 (P = 0.23); I² = 33%

Test for overall effect: Z = 1.83 (P = 0.07)

**Total (95% CI)**: 100.0% [0.46, 0.83]

Heterogeneity: Tau² = 0.06; Chi² = 13.47, df = 10 (P = 0.20); I² = 28%

Test for overall effect: Z = 3.17 (P = 0.002)

Test for subgroup differences: Chi² = 0.18, df = 2 (P = 0.91), P = 0%

**Risk of bias legend**

- (A) Random sequence generation (selection bias)
- (B) Allocation concealment (selection bias)
- (C) Blinding of participants and personnel (performance bias)
- (D) Blinding of outcome assessment (detection bias)
- (E) Incomplete outcome data (attrition bias)
- (F) Selective reporting (reporting bias)
- (G) Other bias
Cont…

- DOAC is associated with a statistically significant higher risk of CRNMB than LMWH (Hazard ratio [HR] 1.60, 95% confidence interval [CI] 1.10–2.33; \( P = 0.01; I^2 = 40\%) \) but a lower risk of CRNMB compared to VKAs (Hazard ratio [HR] 0.60, 95% confidence interval [CI] 0.35–1.02; \( P = 0.06; I^2 = 0\%)\).

- CRNMB (Clinically Relevant NonMajor Bleeding)
Direct oral anticoagulant versus low molecular weight heparin for the treatment of cancer-associated venous thromboembolism: 2022 updated systematic review and meta-analysis of randomized controlled trials

Corinne Frere, Dominique Farge, Deborah Schrag, Pedro H. Prata & Jean M. Connors

Journal of Hematology & Oncology 15, Article number: 69 (2022)
### A. Recurrent venous thromboembolism

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC</th>
<th>LMWH</th>
<th>Risk Ratio</th>
<th>Heterogeneity</th>
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<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
<td>Weight</td>
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<tr>
<td>HOKUSAI-VTE CANCER</td>
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<td>522</td>
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<td>SELECT-D</td>
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<td>203</td>
<td>18</td>
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<tr>
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<td>142</td>
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<td>CANVAS</td>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1856</td>
<td>1840</td>
<td>100.0%</td>
<td>0.67 [0.52, 0.85]</td>
</tr>
<tr>
<td>Total events</td>
<td>90</td>
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</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.36, df = 5 (P = 0.59); I^2 = 0%

Text for overall effect: Z = 3.22 (P = 0.001)

### B. Major bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>DOAC</th>
<th>LMWH</th>
<th>Risk Ratio</th>
<th>Heterogeneity</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
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<tr>
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</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1856</td>
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<td>100.0%</td>
<td>1.17 [0.62, 2.22]</td>
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<td>Total events</td>
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</table>

Heterogeneity: Tau^2 = 0.02; Chi^2 = 5.66, df = 5 (P = 0.34); I^2 = 12%

Text for overall effect: Z = 0.85 (P = 0.39)

### C. Clinically relevant non major bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
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<th>LMWH</th>
<th>Risk Ratio</th>
<th>Heterogeneity</th>
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</thead>
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<td>Events</td>
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<td>Events</td>
<td>Weight</td>
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<td>CARAVAGGIO</td>
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<tr>
<td>CASTA-DIVA</td>
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<td>74</td>
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<tr>
<td>CANVAS</td>
<td>19</td>
<td>330</td>
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<td>306</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>1856</td>
<td>1840</td>
<td>100.0%</td>
<td>1.66 [1.31, 2.09]</td>
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<tr>
<td>Total events</td>
<td>177</td>
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</table>

Heterogeneity: Tau^2 = 0.00; Chi^2 = 4.62, df = 5 (P = 0.44); I^2 = 0%

Text for overall effect: Z = 4.23 (P < 0.0001)
Direct Oral Anticoagulants vs Low-Molecular-Weight Heparin and Recurrent VTE in Patients With Cancer: A Randomized Clinical Trial

Deborah Schrag, MD, MPH; Hajime Uno, PhD; Rachel Rosovsky, MD; Cynthia Rutherford, MD; Kristen Sanfilippo, MD, MPH; John L. Villano, MD, PhD; Monic Drescher, MD; Nagesh Jayaram, MD; Chris Holmes, MD; Lawrence Feldman, MD; Ottavia Zattra, MD; Haley Farrar-Muir, MA; Christine Cronin, BS; Ethan Basch, MD, MSc; Anna Weiss, MD; Jean M. Connors, MD; for the CANVAS Investigators

Published online June 2, 2023.
Patients and physicians selected treatment either from among DOACs or from among LMWH or fondaparinux.

The exclusion criteria used in most RCTs (ECOG Performance Status > 2, brain tumors, platelet count < 50,000–75,000, Cockroft Gault creatinine clearance < 30 ml.min⁻¹) may have limited the generalizability.
Study design

- un blinded comparative effectiveness noninferiority randomized clinical trial
- Included randomized and preference cohort
- 67 US oncology centers
• If the upper bound of the 1-sided 95% CI was less than 3%, noninferiority was concluded.

• The secondary outcomes included major bleeding was assessed using a 2.5% noninferiority margin.
Eligibility criteria

- Age $\geq$ 18 years
- Solid tumors, lymphoma, CLL, or multiple myeloma if advanced disease or diagnosed within the past 12 months.
- Symptomatic or asymptomatic VTE detected on imaging within 30 days prior to enrollment regardless of the type of anticoagulant initiated prior to enrollment.
- Platelet count of $\geq$ 50,000/μL and
- Creatinine clearance of $\geq$ 15 mL/min/1.75 m² within 7 days of enrollment.
Exclusion criteria

- acute leukemia,
- recent or planned stem cell transplant,
- ongoing clinically significant bleeding,
- pregnancy or breastfeeding,
- use of medications that interfered with DOAC metabolism,
- life expectancy of less than 3 months,
- receipt of therapeutic anticoagulation at the time the new VTE was diagnosed
Primary outcome

- Cumulative incidence of recurrent nonfatal VTE at 6 month follow up.
Secondary outcome

- Bleeding graded using CTCAE at 6 month
- Cumulative incidence of death and restricted mean survival time at 6 months
- Health-related quality of life
- Participants’ perceptions of the burdens and benefits of anticoagulation treatment.
Sample size

811 Ambulatory adults with cancer and a new diagnosis of venous thromboembolism enrolled

140 Declined randomization and placed in preference cohort

671 Randomized (randomized cohort)

335 Randomized to receive direct oral anticoagulant
- 330 Received treatment as randomized
  - 193 Received apixaban
  - 122 Received rivaroxaban
  - 9 Received dabigatran
  - 6 Received edoxaban
  - 5 Did not receive treatment as randomized

255 Completed 6-mo follow-up
- 80 Did not complete 6-mo follow-up
  - 73 Died
  - 7 Lost to follow-up
- 330 Included in the primary analysis
- 335 Included in the as-randomized analysis

336 Randomized to receive low-molecular-weight heparin
- 308 Received treatment as randomized
  - 277 Received enoxaparin
  - 23 Received fondaparinux
  - 8 Received dalteparin
  - 28 Did not receive treatment as randomized

265 Completed 6-mo follow-up
- 71 Did not complete 6-mo follow-up
  - 59 Died
  - 12 Lost to follow-up
- 308 Included in the primary analysis
- 336 Included in the as-randomized analysis
The main findings

<table>
<thead>
<tr>
<th>Table 2. Primary and Secondary Clinical Outcomes at 6 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcomes</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
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<tr>
<td>Primary outcome</td>
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<tr>
<td>Recurrent nonfatal VTE, %&lt;sup&gt;c&lt;/sup&gt;</td>
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<tr>
<td>Secondary outcomes</td>
</tr>
<tr>
<td>Death, %</td>
</tr>
<tr>
<td>Restricted mean survival time, d&lt;sup&gt;d&lt;/sup&gt;</td>
</tr>
<tr>
<td>Bleeding, %</td>
</tr>
<tr>
<td>Major bleeding&lt;sup&gt;e&lt;/sup&gt;</td>
</tr>
<tr>
<td>Clinically relevant nonmajor bleeding&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>Minor bleeding&lt;sup&gt;g&lt;/sup&gt;</td>
</tr>
<tr>
<td>Other prespecified outcomes</td>
</tr>
<tr>
<td>Adverse events (safety end point), %</td>
</tr>
<tr>
<td>Any serious adverse event&lt;sup&gt;h&lt;/sup&gt;</td>
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<tr>
<td>Severe serious adverse events&lt;sup&gt;i&lt;/sup&gt;</td>
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Cont…

B. Major bleeding

C. Death

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<tr>
<th>Follow-up, d</th>
<th>Probability of major bleeding</th>
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<table>
<thead>
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<th>Probability of death</th>
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<td>150</td>
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<td>180</td>
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<th>No. at risk</th>
<th>DOACs</th>
<th>LMWH</th>
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<tr>
<td>210</td>
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<td>245</td>
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</table>
Conclusion

- DOAC therapy was noninferior to LMWH therapy for preventing VTE recurrence.

- Rates of major bleeding and death were not significantly different, this might be due to use of apixaban by almost 58.5% of participants.

- DOACs had a higher risk of clinically relevant nonmajor bleeding compared with LMWH.
Cont…

- No significant difference in the burdens or benefits of anticoagulation treatment or in health-related quality of life,

- Adherence to the assigned anticoagulation therapy at 6 months was significantly greater for the DOAC group.
Limitations

- Participants and physicians were not blinded to treatment assignment.

- Randomized was within 30 days of a new VTE hence some were treated with different therapy before randomization.

- In advanced-stage cancer and VTE the cause of death was indistinguishable.
Cont...

• Blacks were 13%, limiting the generalizability of results.

• Detailed medication adherence diaries were not obtained.

• Lower adherence rates with LMWH could have biased results toward noninferiority of DOAC therapy.

• Lacked statistical power for superiority testing.
Take away

• These results increase the level of certainty supporting the use of DOACs as an effective and safe option for the treatment of cancer associated thrombosis in selected cancer patients.

• LMWHs remain the preferred treatment option in those with: high risk of bleeding, requiring frequent dose adjustments with chemotherapy-induced thrombocytopenia, anticancer therapies with potential drug-drug interactions, those with brain metastases.
• American Society of Hematology 2023 Guidelines for Management of Venous Thromboembolism: Thrombophilia Testing
  – May 17 2023
• The purpose of these guidelines is to provide evidence-based recommendations on thrombophilia testing tailored management to improve patient-important outcomes.

• 23 recommendations were set even though nearly all recommendations are based on very low certainty in the evidence.
Cont...

• Testing for hereditary thrombophilias include deficiencies of antithrombin, protein C, or protein S, and the gain-of-function mutations Factor V Leiden (FVL) and prothrombin G20210A (PGM).

• Interpretation is with pitfalls of laboratory testing.
– Thrombophilia testing;
  – young,
  – recurrent episodes,
  – Skin necrosis with warfarin
  – thrombosis at unusual sites, or
  – positive family history

– VTE attributable to genetic effects is as high as 60%.
– Genetic defects linked to VTE account for 1/3 of VTE cases.
Thrombophilia testing in symptomatic VTE

- Unprovoked VTE
- VTE provoked by surgery
- Unspecified type of VTE (provoked or unprovoked)

- ASH guideline panel suggests not testing for thrombophilia to guide treatment duration.
Cont....

- Provoked VTE,
- Nonsurgical major transient risk factor,
- Pregnancy or postpartum,
- Use of COC

- ASH guideline panel suggests testing for thrombophilia to guide treatment duration.
Symptomatic VTE at unusual sites

• Cerebral venous thrombosis planning to discontinue anticoagulation,
  – ASH guideline panel suggests testing for thrombophilia.

• Planning to continue anticoagulation indefinitely,
  – The panel suggests not testing for thrombophilia
Cont…

- Splanchnic venous thrombosis without cirrhosis planning to discontinue anticoagulation,
  - ASH guideline panel suggests testing for thrombophilia

- Planning to continue anticoagulation indefinitely,
  - The panel suggests not testing
Family history of VTE and/or thrombophilia

- Family history (first- or second-degree relative) of VTE and thrombophilia, thrombophilia testing to guide the use of **thromboprophylaxis for a minor provoking risk factor**
  - known FVL or PGM (low-risk thrombophilia) - the panel suggests **not testing**
  - known antithrombin, protein C, or protein S deficiency (high-risk thrombophilia) - suggests **selective or panel testing**

- homozygous defects or combinations of thrombophilia types are not included.
Cont...

• Family history of VTE and unknown thrombophilia status thrombophilia testing to guide the use of thromboprophylaxis for a minor provoking risk factor
  – ASH guideline panel suggests **not testing**

• Testing may be considered if multiple family members with VTE, if the family member with VTE was young, with patient preference and low cost.
Cont…

• Family history of thrombophilia but no VTE thrombophilia testing to guide the use of thromboprophylaxis for a minor provoking risk factor

  – If FVL or PGM (low-risk thrombophilia) – the panel suggests not testing
  – If antithrombin, protein C, or protein S deficiency (high-risk thrombophilia)
    • first-degree- suggests selective testing
    • Second degree – suggests either selective testing or not testing
Cont…

• In women from the general population ASH guideline panel recommends not testing to guide the use of COC and suggests not testing to guide use of HRT.

• In women with a family history of VTE and unknown thrombophilia status, thrombophilia testing is not required to guide the use of COC or use of HRT.
• To guide the use of COC or HRT in women with a family history of VTE with low risk and high risk thrombophilia the panel suggests not testing and selective thrombophilia testing respectively.

• Homozygous defects or combinations of thrombophilia types are not included.
Cont…

- Family history of VTE and known homozygous FVL, combination of FVL and PGM, or antithrombin deficiency the panel suggests selective testing to guide the use of thromboprophylaxis during pregnancy and postpartum and for known protein C or protein S deficiency in the family, the panel suggests either testing or not testing.

- Second-degree family history or heterozygous FVL or PGM alone was not addressed.
• For postpartum thromboprophylaxis
  – Second degree known homozygous FVL, combination of FVL and PGM, or antithrombin deficiency in the family, the panel suggests testing
  – Second degree known protein C or protein S deficiency in the family, the panel suggests either testing or not testing
Family history of VTE and/or thrombophilia to prevent cancer-associated VTE

• In ambulatory cancer patients (without personal history of VTE) receiving systemic therapy with a family history of VTE thrombophilia testing to guide the use of thromboprophylaxis,
  - low or intermediate risk for VTE, the panel suggests testing
Conclusion

• Conditional recommendations are put for thrombophilia testing in the following scenarios:
  • VTE associated with nonsurgical triggering conditions, including COC and pregnancy
  • cerebral or splanchnic venous thrombosis, in settings where short term primary treatment is the standard of care
  • family history of antithrombin, protein C or protein S deficiency when considering VTE prophylaxis for minor VTE risk factors or avoidance of COC/HRT
  • pregnant women with a sibling with homozygous FVL, or a family history of a combination of FVL and PGM or antithrombin deficiency
  • patients with cancer at low or intermediate risk of thrombosis and have a family history of VTE.
• These guidelines are not intended to serve or be construed as a standard of care.

• A patient-centered, individualized approach is adopted whenever appropriate.
The year in review: Infectious diseases

Studies which have had the most impact in clinical practice in 2022/23

Tinsae Alemayehu MD MMed (Peds ID)
A 24-Week, All-Oral Regimen for Rif-resistant TB
TB-PRACTEAL study, Dec 2022

- 465,000 patients had rifampin-resistant TB worldwide in 2019

3% of new TB cases in Ethiopia in 2021 were MDR/RR-TB

• Short version (9 – 12 mo) of MDR-TB Rx
  4 mo of Levo-/Moxi-, Eto, High dose H, E followed by
  5 mo of Levo-/Moxi-, Z, E and Cfz WITH 6 mo of BDQ at the start

• Long version (minimum 20 months)
  Cs, Levo, BDQ, Cfz, L

→ Up to 20 tabs a day
  ! Cost  ! ADRs and monitoring ability  ! Social disruption

• A meta-analysis of the current 9-to-11-month all-oral regimen
  recommended by the WHO showed a successful outcome in
  73% of patients. Mirzayev et al. *Eur Respir J* 2021
Study design

• An open-label, phase 2 – 3, multicenter, non-inferiority RCT to evaluate efficacy and safety of three 24-week, all-oral regimens

<table>
<thead>
<tr>
<th>Standard therapy</th>
<th>24 weeks of BPaLM</th>
<th>24 weeks of BPaLM</th>
<th>24 weeks of BPaL</th>
</tr>
</thead>
</table>

B: Bedaquiline   Pa: Pretomanid   L: Linezolid   M: Moxifloxacin   C: Clofazimine

→ Ages ≥ 15 years
→ Primary outcome: An unfavorable status (a composite of death, treatment failure, treatment discontinuation, LTFU, or recurrence) at 72 weeks after randomization.
- BPaLM (89% favorable outcome), BPaLC (81%) and BPaL (77%) were both non-inferior and superior to the accepted standard care (52%). Terminated early after 75% recruitment.
Strengths

- Representative of countries with a high RR/MDR TB burden
- Included those with FQ-R TB
- Included those with TB/HIV co-infection

Limitations

- Open-label
- Frequent updates in “standard Rx” regimens throughout the trial period (Jan ‘17 – June ‘18) and also differing according to the study site
- Relatively small sample size: 552 underwent randomization into the four arms

**IMPACT**: Prompted WHO to update global DR-TB treatment guidelines
BPaLM x 6 months for …

• Ages $\geq$ 15 years
• Has not been exposed to any of the drugs composing the regimen for $\geq$ 30 days
→ If exposed for $\geq$ 30 days, resistance to the drugs must be ruled out
• Fluoroquinolone-susceptible
• No evidence of XDR-TB
• No evidence of TB involving CNS, miliary TB and osteoarticular TB
• Not breast feeding or pregnant
Ceftriaxone vs anti-staphylococcal penicillins or cefazolin for treating MSSA bacteremia

- 2nd most common cause of hospital-onset sepsis in all age-groups
- 20.3% of pediatric HAIs in Ethiopia – a third being due to MRSA
- *S aureus* almost never a contaminant when isolated from blood culture
  * Tendency for metastatic infections
  * High mortality ~ 30% dying within months of diagnosis
  * Prolonged Rx (2 to 6 weeks)

https://doi.org/10.1007/s10096-023-04575-z
<table>
<thead>
<tr>
<th>Ceftriaxone</th>
<th>Cefazolin or ASPs</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Convenient for out-patient dosing</td>
<td>• Less convenient for out-patient use (frequent dosing)</td>
</tr>
<tr>
<td>• 3rd generation cephalosporins considered as the least effective for treating gram positive bacterial infections</td>
<td>• Highly effective for staphylococcal infections</td>
</tr>
<tr>
<td></td>
<td>• Lack of availability</td>
</tr>
</tbody>
</table>

**Backdrop:**

✓ No prospective or randomized data for use of ceftriaxone for MSSA

✓ Retrospective studies have yielded mixed results
Study design

- A multicenter, retrospective cohort study of adult patients with MSSA bacteremia between (Jan ‘18 - Dec ‘19) at 5 Mayo Clinic campuses.

- Primary outcome: 90-day treatment failure (mortality and/or microbiologic recurrence)
  - Recurrence: + *S. aureus* culture with compatible clinical syndrome

223 patients met study criteria

- Commonest source of bacteremia: SSTis (37%)
- Mean age: 63 years
- Endocarditis: 12%
- Definitive Rx
  - 75% Cefazolin
  - 8.3% Nafcillin/Oxacillin
  - 16.6% Ceftriaxone
Twenty-six (11.7%) developed 90-day treatment failure: 18 deaths and 8 recurrences

After adjusting for comorbidities, duration of Rx & endocarditis: Definitive Rx with ceftriaxone was associated with 2.66x higher rates of treatment failure (6x higher among those with endocarditis – not stat significant)
Lessons and limitations

• Important study highlighting the difference in mortality among CFO vs ASPs/Cefazolin

Limitations

→ Retrospective - ? Bias
→ Not randomized - ? Leftover confounders
→ Few patients (16%) took CFO
Hydrocortisone in Severe Community-Acquired Pneumonia

CAPE-COD study, May 2023

- Globally, 500 million LRTIs are diagnosed per year

<table>
<thead>
<tr>
<th>High income countries</th>
<th>LMICs</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 – 12% mortality among CAP hospitalizations</td>
<td>9 - 15% among non-ICU CAP hospitalizations</td>
</tr>
<tr>
<td>30% mortality among ventilated patients with CAP</td>
<td>22 – 49% among ICU admission</td>
</tr>
</tbody>
</table>

- Pulmonary and systemic inflammation + impaired gas exchange + sepsis = mortality
- Unclear benefits of glucocorticoids in terms of reducing mortality

https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6680311/
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC8203087/
Study design

• A multicenter, double-blinded RCT – 31 French ICUs
  - The primary outcome was death from any cause by day 28

Definitions

➢ Initiation of mechanical ventilation
➢ Initiation of high-flow nasal cannula oxygenation
➢ For patients wearing a non-rebreathing mask, $\text{PaO}_2:\text{FiO}_2 < 300$
➢ A score of more than 130 on the Pulmonary Severity Index

Excluded: septic shock, influenza pneumonia, DNI

Add IV Hydrocortisone for 4 – 7 days based on clinical improvement, then tapered over 8 – 14 days
Outcomes

- The trial was stopped early

<table>
<thead>
<tr>
<th></th>
<th>Hydrocortisone (n = 400)</th>
<th>Placebo (n = 400)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Day 28 mortality</td>
<td>6.2%</td>
<td>11.9%</td>
</tr>
<tr>
<td>Day 90 mortality</td>
<td>9.3%</td>
<td>14.7%</td>
</tr>
<tr>
<td>In initially non-ventilated patients, % ETT</td>
<td>18%</td>
<td>29.5%</td>
</tr>
<tr>
<td>In patients who were not on vasopressors at baseline, % receiving it at day 28</td>
<td>15.3%</td>
<td>25%</td>
</tr>
<tr>
<td>Rates of HAIs, GI bleeding etc</td>
<td></td>
<td>Similar rates</td>
</tr>
</tbody>
</table>
Limitations

- Few immune-compromised patients were included
  - 6.4% immune-suppressed excluding DM

- Limited ADR analysis
  - Higher hyperinsulinemia but not confirmed to be transient
  - Potential neuropsychological and neuromuscular ADRs not assessed
In conclusion …

• Shorter is better when treating RR-TB
• Treating MSSA bacteremia with ceftriaxone will fail
• Steroids lower mortality for severe CAP admissions in the ICU

Thank you
The year in review: 2022-2023
Nuclear Medicine

Takele Lodamo[MD, NMS]
Nuclear Medicine specialist
August 5, 2023
Major practice changing studies

1. Study 1 (DAT Scan in Parkinsonism)
   ✓ Dopamine transporter single photon emission computed tomography (DaT-SPECT) use in the diagnosis and clinical management of parkinsonism: an 8-year retrospective study

2. Study 2 (SPECT use in Cardiac Amyloidosis)
   • The use of PYP scan for evaluation of ATTR cardiac amyloidosis at a tertiary medical centre
1. Study 1 (DAT Scan in Parkinsonism)

- **Study Title**
  - Dopamine transporter single photon emission computed tomography (DaT-SPECT) use in the diagnosis and clinical management of parkinsonism: an 8-year retrospective study

- **Study design**
  - retrospective study involved

- **Sample size**
  - 451 patients who had undergone DaT scans for investigation for Parkinsonism, between 2014 and 2021.
background

- Parkinson’s disease (PD) is a neurodegenerative movement disorder that is typically diagnosed clinically.
- Is characterized by the progressive loss of presynaptic dopaminergic neurons in the brain leading to both motor and cognitive deficits.

- DaT-SPECT scanning (DaT Scan) can be used when there is diagnostic difficulty differentiating from non-neurodegenerative Parkinsonism.
• DaT scan sensitivity and specificity to detect nigrostriatal cell loss is high
  – Differentiating ET from PD = SEN=93%, SPEC=100% [1]

• Scan Interpretation
  ✓ Visual Interpretation
  ✓ semiquantitative analysis

[1] DaT scan in daily practice, Psychiatry and neurology resource center
Objective of the study

- to determine the use of DaT scans in the diagnosis and management of patients who exhibit features of Parkinsonism, where the cause is clinically not clearly distinguishable.

Thus, this study assessed the effect of DaT Scan imaging on diagnosis and subsequent clinical management of these disorders.
The main findings

• Retrospectively a total of 451 scans which were requested by Parkinson’s team were assessed {2014 to 2021}
  – They were clinically diagnosed as follows

<table>
<thead>
<tr>
<th>Pre-scan diagnosis</th>
<th>#</th>
</tr>
</thead>
<tbody>
<tr>
<td>idiopathic PD</td>
<td>190</td>
</tr>
<tr>
<td>Essential tremor (ET),</td>
<td>129</td>
</tr>
<tr>
<td>Lewy-body dementia (LBD)</td>
<td>28</td>
</tr>
<tr>
<td>Drug-Induced Parkinson’s (DIP),</td>
<td>45</td>
</tr>
<tr>
<td>Parkinson’s Plus Syndromes,</td>
<td>16</td>
</tr>
<tr>
<td>Vascular Parkinson’s (VP),</td>
<td>26</td>
</tr>
<tr>
<td>other conditions.</td>
<td>17</td>
</tr>
<tr>
<td>total</td>
<td>451</td>
</tr>
</tbody>
</table>

Scan result

• The scan outcomes were categorized into three groups:
  ✓ abnormal (positive scan),
  ✓ normal (negative scan), and
  ✓ equivocal scan.
From the pre-scan diagnoses
- The dx expected to have an abnormal DaT Scan are
  • PD, LBD, and Parkinson’s plus syndromes.

- expected to be negative on DaT Scan
  • ET, DIP, VP, and other diagnoses

Scan result [from 455 cases]
- abnormal scan result seen= 184 (40%),
- normal scan result =239 (53%)
- an equivocal scan =32 (7%)

Diagnosis that was consistent with the scan result.
- ABNORMAL SCAN= 131/181(73%) consistent with the scan result.
- NORMAL SCAN=154 /238(65%) had a pre-scan diagnoses that was consistent with this DaT result
The number and percentage of scans stratified by the pre-scan diagnosis from 2014 to 2021

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Abnormal scans (%)</th>
<th>Normal scans (%)</th>
<th>Equivocal scans (%)</th>
<th>Total number of scans (pre-scan diagnosis)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Possible PD</td>
<td>55.2</td>
<td>31.1</td>
<td>50.0</td>
<td>190</td>
</tr>
<tr>
<td>ET</td>
<td>8.8</td>
<td>44.1</td>
<td>25.0</td>
<td>129</td>
</tr>
<tr>
<td>LBD</td>
<td>9.9</td>
<td>3.4</td>
<td>6.3</td>
<td>28</td>
</tr>
<tr>
<td>DIP</td>
<td>6.1</td>
<td>13.0</td>
<td>9.4</td>
<td>45</td>
</tr>
<tr>
<td>Parkinson's plus</td>
<td>7.2</td>
<td>0.8</td>
<td>3.1</td>
<td>16</td>
</tr>
<tr>
<td>VP</td>
<td>7.2</td>
<td>4.6</td>
<td>6.3</td>
<td>26</td>
</tr>
<tr>
<td>Other diagnosis</td>
<td>5.5</td>
<td>2.9</td>
<td>0</td>
<td>17</td>
</tr>
<tr>
<td><strong>Total number of scans (scan outcome)</strong></td>
<td><strong>181</strong></td>
<td><strong>238</strong></td>
<td><strong>32</strong></td>
<td></td>
</tr>
</tbody>
</table>


The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition
Post-scan diagnosis and clinical management

• For all DaT scans,[451]
  – the diagnosis was changed for 168 patients (37%), [168/451]
  – the clinical management was changed for 190 patients (42%).

  – The diagnosis was not changed in 283 patients (63%),
  – the clinical management was not changed in 260 patients (58%).

• Change in management involved 63% starting dopaminergic medication, 5% stopping dopaminergic medications, and 31% undergoing other changes in management.
Figure 1 shows the changes in trends of diagnosis and clinical management over the 8 years of the study.
Main findings...

In summary,

• The percentage of patients who had an abnormal scan result was 40% \((n = 184)\), whilst 53% \((n = 239)\) had a normal scan result, and 7% \((n = 32)\) had an equivocal scan.

• Pre-scan diagnosis was consistent with scan results in 71% of cases of neurodegenerative Parkinsonism, whereas this figure was 64% for cases of non-neurodegenerative Parkinsonism.

• For all DaT scans, the diagnosis was changed in 37% of patients \((n = 168)\), whilst the clinical management was changed in 42% of patients \((n = 190)\).

• Change in management involved 63% starting dopaminergic medication, 5% stopping dopaminergic medications, and 31% undergoing other changes in management.
Conclusion

• The study demonstrated that the number of scans has increased following the introduction of DaT scans.

• This study concludes that DaT imaging is useful for supporting the correct diagnosis and clinical management for patients with clinically indeterminate Parkinsonism.

• In patients with mild symptoms, DaT scans are valuable assets to rule out non-neurodegenerative disease, which would allow patients to access alternative treatment sooner.
Conclusion...

• ruling out diagnoses of neurodegenerative Parkinsonism provides clinicians with more certainty when stopping unnecessary dopaminergic medication.

• From a broader perspective, negative DaT scan allows easier recognition of patients who would be appropriate for discharge from the Parkinson’s service.
  ‒ This ultimately helps reduce clinical pressures and renders the service more accessible to new patients awaiting assessment.
Limitations of the study

• Some of the limitations of this study include
  – the retrospective nature of the study
  – The study only involved one centre, which limits the generalizability of the data.
  – This study also did not correlate the clinicopathological data with post-mortem data
Take home messages

- Since change in diagnosis and management due to the scan is **significant**, it is important to **consider the scan** in our set up.
  - **Advantage**
    - Uses SPECT\// no need of cyclotron, no PET needed\//
    - Can avoid
      - Unnecessary medication
      - related drug complication
      - economic burden
      - Patient burden
Study 2
(PYP scan for suspected cardiac amyloidosis)

• Study title
  • The use of PYP scan for evaluation of ATTR cardiac amyloidosis at a tertiary medical centre

• Study design
  • Retrospective review of all patients who underwent a PYP scan for suspected cardiac amyloidosis at Tufts Medical Center between 2017 and 2020.

• Sample size
  – a total of 273 patients were included in the study.

Background

• **Cardiac amyloidosis** is protein folding disorders characterized by the extracellular deposition of insoluble polymeric protein fibrils in tissues and organs.

• is widely considered to be **underdiagnosed** as patients often present in the late stages of disease.

• **Endomyocardial biopsy**
  – considered a gold standard for diagnosis,
  – the procedure poses **potential risks** including pericardial tamponade, arrhythmia, haematoma and other morbidity.
Transthyretin (ATTR) cardiac amyloidosis is a disorder characterised by the deposition of amyloid fibrils into the heart’s extracellular space.
Diagnostic approach for Cardiac amyloidosis

- Medical History, Symptoms, and Physical Findings
- Blood Sampling Test
- Electrocardiogram (ECG)
- Echocardiography
- Cardiac Magnetic Resonance Imaging (MRI)/CT
- Nuclear Imaging
- Biopsy
- Immunohistochemistry/Mass Spectrometry
- Genetic Testing and Counseling

**Scintigraphy**
- a noninvasive method that may facilitate early diagnosis, distinguish various forms of cardiac amyloid, and may be useful in following disease burden
**Cardiac amyloidosis** in a 62-year-old male with chronic congestive heart failure. Echocardiography was suggestive of an **infiltrative cardiomyopathy**. **Tc-99m pyrophosphate** was administered intravenously. Diffuse uptake greater than bone is seen in the myocardium. This is consistent with transthyretin-related amyloidosis of the left ventricle.

99mTc-PYP scintigraphy in cardiac amyloidosis. Significant myocardial uptake is observed in ATTR amyloidosis.

ASNC American Society of Nuclear Cardiology
Interpretation

- two approaches of interpretation of Myocardial uptake
  - 1. Quantitative:
    - myocardial to contralateral lung ratio of uptake at 1 hour
      - H/CL ratios of ≥ 1.5 at one hour are classified as ATTR positive and
      - ratios < 1.5 as ATTR negative
  - 2. Semi-quantitative:
    - visual comparison to bone (rib) uptake at 3 hours
      - visual scores of ≥2 are classified as ATTR positive, and
      - scores of less than 2 as ATTR negative

- An overall interpretation of the findings is categorized into 3, for ATTR cardiac amyloidosis,
  A. Not suggestive: A semi-quantitative visual score of 0 or H/CL ratio < 1
  B. Strongly suggestive: A semi-quantitative visual score of 2 or 3 or H/CL ratio >1.5
  C. Equivocal: A semi-quantitative visual score of 1; H/CL ratio 1-1.5

The American Society of Nuclear Cardiology produced imaging protocol for cardiac Amyloidosis 99m-labeled bone seeking agent in 2019
Quantitative:
### Visual/ Semi-quantitative:

<table>
<thead>
<tr>
<th>Grade</th>
<th>Myocardial $^{99m}$Tc-PYP Uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>no uptake and normal bone uptake</td>
</tr>
<tr>
<td>Grade 1</td>
<td>uptake less than rib uptake</td>
</tr>
<tr>
<td>Grade 2</td>
<td>uptake equal to rib uptake</td>
</tr>
<tr>
<td>Grade 3</td>
<td>uptake greater than rib uptake with mild/absent rib uptake</td>
</tr>
</tbody>
</table>
Materials and Methods

• Retrospective study done in 273 patients who underwent a PYP scan for suspected cardiac amyloidosis, 2017–2020.

• Chart reviewed for the ff records:
  ✓ Patient demographics,
  ✓ clinical characteristics,
  ✓ laboratory studies,
  ✓ imaging results,
  ✓ biopsy results, and
  ✓ therapy-related information

✓ Single-photon emission computed tomography (SPECT) imaging was done at 1hr and 3 hr according to guideline
  ✓ Qualitative grade (0 to 3) and
  ✓ Heart to contralateral lung ratios (H:L) used

✓ Troponin I,
✓ B-type natriuretic peptide (BNP),
✓ N-terminal pro-BNP (NT-proBNP), and
✓ echocardiography
The main findings

• **Scan positivity rate**
  
  – Of the 273 patients evaluated
  • **55** patients (20%) had a positive scan.
  • **16** were considered equivocal.
  • **202** negative scans,

<table>
<thead>
<tr>
<th>PYP result /273/</th>
<th>EMB Done for 27/273</th>
<th>ATTR +ve</th>
<th>AL +ve</th>
<th>No CA</th>
</tr>
</thead>
<tbody>
<tr>
<td>55+ve</td>
<td>7</td>
<td>5</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>202-ve</td>
<td>18</td>
<td>0</td>
<td>2</td>
<td>16</td>
</tr>
<tr>
<td>16equiv</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

**Table //Biopsy results**

**Key:** AL = amyloid light-chain; ATTR = transthyretin; PYP scan = technetium pyrophosphate scintigraphy
• In the negative group, **18 patients underwent biopsy**, none of which were positive for **ATTR amyloid** while **two were positive for AL amyloidosis**.
  – These results support the high accuracy of the imaging study when evaluating for this condition.

• **Patients laboratory studies and imaging results were analyzed in relation to PYP scan result**
  – Patients with a **positive scan** were found to have a statistically **significantly higher measurement** in troponin, BNP and pro-BNP, as well as IVSd measurement on echocardiography compared with those with a negative result.
Conclusion

• The PYP scan has emerged as a low-risk imaging study that helps medical teams diagnose ATTR cardiomyopathy.

• higher biomarker values and increased IVSd on echocardiogram can correlate with positive scans, and, thus, can help the medical team in deciding to pursue this study.

• PYP scan results have greatly impacted clinical decision making when diagnosing and treating cardiac amyloid.
• The study showed that, the high sensitivity and specificity of the test have resulted in limited need for endomyocardial biopsy, reinforcing this imaging modality to be a lower risk alternative for diagnosis.

• A positive result would justify the early introduction of disease-modifying agents for management of ATTR, and considering this test early, when there is an index of suspicion, could lead to improved overall outcomes for patients.
limitations to this study

- Retrospective nature of the study.
- Not all patients evaluated with a PYP scan had cardiac biomarkers and echocardiographic parameters available in the clinical record, making trends less conclusive.
Other literatures

– Brownrigg, J. et al. (2019)

• assessed / /MRI, NMscan/ /

➢ CMR was unable to reliably differentiate ATTR from AL amyloidosis (sensitivity 28.1–99.0% and specificity 11.0–60.0%).

➢ Sensitivity and specificity of nuclear scintigraphy in the differentiation of ATTR from AL amyloidosis ranged from 90.9% to 91.5% and from 88.6% to 97.1%.

• Brown A et.al. (2019)  
  – done a retrospective review of previous literature  
• Title: A new application for an old tracer.  
• Results:  
  – 99m Tc PYP has shown to be a useful method with 97% sensitivity and 100% specificity for differentiating AL vs ATTR cardiac amyloidosis.  
• Conclusions:  
  – The use of 99m Tc PYP is an easy noninvasive exam to diagnose cardiac amyloidosis caused by ATTR proteins.  
  – 99m Tc PYP has been found to have both high sensitivity and specificity for differentiating between the types of cardiac amyloidosis.
Take home messages

• Pyrophosphate scintigraphy (PYP scanning)
  – is a non invasive, clinically significant and effective imaging modality
  – High sensitivity and specificity
  – can led to early amyloid-directed treatment
  – Uses SPECT
2023 : PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging

• Name of the guideline:
  – PSMA PET/CT: joint EANM procedure guideline/SNMMI procedure standard for prostate cancer imaging 2.0

• Authority:
  – European Association of Nuclear Medicine (EANM)
  – Society of Nuclear Medicine and Molecular Imaging (SNMMI)

• Month and year of issue : 5 January 2023
68Ga-PSMA PET/CT: Joint EANM and SNMMI procedure guideline for prostate cancer imaging

Background

• Prostate cancer:
  – For staging,
  – restaging,
  – diagnosis of recurrence, and
  – therapeutic monitoring,

  noninvasive tests such as MRI, contrast-enhanced CT, and NM imaging used.
– CT and MRI have limited value because of their low sensitivity for detecting nodal involvement.

– molecular imaging has the potential to better characterize
  • primary prostate cancer,
  • perform staging before radiotherapy or surgery,
  • localize the site of recurrence in patients with a rising PSA level after primary therapy,
  • monitor tumor response to therapy, and
  • select patients for targeted radionuclide therapy
NM imaging of prostate cancer uses PSMA as target:

- *Prostate-specific membrane antigen* (PSMA) is overexpressed in primary and metastatic cancer of the prostate.
- The level of PSMA expression *rises* with increasing tumor dedifferentiation
Important updates(changes in the guideline from the previous one

- **New and Additional PSMA-ligands** for PET/CT imaging were included
  - demonstrated **high affinity to human PSMA targets the prostate-specific membrane antigen.**

  **PSMA-ligand:**
  - $[^{68}\text{Ga}]\text{Ga-PSMA-11}$,
  - $[^{68}\text{Ga}]\text{Ga-PSMA-I&}T$,
  - $[^{18}\text{F}]\text{F-DCFPyL}$,
  - $[^{18}\text{F}]\text{F-PSMA-1007}$, or
  - $[^{18}\text{F}]\text{F-rhPSMA-7.3}$

**But in 2017**
- ✓ $[^{68}\text{Ga}]\text{-PSMA PET/CT}$
PSMA targeted PET/CT
Newly diagnosed prostate cancer with focal uptake at left prostate apex
F-18 DCFPyL prostate-specific membrane antigen (PSMA)-targeted (PET/CT) images.

Rising prostate-specific antigen (PSA) postsurgery for prostate cancer.
A recurrence of prostate cancer is detected in the **posterolateral left aspect of the prostate bed**.

Conventional imaging was negative.
Frameworks for standardized reporting of PSMA-ligand PET/CT have been developed

- Comparison with previous examinations should be part of each PSMA-targeted PET report.
- Assessment is more valuable if the examination is interpreted in the context of other imaging examinations (bone scan, CT, PET/CT, MRI, etc.) and clinical data.

But in 2017

- standardized reporting was not set
• **Reporting**
  - **The EANM standardized reporting guidelines: E-PSMA Standardized reporting**
    - These classifications are usually based on a *5-point scale* that concords with the probability of a lesion being benign or malignant.

<table>
<thead>
<tr>
<th>Score</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Benign lesion without abnormal PSMA uptake</td>
</tr>
<tr>
<td>2</td>
<td>Probably benign lesion: faint PSMA uptake (equal or lower than background) in a site atypical for prostate cancer</td>
</tr>
<tr>
<td>3</td>
<td>Equivocal finding: faint uptake in a site typical for prostate cancer or intense uptake in a site atypical for prostate cancer</td>
</tr>
<tr>
<td>4</td>
<td>Probably prostate cancer: intense uptake in typical site of prostate cancer, but without definitive findings on CT*</td>
</tr>
<tr>
<td>5</td>
<td>Definitive evidence of prostate cancer: intense uptake in typical site of prostate cancer, with definitive findings on CT</td>
</tr>
</tbody>
</table>
### Qualitative evaluation of PSMA expression through a 4-point scale

<table>
<thead>
<tr>
<th>PSMA expression V (visual score)</th>
<th>Grade of PSMA expression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score = 0</td>
<td>Below blood pool</td>
</tr>
<tr>
<td>Score = 1</td>
<td>Equal to or above blood pool and lower than liver</td>
</tr>
<tr>
<td>Score = 2</td>
<td>Equal to or above liver and lower than parotid gland</td>
</tr>
<tr>
<td>Score = 3</td>
<td>Equal to or above parotid gland</td>
</tr>
</tbody>
</table>
### Table 3  Regional classification of PSMA-PET findings

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Local tumor (T)</td>
<td></td>
</tr>
<tr>
<td>miT0</td>
<td>No local tumor</td>
</tr>
<tr>
<td>miT2</td>
<td>Organ-confined tumor</td>
</tr>
<tr>
<td>miT3a</td>
<td>Non-organ-confined tumor (extracapsular extension)</td>
</tr>
<tr>
<td>miT3b</td>
<td>Non-organ-confined tumor (seminal vesicles invasion)</td>
</tr>
<tr>
<td>miT4</td>
<td>Tumor invading adjacent structures (other than seminal vesicles)</td>
</tr>
<tr>
<td>miTr</td>
<td>Presence of local recurrence after radical prostatectomy</td>
</tr>
<tr>
<td>Regional nodes (N)</td>
<td></td>
</tr>
<tr>
<td>miN0</td>
<td>No positive regional lymph nodes</td>
</tr>
<tr>
<td>miN1</td>
<td>Positive regional lymph nodes</td>
</tr>
<tr>
<td>Distant metastases (M)</td>
<td></td>
</tr>
<tr>
<td>miM0</td>
<td>No distant metastases</td>
</tr>
<tr>
<td>miM1a</td>
<td>Extra-pelvic lymph nodes</td>
</tr>
<tr>
<td>miM1b</td>
<td>Bone metastasis</td>
</tr>
<tr>
<td>miM1c</td>
<td>Non-nodal visceral metastasis: report involved organ(s)</td>
</tr>
</tbody>
</table>
current advances in nuclear medicine

• Combined modality imaging
  – PET/CT (PET/MRI)

• Radiotheranostics
  – an approach that integrate nuclear medicine techniques for diagnosis with those for treatment
    • Eg... Ga 68 PSMA VS Lutetium-177 (Lu-177) PSMA-Targeted Therapy of Prostate Cancer (Lutathera)

• Molecularly targeted and individualized therapy

• New radiopharmaceuticals for oncology and non-oncology application
References


The year in review: 2022-2023
Pulmonology

Andargew Yohannes
Internist, Pulmonary & Critical Care Physician
Major practice changing studies

1. Treatment Strategy for Rifampin-Susceptible Tuberculosis (TRUNCATE-TB Trials)\(^1\)

1. Hydrocortisone in Severe Community-Acquired Pneumonia (CAPE COD trial)\(^2\)

\(^1\)N Engl J Med 2023; 388:1931-1941 DOI: 10.1056/NEJMoa2215145
Treatment Strategy for Rifampin-Susceptible Tuberculosis

- Phase 2–3, international, adaptive, randomized, open-label, non-inferiority trial

674 participants of age 18 to 65 years were randomly assigned. The 8th ESIM Annual Internal Medicine Conference and Medical Exhibition assessed the efficacy and safety of a strategy involving shorter initial treatment for rifampin-susceptible tuberculosis.
The main findings

- **Efficacy**: Strategy with initial bedaquiline–linezolid regimen was non-inferior to standard treatment and was associated with shorter total duration of treatment.

- **Safety**: Incidence of grade 3 or 4 adverse events, serious adverse events, and respiratory disability did not differ significantly between the standard treatment and two strategy groups.
## Table 2. Primary Efficacy Outcome.

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Intention-to-treat population:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome: composite of death, ongoing treatment, or active disease at wk 96 — no. (%)</td>
<td>7 (3.9)</td>
<td>21 (11.4)</td>
<td>7.4 (1.7 to 13.2)</td>
<td>11 (5.8)</td>
</tr>
<tr>
<td>Death before wk 96</td>
<td>2 (1.1)</td>
<td>5 (2.7)</td>
<td>—</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Ongoing treatment at wk 96</td>
<td>2 (1.1)</td>
<td>8 (4.3)</td>
<td>—</td>
<td>5 (2.6)</td>
</tr>
<tr>
<td>Active disease at wk 96</td>
<td>1 (0.6)</td>
<td>4 (2.2)</td>
<td>—</td>
<td>3 (1.6)</td>
</tr>
<tr>
<td>Evaluation by telephone at wk 96 with no evidence of active disease but insufficient evidence of disease clearance when last seen</td>
<td>2 (1.1)</td>
<td>3 (1.6)</td>
<td>—</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>No evaluation at wk 96 and insufficient evidence of disease clearance when last seen</td>
<td>0</td>
<td>1 (0.5)</td>
<td>—</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Outcomes classified as unassessable — no. (%)</td>
<td>1 (0.6)</td>
<td>1 (0.5)</td>
<td>—</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Single positive culture at wk 96 but no other evidence of active disease</td>
<td>0</td>
<td>1 (0.5)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death from a cause that was definitively unrelated to tuberculosis*</td>
<td>1 (0.6)</td>
<td>0</td>
<td>—</td>
<td>0</td>
</tr>
<tr>
<td>No evaluation at wk 96 and sufficient evidence of disease clearance when last seen</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>No primary outcome or outcome classified as unassessable — no. (%)</td>
<td>173 (95.6)</td>
<td>162 (88.0)</td>
<td>—</td>
<td>175 (93.1)</td>
</tr>
<tr>
<td><strong>Assessable population:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome — no./total no. (%)</td>
<td>7/180 (3.9)</td>
<td>21/183 (11.5)</td>
<td>7.5 (1.7 to 13.2)</td>
<td>11/187 (5.9)</td>
</tr>
<tr>
<td><strong>Per-protocol population:</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome — no./total no. (%)</td>
<td>6/177 (3.4)</td>
<td>17/160 (10.6)</td>
<td>6.9 (0.9 to 12.8)</td>
<td>9/176 (5.1)</td>
</tr>
</tbody>
</table>
### Table 3. Secondary Outcomes.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Treatment (N = 181)</th>
<th>Strategy with Rifampin–Linezolid (N = 184) vs. Standard Treatment</th>
<th>Strategy with Bedaquiline–Linezolid (N = 189) vs. Standard Treatment</th>
<th>Difference (95% CI)†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participant-centered outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total treatment time through wk 96 — days‡</td>
<td>180.2±37.9</td>
<td>105.7±80.1</td>
<td>-74.5 (-87.4 to -61.6)</td>
<td>-95.3 (-106.2 to -84.5)</td>
</tr>
<tr>
<td>Total duration of treatment</td>
<td>177.3±35.6</td>
<td>101.6±74.9</td>
<td>-75.7 (-87.7 to -63.6)</td>
<td>-93.5 (-104.0 to -82.9)</td>
</tr>
<tr>
<td>Acceptability scores§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Difficulty score</td>
<td>1.5±1.7</td>
<td>2.4±2.2</td>
<td>1.0 (0.6 to 1.4)</td>
<td>0.4 (0.0 to 0.8)</td>
</tr>
<tr>
<td>Anxiety score</td>
<td>3.6±2.2</td>
<td>3.9±2.0</td>
<td>0.3 (-0.1 to 0.8)</td>
<td>-0.2 (-0.6 to 0.3)</td>
</tr>
<tr>
<td>Motivation score</td>
<td>6.2±3.9</td>
<td>8.0±3.0</td>
<td>1.8 (1.1 to 2.5)</td>
<td>1.9 (1.2 to 2.6)</td>
</tr>
<tr>
<td>Preferred treatment recommendation to others — no. (%)</td>
<td>NA</td>
<td>126/176 (71.6)</td>
<td>—</td>
<td>141/180 (78.3)</td>
</tr>
<tr>
<td>2-Mo treatment</td>
<td>NA</td>
<td>35/176 (19.9)</td>
<td>—</td>
<td>25/180 (13.9)</td>
</tr>
<tr>
<td>6-Mo treatment</td>
<td>NA</td>
<td>15/176 (8.5)</td>
<td>—</td>
<td>14/180 (7.8)</td>
</tr>
<tr>
<td>Quality-of-life scores¶</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mental health summary score</td>
<td>57.5±0.5</td>
<td>57.5±0.5</td>
<td>0.0 (-1.35 to 1.30)</td>
<td>0.33 (-1.02 to 1.68)</td>
</tr>
<tr>
<td>Physical health summary score</td>
<td>56.7±0.5</td>
<td>56.8±0.5</td>
<td>0.06 (-1.24 to 1.37)</td>
<td>0.00 (-1.25 to 1.26)</td>
</tr>
<tr>
<td>Health-status score</td>
<td>0.99±0.0</td>
<td>0.98±0.1</td>
<td>-0.01 (-0.02 to 0.00)</td>
<td>0.01 (-0.02 to 0.01)</td>
</tr>
<tr>
<td>Body weight†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change from baseline — kg</td>
<td>5.8±4.8</td>
<td>5.6±4.7</td>
<td>-0.3 (-1.3 to 0.6)</td>
<td>0.2 (-0.7 to 1.2)</td>
</tr>
<tr>
<td>Change from baseline — %</td>
<td>11.9±10.0</td>
<td>11.4±9.8</td>
<td>-0.8 (-2.8 to 1.3)</td>
<td>0.3 (-1.7 to 2.4)</td>
</tr>
<tr>
<td><strong>Safety outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adverse events through wk 96 — no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any grade 3 or 4 adverse event</td>
<td>29 (16.0)</td>
<td>32 (17.4)</td>
<td>1.4 (-6.4 to 9.2)</td>
<td>-0.2 (-7.9 to 7.4)</td>
</tr>
<tr>
<td>Any serious adverse event</td>
<td>11 (6.1)</td>
<td>18 (9.8)</td>
<td>3.7 (-2.1 to 9.7)</td>
<td>1.3 (-4.2 to 6.9)</td>
</tr>
<tr>
<td>Death††</td>
<td>3 (1.7)</td>
<td>5 (2.7)</td>
<td>1.1 (-2.4 to 4.8)</td>
<td>-1.1 (-4.3 to 1.5)</td>
</tr>
<tr>
<td>Respiratory disability at wk 96 — no. (%)‡‡</td>
<td>0</td>
<td>2.7 (1.5)</td>
<td>1.5 (-0.5 to 3.5)</td>
<td>1.4 (-0.5 to 3.3)</td>
</tr>
<tr>
<td>FEV1, &lt;50% of predicted value</td>
<td>24.3 (13.4)</td>
<td>20.5 (11.1)</td>
<td>-11 (-8.7 to 6.4)</td>
<td>0.1 (-7.8 to 7.9)</td>
</tr>
<tr>
<td><strong>Program-centered outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Treatment adherence§§</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adherence within first 56 days — % of days</td>
<td>98.8±5.5</td>
<td>95.9±10.0</td>
<td>-2.9 (-4.6 to 1.3)</td>
<td>-0.5 (-1.7 to 0.8)</td>
</tr>
<tr>
<td>Cessation within first 56 days — no. (%)</td>
<td>1 (0.6)</td>
<td>3 (1.6)</td>
<td>—</td>
<td>1 (0.5)</td>
</tr>
<tr>
<td>Acquired drug resistance — no. (%)¶¶</td>
<td>0</td>
<td>0</td>
<td>—</td>
<td>2 (1.1)</td>
</tr>
<tr>
<td>Relapse-associated transmission risk†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transmission risk period — days</td>
<td>0.5±4.3</td>
<td>2.4±8.3</td>
<td>1.9 (0.5 to 3.2)</td>
<td>2.7 (0.6 to 4.8)</td>
</tr>
</tbody>
</table>

*The Society of Internal Medicine Antiretroviral Conference and Medical Exhibition (ISIM) is an annual event that focuses on the latest developments in internal medicine and HIV therapy.**
• pragmatic design,
• use of outcome measures that are relevant individually and for the program
• inclusion of high-burden countries.
• ?open-label design
• use of standardized assessments, a prespecified algorithm
• negligible trial attrition minimizes potential bias

• No HIV-positive participants were enrolled
Conclusion

- Among participants with rifampin-susceptible pulmonary tuberculosis, strategy involving initial treatment with 8-week bedaquiline-linezolid regimen was
  - non-inferior to standard treatment with respect to clinical outcomes,
  - with no apparent safety concern
Take away

• **Bottom line:** Strategy involving initial treatment with an 8-week bedaquiline–linezolid regimen was non-inferior to standard treatment for tuberculosis with respect to clinical outcomes

Shorter regimen? implementation strategy
Hydrocortisone in Severe Community-Acquired Pneumonia (CAPE COD trial)

- Phase 3,
  - multicenter,
  - double-blind,
  - randomized, and
  - controlled trial

- A total of 800 patients had undergone randomization when the trial was stopped after the second planned interim analysis.
The main findings

- **Efficacy**: number of deaths by day 28 was significantly lower in the hydrocortisone group than in the placebo group.

- **Safety**: incidence of HAI and GI bleeding was similar in the two groups.
  
  – median insulin dose during the first week of the trial was higher in the hydrocortisone group.
## Table 2. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Hydrocortisone</th>
<th>Placebo</th>
<th>Treatment Effect (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death by day 28 — no./total no. (%)</td>
<td>25/400 (6.2)</td>
<td>47/395 (11.9)</td>
<td>Difference, -5.6</td>
<td>0.006</td>
</tr>
<tr>
<td>95% CI — percentage points</td>
<td>3.9 to 8.6</td>
<td>8.7 to 15.1</td>
<td>-9.6 to -1.7</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death by day 90 — no./total no.</td>
<td>36/388 (9.3)</td>
<td>57/389 (14.7)</td>
<td>Difference, -5.4</td>
<td></td>
</tr>
<tr>
<td>95% CI — percentage points</td>
<td>6.4 to 12.2</td>
<td>11.1 to 18.2</td>
<td>-9.9 to -0.8</td>
<td></td>
</tr>
<tr>
<td>Patients not receiving any mechanical ventilation at baseline — no./total no. (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of endotracheal intubation by day 28</td>
<td>40/222 (18.0)</td>
<td>65/220 (29.5)</td>
<td>HR, 0.59 (0.40 to 0.86)</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of noninvasive ventilation by day 28</td>
<td>15/222 (6.8)</td>
<td>24/220 (10.9)</td>
<td>HR, 0.60 (0.32 to 1.15)</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of endotracheal intubation by day 28 in patients not receiving endotracheal intubation at baseline — no./total no. (%)</td>
<td>60/308 (19.5)</td>
<td>86/310 (27.7)</td>
<td>HR, 0.69 (0.50 to 0.94)</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of initiation of vasopressors by day 28 in patients not receiving vasopressor at baseline — no./total no. (%)</td>
<td>55/359 (15.3)</td>
<td>86/344 (25.0)</td>
<td>HR, 0.59 (0.43 to 0.82)</td>
<td></td>
</tr>
<tr>
<td><strong>Safety outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of hospital-acquired infection by day 28 — no./total no. (%)</td>
<td>39/400 (9.8)</td>
<td>44/395 (11.1)</td>
<td>HR, 0.87 (0.57 to 1.34)</td>
<td>0.54</td>
</tr>
<tr>
<td>Ventilator-associated pneumonia</td>
<td>32/152 (21.0)</td>
<td>38/171 (22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bloodstream infection</td>
<td>5/400 (1.2)</td>
<td>9/395 (2.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence of gastrointestinal bleeding by day 28</td>
<td>9/400 (2.2)</td>
<td>13/395 (3.3)</td>
<td>HR, 0.68 (0.29 to 1.59)</td>
<td>0.38</td>
</tr>
<tr>
<td>Median daily dose of insulin by day 7 in patients receiving insulin therapy (IQR) — IU/day</td>
<td>35.5 (15.0 to 57.5)</td>
<td>20.5 (9.4 to 48.5)</td>
<td>Median difference, 8.7 (4.0 to 13.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Median weight change from baseline to day 7 (IQR) — kg</td>
<td>2.0 (-0.5 to 5.0)</td>
<td>1.0 (-3.0 to 6.0)</td>
<td>Median difference, 1.0 (0 to 2.0)</td>
<td>0.18</td>
</tr>
</tbody>
</table>
• Limitations and Remaining Questions
  – Mortality in the placebo group was lower than anticipated
  – Did not mandate a standardized microbiologic investigation
  – Small proportion of patients were immune-compromised
Conclusion

• Among patients admitted to ICU with severe CAP, treatment with intravenous hydrocortisone was associated with lower risk of death by day 28 than placebo.
Take away

**Bottom line:** early treatment with hydrocortisone reduced 28-day mortality among patients who had been admitted to the ICU with severe community-acquired pneumonia.
Guideline

• Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease (GOLD 2023 report)
Key updates

- GOLD proposes a new, more inclusive definition of COPD that focuses on:
  - respiratory symptoms,
  - anatomic area of abnormality (airways and alveoli), and
  - airflow obstruction as demonstrated by FVC/FEV1 <0.7.

- A new definition of COPD exacerbation is also included:
  - dyspnea or cough and sputum that worsen during ≤14 days,
  - associated inflammation due to airway infection, pollution, or other insult to the airways.
  - Dyspnea intensity, respiratory rate, heart rate, and oxygen saturation determine severity.
A new recommendation is made for chest computed tomography
– persistent exacerbations,
– symptoms out of proportion to airflow obstruction, or
– evidence of air trapping/hyperinflation,
– to reveal alternate diagnoses or target specific therapies.

Treatments are determined by
(1) degree of airflow obstruction,
(2) current symptoms,
(3) history of moderate and severe exacerbations, and
(4) comorbidities.
- Previous treatment categories C and D have been combined into a new category, named E (for exacerbations).

GOLD provides new guidance based on blood eosinophil levels. Initial therapy for categories A, B, and E:

- A: Long-acting β-agonist (LABA) or long-acting muscarinic antagonist (LAMA)
- B: LABA + LAMA (change from monotherapy)
- E: LABA + LAMA; if blood eosinophils are ≥300 cells/µL, consider LABA + LAMA + inhaled corticosteroid (ICS). No recommendation is made (at any eosinophil level) for ICS without combined LABA + LAMA.

- For patients with persistent exacerbations despite LABA + LAMA + ICS or for those who have >100 eosinophils/µL,
  - roflumilast (for patients with chronic bronchitis and FEV1 <50% of predicted) or
  - azithromycin (in nonsmokers) can be considered.
- Pulmonary rehabilitation is recommended for patients in treatment groups B and E.

- Recommendations for oxygen therapy, ventilatory support, and lung volume reduction surgery are unchanged in this update,
  - although endobronchial valve and endoscopic lung volume reduction surgery now are included

- Exacerbations should be treated with bronchodilators and prednisone (40 mg daily for 5 days)

- A 5-to-7–day course of antibiotics is appropriate for patients with increased sputum volume and purulence or for patients on mechanical ventilation
Take home message from this guideline

Six years after the last update, the 2023 GOLD report emphasizes:

- New definitions of both COPD and COPD exacerbation
- Stress for history of exacerbation & substantial changes to therapy by creating the “E” category
- More emphasis on LABA + LAMA combination treatment for most patients, and minimizing the use of ICS
The year in review: 2022-2023
Rheumatology

Birhanu D Desyibelew, MD
Consultant Internist, Rheumatologist
Head, Rheumatology Unit,
Department of Internal Medicine
CHS, AAU
The first ACR guideline on the use of exercise, rehabilitation, diet and additional interventions in conjunction with DMARDs.
Critical outcomes

- Pain improvement
- Physical function
- Disease activity
- Work outcome
The guideline strongly recommend consistent engagement in exercise over no exercise.

Table 3. Exercise recommendations for the management of rheumatoid arthritis*

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Certainty of evidence</th>
<th>PICO questions used for the Evidence Report</th>
<th>Evidence Summary page nos. in Supplementary Appendix 3†</th>
</tr>
</thead>
<tbody>
<tr>
<td>We <strong>strongly</strong> recommend consistent engagement in exercise over no exercise.</td>
<td>Moderate</td>
<td>4-7</td>
<td>194-344</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend consistent engagement in aerobic exercise over no exercise.</td>
<td>Very low to low</td>
<td>4</td>
<td>194-242</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend consistent engagement in aquatic exercise over no exercise.</td>
<td>Low</td>
<td>5</td>
<td>243-260</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend consistent engagement in resistance exercise over no exercise.</td>
<td>Very low</td>
<td>6</td>
<td>261-317</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend consistent engagement in mind-body exercise over no exercise.</td>
<td>Very low to low</td>
<td>7</td>
<td>318-344</td>
</tr>
</tbody>
</table>

* Intervention definitions and examples are provided in Table 1. PICO = Population, Intervention, Comparator, and Outcome.
<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Quality Assessment</th>
<th>Score</th>
<th>Code</th>
</tr>
</thead>
<tbody>
<tr>
<td>We <strong>conditionally</strong> recommend participation in comprehensive occupational therapy over no comprehensive occupational therapy.</td>
<td>Very low</td>
<td>17</td>
<td>409-427</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend participation in comprehensive physical therapy over no comprehensive physical therapy.</td>
<td>Very low</td>
<td>18</td>
<td>428-443</td>
</tr>
<tr>
<td>For patients with hand involvement, we <strong>conditionally</strong> recommend performing hand therapy exercises over no hand therapy exercises.</td>
<td>Low</td>
<td>8</td>
<td>345-368</td>
</tr>
<tr>
<td>For patients with hand and/or wrist involvement and/or deformity, we <strong>conditionally</strong> recommend use of splinting, orthoses, and/or compression over no splinting, orthoses, and/or compression.</td>
<td>Very low</td>
<td>9</td>
<td>369-376</td>
</tr>
<tr>
<td>For patients with foot and/or ankle involvement, we <strong>conditionally</strong> recommend use of bracing, orthoses, and/or taping over no bracing, orthoses, and/or compression.</td>
<td>Very low</td>
<td>10</td>
<td>377-398</td>
</tr>
<tr>
<td>For patients with knee involvement, we <strong>conditionally</strong> recommend use of bracing and/or orthoses over no bracing and/or orthoses.</td>
<td>No studies met eligibility criteria</td>
<td>11</td>
<td>399</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend use of joint protection techniques over no joint protection techniques.</td>
<td>Low</td>
<td>12</td>
<td>400-404</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend use of activity pacing, energy conservation, activity modification, and/or fatigue management over no activity pacing, energy conservation, activity modification, and/or fatigue management.</td>
<td>No studies met eligibility criteria</td>
<td>13</td>
<td>405</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend use of assistive devices over no assistive devices.</td>
<td>No studies met eligibility criteria</td>
<td>14</td>
<td>406</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend use of adaptive equipment over no adaptive equipment.</td>
<td>No studies met eligibility criteria</td>
<td>15</td>
<td>407</td>
</tr>
<tr>
<td>We <strong>conditionally</strong> recommend use of environmental adaptations over no environmental adaptations.</td>
<td>No studies met eligibility criteria</td>
<td>16</td>
<td>408</td>
</tr>
<tr>
<td>For patients who are currently employed or desire to become employed, we <strong>conditionally</strong> recommend use of vocational rehabilitation over no work interventions.</td>
<td>No studies met eligibility criteria</td>
<td>21</td>
<td>500</td>
</tr>
<tr>
<td>For patients who are currently employed or desire to become employed, we <strong>conditionally</strong> recommend work site evaluations and/or modifications over no work site evaluations and/or modifications.</td>
<td>Low</td>
<td>22</td>
<td>501-507</td>
</tr>
</tbody>
</table>
The guideline conditionally recommend adherence to Mediterranean-style diet over no formally defined diet

• The Mediterranean-style diet pattern emphasizes the intake of vegetables, fruits, whole grains, nuts, seeds, and olive oil and the intake of moderate amount of low-fat dairy and fish and limits the use of added sugars, sodium, highly processed foods, refined carbohydrates and saturated fats.

• It has shown benefit in improving pain and no difference on physical function or disease activity.
• The guideline conditionally recommend against adherence to formally defined diet other than a Mediterranean-style diet.

• The guideline conditionally recommend following established dietary recommendations without use of dietary supplements over adding dietary supplements.
# Additional Integrative interventions

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Pain redaction</th>
<th>Physical Fxn Imp.</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Behavioral therapy/mind-body interventions</td>
<td>0</td>
<td>0</td>
<td>Improve anxiety, depression, fatigue</td>
</tr>
<tr>
<td>Acupuncture</td>
<td>0/+</td>
<td>0+</td>
<td></td>
</tr>
<tr>
<td>Massage therapy</td>
<td>+</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Thermal therapy</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Electrotherapy</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Chiropractic</td>
<td>0</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Take Home message

• Multidisciplinary approach is the key for your RA management.
• Work out is a must!
EULAR recommendations for the non-pharmacological management of systemic lupus erythematosus and systemic sclerosis

Ioannis Parodis 1,2,3, Charlotte Girard-Guyonvarc’h 4,5, Laurent Arnaud 6, Oliver Distler 7, Andrea Domján 8, Cornelia H M Van den Ende 9,10, Kim Fligelstone 11, Agnes Kocher 12, Maddalena Larosa 13, Martin Lau 14, Alexandros Mitropoulos 15, Mwidimi Ndosi 16, Janet L Poole 17, Anthony Redmond 18, Valentin Ritschl 19,20, Helene Alexanderson 1,21, Yvonne Sjöberg 22, Gunilla von Perner 22, Till Uhlig 23, Cecilia Varju 24, Johanna E Vriezekolk 9, Elisabet Welin 25, René Westhovens 26, Tanja A Stamm 19,20, Carina Boström 21,27
• Non-pharmacological management of CTDs aims for amelioration of disease symptoms, improvement of HRQoL as well as prevention of disease progression, organ damage accrual, comorbidities and adverse events. Additional aims include contribution to *improved knowledge of the disease*. 
WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT?

⇒ Non-pharmacological management of systemic lupus erythematosus (SLE) and scleroderma (SSc) is often underutilized.

WHAT DOES THIS STUDY ADD?

⇒ We developed recommendations to provide guidance for non-pharmacological management of people living with SLE and SSc.
⇒ In this work, we present evidence to support common and disease-specific non-pharmacological interventions for SLE and SSc.
⇒ We generated a research agenda as well as an educational agenda to support non-pharmacological management of people with SLE and SSc.
Non-pharmacological management should be directed towards improving HRQoL in people with SLE

- Physical exercise and psychological interventions were found to improve HRQoL in SLE patients
- Occupations therapy of upper limb has shown to improve HRQoL in SSc patients
People with SLE and SSc should be offered patient education and self-management support

• Structured patient education as a part of physical exercise has improved aerobic capacity and improved HRQoL and favorable lifestyle change
### Recommendations for the non-pharmacological management of SLE and SSc

1. Non-pharmacological management should be directed toward improving health-related quality of life in people with SLE (LoE: 1–3) and SSc (LoE: 2–4).

2. People with SLE and SSc should be offered patient education and self-management support (LoE: 2–4).

3. In people with SLE (LoE: 3) and SSc (LoE: 4), smoking habits should be assessed, and cessation strategies should be implemented.

4. In people with SLE (LoE: 5) and SSc (LoE: 4), avoidance of cold exposure should be considered for the prevention of Raynaud’s phenomenon. In people with SSc, this is of particular importance for the mitigation of severe Raynaud’s phenomenon (LoE: 4).

5. Physical exercise should be considered for people with SLE (LoE: 1–3) and SSc (LoE: 2–4).
**Recommendations for the non-pharmacological management of SLE**

1. In people with SLE, patient education and self-management support should be considered for improving physical exercise outcomes (LoE: 2) and HRQoL (LoE: 2–4), and could be considered for enhancing self-efficacy (LoE: 3).

2. In people with SLE, photoprotection should be advised for the prevention of flares (LoE: 4).

3. In people with SLE, psychosocial interventions should be considered for improving health-related quality of life (LoE: 1–2), anxiety (LoE: 1) and depressive symptoms (LoE: 1).

4. In people with SLE, aerobic exercise should be considered for increasing aerobic capacity (LoE: 1), and for reducing fatigue (LoE: 1–3) and depressive symptoms (LoE: 3).
Recommendations for the non-pharmacological management of SSc

1. In people with SSc, patient education and self-management support should be considered for improving hand function (LoE: 2–4), mouth-related outcomes (LoE: 2), HRQoL (LoE: 2–4) and ability to perform daily activities (LoE: 2–3).

2. In people with SSc, orofacial, hand, and aerobic and resistance exercise should be considered for improving microstomia (LoE: 2–4), hand function (LoE: 2–4) and physical capacity (LoE: 2–4), respectively.

3. In people with SSc and puffy hands, manual lymph drainage could be considered for improving hand function (LoE: 2).
Take Home Message

• Structured education of your patient about the disease has a paramount importance on improving HRQoL
8th Annual Internal Medicine Conference and Health Exhibition

Theme: Harmonizing Medical Education with Clinical Services to Improve Healthcare Quality in Ethiopia

Opportunities, Challenges and the way Forward

04-05 August, 2023 | Inter Luxury Hotel Addis Ababa, Ethiopia