TOP 10 ARTICLES 2019
#1
Treating Delirium in the ICU
Delirium in the ICU

1) Common: occurs in 50-75% of ventilated patients

2) Associated with poor outcomes
   - increased mortality
   - longer time on mechanical ventilation
   - longer hospital stay
   - higher risk of long term cognitive impairment
   - higher care cost
Worldwide ABCDEF Survey
(Assessing Pain, Both Spontaneous Awakening and Breathing Trials, Choice of Drugs, Delirium monitoring/management, Early exercise/mobility, and Family Empowerment)
(Critical Care Medicine 2017)

Intensivists: 65% treat delirium with haloperidol

Intensivists: 53% use quetiapine or other atypical antipsychotic for delirium with agitation
FDA Approved Indications

haloperidol: schizophrenia; Tourette’s disorder
ziprasidone: schizophrenia; bipolar I disorder
Haloperidol and Ziprasidone for Treatment of Delirium in Critical Illness

Randomized, Double-Blind, Placebo-Controlled Trial

- conducted at 16 US medical centers
- enrolled adults in a medical or surgical ICU
  - invasive/noninvasive ventilation
  - vasopressors
  - intra-aortic balloon pump,
- goal to enroll subjects prior to onset of delirium and randomize to study group if delirium occurred
- delirious subjects enrolled with surrogate consent
MANY exclusion criteria:

severe cognitive impairment, high risk for medication side effects because of pregnancy, breast-feeding, a history of torsades de pointes, QT prolongation, a history of neuroleptic malignant syndrome, or allergy to haloperidol or ziprasidone; ongoing treatment with an antipsychotic medication; moribund state; rapidly resolving organ failure; were blind, deaf, or unable to speak or understand English; were incarcerated; and more.....
Subjects randomized to receive:

A. Haloperidol: 2.5 mg → 20 mg/day
B. Ziprasidone: 5 mg → 40 mg/day
C. Placebo

All received “ABCDE” treatment bundle (assess, prevent, and manage pain; both spontaneous awakening and breathing trials; choice of analgesia and sedation; assess, prevent, and manage delirium; and early mobility and exercise).
20,914 patients screened for eligibility

1183 provided written consent and enrolled
571 did not develop delirium
46 excluded for other reasons
566 Underwent randomization
  • hypoactive delirium 89%
  • hyperactive delirium 11%
  • median age 60 years
A Days Alive without Delirium or Coma

- Ziprasidone
- Haloperidol
- Placebo

Adjusted Median Days (95% CI)

Girard TD et al. New Engl J Med 2018
Girard TD et al. New Engl J Med 2018
Figure 3. Effects of Haloperidol, Ziprasidone, and Placebo on 90-Day Survival.

Girard TD et al. New Engl J Med 2018
Hepatocellular Carcinoma in Non-Alcoholic Fatty Liver Disease
Established major risk factors for HCC:

- excessive alcohol consumption
- hepatitis B and C
- 20-40% of HCC patients lack these risk factors

NAFLD has become leading cause of chronic liver disease in USA

- 20-30% of cases develop necrosis and fibrosis
- 10-20% of these develop cirrhosis
- risk of HCC due to NAFLD is conflicting in the published studies (variable size and quality of studies)
Risk of Hepatocellular Cancer in Patients With Non-Alcoholic Fatty Liver Disease

Fasiha Kanwal, Jennifer R. Kramer, Srikar Mapakshi, Yamini Natarajan, Maneerat Chayanupatkul, Peter A. Richardson, Liang Li, Roxanne Desiderio, Aaron P. Thrift, Steven M. Asch, Jinna Chu, and Hashem B. El-Serag

1Section of Gastroenterology and Hepatology, Baylor College of Medicine and Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; 2Center for Innovations in Quality, Effectiveness and Safety, Michael E. DeBakey Veterans Affairs Medical Center, Houston, Texas; 3Section of Health Services Research, Department of Medicine, Baylor College of Medicine, Houston, Texas; 4Department of Biostatistics, University of Texas MD Anderson Cancer Center, Houston, Texas; 5Section of Epidemiology and Population Sciences, Baylor College of Medicine, Houston, Texas; 6Dan L. Duncan Comprehensive Cancer Center, Baylor College of Medicine, Houston, Texas; 7Center for Innovation to Implementation, Palo Alto Veterans Affairs Medical Center, Palo Alto, California; and 8Division of Primary Care and Population Health, Stanford University, Palo Alto, California
Searched the VHA Corporate Data Warehouse (CDW) and Central Cancer Registry (CCR) to identify all patients with at least one visit to a VHA hospital between Jan 1, 2003 and Dec 31, 2011.
Operational Definition of NAFLD:

- 2 or more elevated ALT values (alanine aminotransferase concentration ≥ 40 IU/ml for men or 31 IU/ml for women) more than 6 months apart.
- No positive serology for HBV or HCV
- No alcohol-related ICD 9 code
- No positive AUDIT-C score (alcoholism screening test)
- No evidence of rare chronic hepatitides
Operational Control Group Definition:
• had normal ALT test performed between Jan 1, 2004 and Dec 31, 2018
• did not meet definition of NAFLD
• did not have any other liver-related risk factors (HBV, HCV, + AUDIT-C, chronic rare hepatitides)
Identified 296,707 NAFLD patients and an equal number of controls matched for age, sex, index date of initial ALT test and duration of care within VA system

Randomly chose 150 NAFLD patients and 150 Control patients and reviewed EMR in detail to validate diagnosis of NAFLD or lack of NAFLD:

- PPV NAFLD 89%
- NPV NAFLD 98%
For NAFLD and Control groups, authors:

- Identified hepatocellular carcinoma cases in the CCR through histology codes and text searches. Verified by EMR review.
- Identified hepatocellular carcinoma cases in CDW inpatient and outpatient EMR using ICD-9 code.
- Discordance between CCR and CDW settled by manual review.
Figure 1. Cumulative incidence of hepatocellular cancer in patients with and without NAFLD.
Figure 2. Incidence of hepatocellular cancer in different subgroups of NAFLD patients with cirrhosis.
#3 Aspartame and Dementia
ASPARTAME

The effect of aspartame and its metabolites on brain chemistry has been delineated in detail from a biochemical perspective.

Aspartame

- 200-330 x sweeter than sucrose
- lacks metallic or bitter aftertaste
- less expensive than sugar
- added to more than 6000 different commercial food items/vitamins
- added to more than 600 different pharmaceuticals
- European Food Safety Authority: ADI 40 mg/kg of body weight
- The US Food and Drug Administration: ADI 50 mg/kg of body weight
- Rats metabolize aspartame 5-6 x more rapidly than humans, thus safe rat dose must be divided by 5-6 to yield equivalent human dose

ADI: acceptable daily intake
Why would concern be raised regarding aspartame intake and brain function?
Studies of Rats Receiving the Equivalent of Aspartame 40 mg/kg/day

Ashok I & Sheeladevi R. Biochemical responses and mitochondrial mediated activation of apoptosis on long-term effect of aspartame in rat brain. *Redox Biology* 2014:

*Increased production of brain free-radicals and decreased anti-apoptotic activity with aspartame dose-equivalent of 40 mg/kg/day*

Ahok I et al. Neurobehavioral changes and activation of neurodegenerative apoptosis on long-term consumption of aspartame in the rat brain. *J Nutr Intermed Metabol* 2015:

*Increased immobilization; decreased ambulation, rearing, and grooming. Up regulation in apoptotic gene expression along with protein expression in the respective brain region indicating the enhancement of neuronal cell death.*

El-Samad AAA. Light and Electron Microscopic Study on the Effect of Aspartame on the Cerebellar Cortex of the Male Albino Rat. *Egypt J Histol* 2010:

*Demonstrated various abnormalities in Purkinje cell morphology.*
Pase MP et al. Stroke 2017
(published more than a year ago, but there was no room for it in last year’s presentation)
Framingham Heart Study Offspring Cohort

- cohort initiated in 1971 and enrolled 5124 subjects
- subjects examined every 4 years, most recent 2014
- estimated intake of sugary beverages, sugar-sweetened soft drinks, and artificially-sweetened soft drinks
- related beverage intake to 10-year risk of total stroke, ischemic stroke, total dementia, Alzheimer-type dementia beginning with 7th examination cycle (1998-2001)
Three Different Statistical Models

1. adjusted for age, sex, education, total caloric intake

2. model 1 plus adjustment for lifestyle factors (diet, exercise, smoking)

3. model 2 plus adjustment for systolic BP, presence of CVD, AF, LVH, total cholesterol, *diabetes mellitus*, waist-to-hip ratio
### Statistical Model 1

#### Recent Intake: based upon examination cycle 7 only

<table>
<thead>
<tr>
<th>Total Sugary Beverages</th>
<th>Recent Intake</th>
<th>Cumulative Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Dementia</td>
<td>AD Dementia</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>&lt;1/day (ref)</td>
<td>1.13 (0.70, 1.82)</td>
<td>0.62</td>
</tr>
<tr>
<td>1-2/day</td>
<td>1.06 (0.53, 2.13)</td>
<td>0.87</td>
</tr>
<tr>
<td>&gt;2/day</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Sugar-Sweetened Soft Drinks

<table>
<thead>
<tr>
<th>0/week (ref)</th>
<th>Recent Intake</th>
<th>Cumulative Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Dementia</td>
<td>AD Dementia</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>&gt;0-3/week</td>
<td>0.98 (0.60, 1.61)</td>
<td>0.94</td>
</tr>
<tr>
<td>&gt;3/week</td>
<td>0.77 (0.34, 1.74)</td>
<td>0.53</td>
</tr>
</tbody>
</table>

#### Artificially-Sweetened Soft Drinks

<table>
<thead>
<tr>
<th>0/week (ref)</th>
<th>Recent Intake</th>
<th>Cumulative Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Dementia</td>
<td>AD Dementia</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>&gt;0-6/week</td>
<td>1.24 (0.76, 2.03)</td>
<td>0.40</td>
</tr>
<tr>
<td>≥1/day</td>
<td>1.58 (0.81, 3.07)</td>
<td>0.18</td>
</tr>
</tbody>
</table>

Recent Intake: based upon examination cycle 7 only
Cumulative Intake: based upon average of all three examination cycles
### Beverages Intake and Risk for Dementia

#### Statistical Models 2 and 3

<table>
<thead>
<tr>
<th>Model</th>
<th>Recent Intake</th>
<th>Cumulative Intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All-Cause Dementia</td>
<td>AD Dementia</td>
</tr>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>P Value</td>
</tr>
<tr>
<td>Model</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0/wk (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0–6/wk</td>
<td>1.39 (0.79–2.43)</td>
<td>0.25</td>
</tr>
<tr>
<td>≥1/d</td>
<td>2.20 (1.09–4.45)</td>
<td>0.03</td>
</tr>
<tr>
<td>O/wk (ref)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;0–6/wk</td>
<td>1.00 (0.60–1.67)</td>
<td>0.99</td>
</tr>
<tr>
<td>≥1/d</td>
<td>1.08 (0.54–2.17)</td>
<td>0.83</td>
</tr>
</tbody>
</table>

Artificially sweetened soft drinks

Red flags indicate significant differences.
Statistical Mediation Analysis:

Does the presence of diabetes mellitus mediate the association between artificially-sweetened soft drink intake and dementia?
Individuals with type 2 diabetes are at $\sim60\%$ greater risk for the development of dementia compared with those without diabetes.

My conclusion: This study does not demonstrate that the dementia associated with artificial soft-drink sweeteners cannot be explained adequately by factors such as diabetes. However, there is good basic science suggesting aspartame can damage brain tissue at usual doses, so I have switched to.....
E-Cigarettes
DOES THE USE OF E-CIGARETTES IMPROVE THE RATE OF SMOKING CESSATION AMONG ESTABLISHED CIGARETTE SMOKERS?
A Randomized Trial of E-Cigarettes versus Nicotine-Replacement Therapy

Peter Hajek, Ph.D., Anna Phillips-Waller, B.Sc., Dunja Przulj, Ph.D., Francesca Pesola, Ph.D., Katie Myers Smith, D.Psych., Natalie Bisal, M.Sc., Jinshuo Li, M.Phil., Steve Parrott, M.Sc., Peter Sasieni, Ph.D., Lynne Dawkins, Ph.D., Louise Ross, Maciej Goniewicz, Ph.D., Pharm.D., Qi Wu, M.Sc., and Hayden J. McRobbie, Ph.D.

1. National Health Service (NHS) stop-smoking services are available free across the United Kingdom.

2. Invited adult smokers who
   a. had no strong preference for nicotine replacement vs. e-cigarettes
   b. not currently using either product.

3. Randomization and product use occurred on subject-chosen “quit date”

4. Weekly one-on-one sessions with local clinicians
INTERVENTIONS

Nicotine Replacement: choice of one or more of patch, gum, lozenge, nasal spray, inhalator, mouth spray, mouthstrip, and microtabs
  a. free to switch type(s) at will
  b. NHS paid for first 3 months

E-Cigarette: device plus 30-ml bottle e-liquid
  a. NHS paid for device and initial bottle
PRIMARY OUTCOME

One-year sustained abstinence, calculated as a self-report of smoking no more than five cigarettes from two weeks after the quit date, validated by expired carbon monoxide level

884 subjects included in Primary Analysis
### Table 2. Abstinence Rates at Different Time Points and Smoking Reduction at 52 Weeks.*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>E-Cigarettes (N = 438)</th>
<th>Nicotine Replacement (N = 446)</th>
<th>Primary Analysis: Relative Risk (95% CI)†</th>
<th>Sensitivity Analysis: Adjusted Relative Risk (95% CI)‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome: abstinence at 52 wk — no. (%)</td>
<td>79 (18.0)</td>
<td>44 (9.9)</td>
<td>1.83 (1.30–2.58)</td>
<td>1.75 (1.24–2.46)‡</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abstinence between wk 26 and wk 52 — no. (%)</td>
<td>93 (21.2)</td>
<td>53 (11.9)</td>
<td>1.79 (1.32–2.44)</td>
<td>1.82 (1.34–2.47)‡</td>
</tr>
<tr>
<td>Abstinence at 4 wk after target quit date — no. (%)</td>
<td>192 (43.8)</td>
<td>134 (30.0)</td>
<td>1.45 (1.22–1.74)</td>
<td>1.43 (1.20–1.71)¶</td>
</tr>
<tr>
<td>Abstinence at 26 wk after target quit date — no. (%)</td>
<td>155 (35.4)</td>
<td>112 (25.1)</td>
<td>1.40 (1.14–1.72)</td>
<td>1.36 (1.15–1.67)‡</td>
</tr>
<tr>
<td>Carbon monoxide–validated reduction in smoking of ≥50% in participants without abstinence between wk 26 and wk 52 — no./total no. (%)</td>
<td>44/345 (12.8)</td>
<td>29/393 (7.4)</td>
<td>1.75 (1.12–2.72)</td>
<td>1.73 (1.11–2.69)¶</td>
</tr>
<tr>
<td>Variable</td>
<td>1 Wk after Quit Date</td>
<td>Mean Difference (95% CI)</td>
<td>4 Wk after Quit Date</td>
<td>Mean Difference (95% CI)</td>
</tr>
<tr>
<td>---------------------------</td>
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<td>--------------------------</td>
</tr>
<tr>
<td></td>
<td>E-Cigarettes (N = 158)</td>
<td>Nicotine Replacement (N = 131)</td>
<td>E-Cigarettes (N = 186)</td>
<td>Nicotine Replacement (N = 132)</td>
</tr>
<tr>
<td>Score for frequency of urge</td>
<td>2.5±1.1</td>
<td>2.8±0.9</td>
<td>-0.4 (-0.6 to -0.1)</td>
<td>1.9±0.9</td>
</tr>
<tr>
<td>Score for strength of urge</td>
<td>2.7±1.1</td>
<td>3.2±1.0</td>
<td>-0.5 (-0.7 to -0.2)</td>
<td>2.1±1.1</td>
</tr>
<tr>
<td>Composite urge score</td>
<td>2.6±1.0</td>
<td>3.0±0.9</td>
<td>-0.4 (-0.6 to -0.2)</td>
<td>2.0±1.0</td>
</tr>
</tbody>
</table>

A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products

David T. Levy¹, K. Michael Cummings², Andrea C. Villanti³,⁴, Ray Niaura¹,³,⁴, David B. Abrams¹,³,⁴, Geoffrey T. Fong⁵,⁶,⁷ & Ron Borland⁸

¹Department of Oncology, Lombardi Comprehensive Cancer Center, Georgetown University Medical Center, Washington, DC USA, ²Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, SC USA, ³The Schroeder Institute for Tobacco Research and Policy Studies at Truth Initiative, Washington, DC USA, ⁴Department of Health, Behavior and Society, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD USA, ⁵Department of Psychology, University of Waterloo, Waterloo, Ontario Canada, ⁶School of Public Health and Health Systems, University of Waterloo, Waterloo, Ontario Canada, ⁷Ontario Institute for Cancer Research, Toronto, Ontario Canada, ⁸and Nigel Gray Distinguished Fellow in Cancer Prevention, The Cancer Council Victoria, Melbourne, Victoria Australia.
“From a public health perspective, VNP (vaporized nicotine products) policies should aim to discourage experimental and regular use of VNPs by never smokers who would not have smoked otherwise while encouraging innovations in VNP products that promote smoking cessation.”

“A never smoker may transition from trying VNP to exclusive VNP use, exclusive cigarette use, dual use or quit using cigarettes and VNPs. The population health impact depends critically upon whether the never smoker who tries VNPs would have smoked cigarettes in the absence of VNPs.”

National Institute on Drug Abuse

Teens are more likely to use e-cigarettes than cigarettes.\textsuperscript{1}

- 8th grade: 3.6% cigarettes, 9.5% e-cigarettes
- 10th grade: 6.3% cigarettes, 14.0% e-cigarettes
- 12th grade: 11.4% cigarettes, 16.2% e-cigarettes

\textsuperscript{1}Past-month use
TEEN E-CIG USERS ARE MORE LIKELY TO START SMOKING.²

Start Smoking Within 6 Months

- E-CIG USER: 30.7%
- NON USER: 8.1%

*Includes combustible tobacco products (cigarettes, cigars, and hookahs)

National Institute on Drug Abuse
HIGH TEEN EXPOSURE TO E-CIG ADVERTISING

7 in 10 exposed to ads

52.8% 56.3%
Retail Ads

35.8% 42.9%
Internet Ads

34.1% 38.4%
TV/Movie Ads

25.0% 34.6%
Newspaper & Magazine Ads

Middle School Students
High School Students

Nat’l Inst. on Drug Abuse
CIGARETTE USE among adults and high school students

**ADULTS**
- Arkansas: 23.6%
- U.S.: 17.1%
- 2016

**HIGH SCHOOL STUDENTS**
- Arkansas: 13.7%
- U.S.: 8.8%
- 2017
### Other Tobacco Product Use
among adults and high school students

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>E-Cigarettes</td>
<td>2.8%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Smokeless Tobacco</td>
<td>4.0%</td>
<td>12.7%</td>
</tr>
<tr>
<td>Cigars</td>
<td>1.9%</td>
<td>14.1%</td>
</tr>
</tbody>
</table>

Truth Initiative
900 G Street, NW
Fourth Floor
Washington, DC 20001
“A growing number of prospective studies indicate that ENDS (electronic nicotine delivery systems) use among never cigarette smokers/cigarette-naïve participants is associated with subsequent cigarette initiation up to 16 months later, even after controlling for various socio-demographic, intrapersonal, and contextual factors (Barrington-Trimis et al., 2016; Leventhal et al., 2015; Primack, Soneji, Stoolmiller, Fine, & Sargent, 2015; Wills et al., 2016; Wills, Sargent, Gibbons, Pagano, & Schweitzer, 2016).”

Loukas A et al. Addictive Behaviors 2018
Exclusive e-cigarette use predicts cigarette initiation among college students

Alexandra Loukas\textsuperscript{a,∗}, C. Nathan Marti\textsuperscript{a}, Maria Cooper\textsuperscript{b}, Keryn E. Pasch\textsuperscript{a}, Cheryl L. Perry\textsuperscript{b}

\textsuperscript{a} University of Texas at Austin, 2109 San Jacinto Blvd, Austin, TX 78712-1415, USA
\textsuperscript{b} UTHealth School of Public Health in Austin, 1616 Guadalupe Street Suite 6.300, Austin, TX 78701, USA

HIGHLIGHTS

- 11\% of college students initiated cigarette use over the 1.5 year study period.
- More ENDS users than non-users initiated cigarette use during the study period.
- Exclusive ENDS use predicted subsequent cigarette initiation.
Project M-PACT
(Marketing and Promotion across Colleges in Texas)

Repetitive rapid-response survey of a cohort of 2558 “never-used cigarettes at baseline” students attending 24 colleges in Texas

Wave 1 survey: Nov. 2014 – Feb. 2015
Wave 2 survey: 6 months later after wave 1; retention rate 90%
Wave 3 survey: 12 months after wave 1; retention rate 89%
Wave 4 survey: 18 months after wave 1; retention rate 92%
Cigarette Use Susceptibility

Question 1: “If one of your friends were to offer you these products, would you smoke/use it?”

Question 2: “Do you think you will use any of the following in the next 12 months?”

Susceptible Response: “probably not,” “probably yes,” or “definitely yes”

Not Susceptible Response: “definitely not”
<table>
<thead>
<tr>
<th>Period</th>
<th>Number of cigarette initiators in period</th>
<th>Number of students at risk for initiation$^a$</th>
<th>Hazard</th>
<th>Hazard standard error</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 (wave 1–2)</td>
<td>119</td>
<td>2558</td>
<td>0.05</td>
<td>0.004</td>
<td>0.95</td>
</tr>
<tr>
<td>2 (wave 2–3)</td>
<td>85</td>
<td>2347</td>
<td>0.04</td>
<td>0.004</td>
<td>0.92</td>
</tr>
<tr>
<td>3 (wave 3–4)</td>
<td>78</td>
<td>2151</td>
<td>0.04</td>
<td>0.004</td>
<td>0.89</td>
</tr>
</tbody>
</table>

$^a$ The number of students at risk after period 1 is the number from the prior period minus those who initiated cigarettes in the prior period and those missing data at each period ($n = 92$ and 111 in period 2 and 3, respectively).
Baseline Predictors of Subsequent Cigarette Use

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Adj. Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>cigarette susceptibility</td>
<td>3.02</td>
</tr>
<tr>
<td>family of origin tobacco use</td>
<td>1.35</td>
</tr>
<tr>
<td>friend’s cigarette use</td>
<td>1.44</td>
</tr>
<tr>
<td>ever other tobacco use</td>
<td>2.85</td>
</tr>
<tr>
<td>ever e-cigarette use</td>
<td>1.36</td>
</tr>
</tbody>
</table>
How can we better isolate the effect of starting ENDS use in predicting risk of initiating cigarette smoking?

Compare the effect of using ENDS on future cigarette use for “never user of tobacco product” students:

Never tobacco user/ yes ENDS use
Never tobacco user/ no ENDS use  OR = 2.26

(Odds Ratio = 2.26; CI = 1.35 – 3.76)
#6
Hypertension and Dementia
Observational Studies: hypertension is a risk factor for dementia and mild cognitive impairment (MCI)

Pathologic Studies: Alzheimer’s dementia exhibits vascular damage in combination with β-amyloid and tau neuropathology

Literature: no long-term study of treating hypertension with expert assessment of cognitive outcomes are available
CNS Small Vessel Disease

(white matter hyperintensities; lacunar infarctions; hypertension-related microangiopathy)

Contributes to 45% of dementia cases

Leading risk factor is hypertension
  • relative risk for hypertension: 1.5 – 4.9
Transition from independence in instrumental activities daily living to disability or death according to baseline severity grades in age related changes in white matter. Inzitari D et al. BMJ 2009
Effect of Intensive vs Standard Blood Pressure Control on Probable Dementia
A Randomized Clinical Trial

The SPRINT MIND Investigators for the SPRINT Research Group
Multicenter randomized clinical trial (sub-study of the SPRINT Trial)

Hypertensive older adults @ increased cardiovascular risk

Compared 2 BP targets: 140 systolic vs. 120 systolic
Inclusion Criteria:

- age greater than 50 years
- BP systolic 130-180
- known cardiovascular disease or EGFR < 60 or Framingham Risk Score of ≥15% or age > 75 years
Exclusion Criteria:

• nursing home resident
• dementia diagnosis or receiving drug used for dementia therapy
• diabetes mellitus
• history of stroke
INTERVENTION

Randomized to:
1. systolic BP goal of < 140 mm Hg
2. systolic BP goal of < 120 mm Hg

Specific anti-hypertensive drugs up to local MD

Study “encouraged”
- a. thiazide as a first-line agent
- b. loop diuretics for participants with chronic kidney disease
- c. β-blockers for participants with coronary artery disease
Systolic Blood Pressure Intervention Trial (SPRINT)

Primary End Point: cardiovascular events

Secondary End Point: renal function

Secondary End Point: probable dementia, MCI
• 9361 subjects randomized between November 2010 and March 2013
• cognitive assessments planned at baseline, 2 years, and 4 years after entry (end March 2017)
• study stopped early (August 20, 2015) because the primary endpoint had been reached
• BP goals returned to PCP after August 20, 2015 but follow up for BP and cognitive function was continued
Figure 3. Systolic Blood Pressure in the Two Treatment Groups Over the Course of Follow-up

SPRINT MIND investigators. JAMA 2019
median follow-up of 5.1 years

SPRINT MIND investigators. JAMA 2019
Figure 2. Probable Dementia by Treatment Group

**Trial phase** | **Trial and cohort phase** | **Cohort phase**

Cumulative Incidence

Follow-up, y

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Standard treatment</th>
<th>Intensive treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4285</td>
<td>4278</td>
</tr>
<tr>
<td></td>
<td>4282</td>
<td>4277</td>
</tr>
<tr>
<td></td>
<td>4168</td>
<td>4171</td>
</tr>
<tr>
<td></td>
<td>3886</td>
<td>3917</td>
</tr>
<tr>
<td></td>
<td>2829</td>
<td>2893</td>
</tr>
<tr>
<td></td>
<td>2107</td>
<td>2189</td>
</tr>
<tr>
<td></td>
<td>989</td>
<td>1027</td>
</tr>
<tr>
<td></td>
<td>87</td>
<td>93</td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

shaded areas represent 95% confidence intervals
7#
Nutritional Support of the Medical Inpatient
Does individualized nutritional support of general medical inpatients who are at nutritional risk improve outcome?
Individualised nutritional support in medical inpatients at nutritional risk: a randomised clinical trial

Philipp Schuetz, Rebecca Fehr, Valerie Baechli, Martina Geiser, Manuela Deiss, Filomena Gomes, Alexander Kutz, Pascal Trbolet, Thomas Bregenzer, Nina Braun, Claus Hoess, Vojtech Pavlicek, Sarah Schmid, Stefan Bilz, Sarah Sigrist, Michael Brändle, Carmen Benz, Christoph Henzen, Silvia Mattmann, Robert Thomann, Claudia Brand, Jonas Rutishauser, Drahomir Aujesky, Nicolas Rodondi, Jacques Donzé, Zeno Stanga*, Beat Mueller*
Eight Swiss secondary and tertiary care hospitals evaluated all general medicine admissions for nutritional status and nutritional requirements. Randomized subjects to individualized nutritional support program or usual hospital food based upon patient preference/appetite.
## Nutritional Risk Screening (NRS 2002)

### Impaired nutritional status

<table>
<thead>
<tr>
<th>Score</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal nutritional status</td>
</tr>
<tr>
<td>1</td>
<td>Wt loss &gt;5% in 3 months or Food intake below 50–75% of normal requirement in preceding week</td>
</tr>
<tr>
<td>2</td>
<td>Wt loss &gt;5% in 2 months or BMI 18.5 – 20.5 + impaired general condition or Food intake 25–50% of normal requirement in preceding week</td>
</tr>
<tr>
<td>3</td>
<td>Wt loss &gt;5% in 1 month (≈ &gt;15% in 3 months) or BMI &lt;18.5 + impaired general condition or Food intake 0–25% of normal requirement in preceding week</td>
</tr>
<tr>
<td>Severity of disease (≈ stress metabolism)</td>
<td></td>
</tr>
<tr>
<td>------------------------------------------</td>
<td></td>
</tr>
<tr>
<td><strong>Absent</strong></td>
<td>Normal nutritional requirements</td>
</tr>
<tr>
<td><strong>Score 0</strong></td>
<td></td>
</tr>
</tbody>
</table>
| **Mild** | Hip fracture  
Chronic patients, in particular with acute complications: cirrhosis  
COPD (12)  
*Chronic hemodialysis, diabetes, oncology* |
| **Score 1** |
| **Moderate** | Major abdominal surgery (13–15). Stroke (16)  
*Severe pneumonia, hematologic malignancy* |
| **Score 2** |
| **Severe** | Head injury (18, 19)  
Bone marrow transplantation (20)  
*Intensive care patients (APACHE I)* |
<p>| <strong>Score 3</strong> |</p>
<table>
<thead>
<tr>
<th>Individual nutrition targets</th>
<th>Caloric requirements</th>
<th>Protein requirements</th>
<th>Micronutrient requirements</th>
<th>Specific targets</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Harris-Benedict equation with adjusted bodyweight or indirect calorimetry</td>
<td>1.2–1.5 g/kg bodyweight per day (0.8 g/kg of bodyweight per day in patients with renal failure with no dialysis)</td>
<td>Multivitamin use; other micronutrients according to specific laboratory results</td>
<td>Disease-specific adaptations (e.g., medium-chain triglycerides, low potassium in patients with renal failure)</td>
</tr>
</tbody>
</table>
Strategy to reach the nutrition targets

Level 1: oral nutrition (meals adapted to preferences, food fortification or enrichment, and snacks between meals and oral nutritional supplements) + Multivitamins and multimineral supplements according to 100% of recommended dietary allowance

Yes

Reassessment every 24-48 h: ≥75% of caloric and protein targets met?

No

After 5 days escalate to level 2
Level 2: enteral nutrition + Oral nutrition, no additional vitamins and mineral supplements needed if enteral nutrition provides ≥1500 kcal per day

Yes

Reassessment every 24-48 h: ≥75% of caloric and protein targets met?

No

After 5 days escalate to level 3
Level 3: parenteral nutrition + Enteral and oral nutrition

Use concomitant minimal oral or enteral nutrition (to avoid villous atrophy)
Inclusion Criteria:  
Age ≥ 18 years  
Nutrition Risk Score ≥ 3  
Expected LOS > 4 days

Exclusion Criteria: surgical patients; unable to ingest oral nutrition; terminal condition; already receiving nutritional therapy on admission; hospitalized because of anorexia nervosa; acute pancreatitis; acute liver failure; cystic fibrosis; stem cell transplantation; malnutrition after gastric bypass operations
Composite Primary Endpoint

Adverse clinical outcome within 30 days comprising all-cause mortality; admission to ICU; non-elective re-admission; major complications as a new occurrence including nosocomial infection, respiratory failure, a major cardiovascular event, acute renal failure, gastro-intestinal failure (i.e., hemorrhage, intestinal perforation, acute pancreatitis); decline in functional status of ≥ 10%
Percent achieving caloric requirements

Days after random group assignment

Proportion of patients (%)

Control
Intervention
Percent achieving protein requirements
<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Intervention group (n=1015)</th>
<th>Control group (n=1013)</th>
<th>Odds ratio or coefficient (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>Adverse outcome within 30 days</td>
<td>232 (23%)</td>
<td>272 (27%)</td>
<td>0.79 (0.64 to 0.97)</td>
<td>0.023</td>
</tr>
<tr>
<td><strong>Single components of primary outcome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>73 (7%)</td>
<td>100 (10%)</td>
<td>0.65 (0.47 to 0.91)</td>
<td>0.011</td>
</tr>
<tr>
<td>Decline in functional status of ≥10%*</td>
<td>35 (4%) of 942</td>
<td>55 (6%) of 913</td>
<td>0.62 (0.40 to 0.96)</td>
<td>0.034</td>
</tr>
<tr>
<td><strong>Additional secondary outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean length of stay (days)</td>
<td>9.5 (7.0)</td>
<td>9.6 (6.1)</td>
<td>-0.21 (-0.76 to 0.35)</td>
<td>0.46</td>
</tr>
<tr>
<td>Mean Barthel score (points)*</td>
<td>88 (26)</td>
<td>85 (30)</td>
<td>3.26 (0.93 to 5.60)</td>
<td>0.006</td>
</tr>
<tr>
<td>Mean EQ-5D VAS (points)†</td>
<td>59 (26)</td>
<td>56 (29)</td>
<td>3.06 (0.53 to 5.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mean EQ-5D index (points)</td>
<td>0.75 (0.32)</td>
<td>0.73 (0.34)</td>
<td>0.13 (0.09 to 0.17)</td>
<td>0.018</td>
</tr>
</tbody>
</table>
#8
CANCER THERAPY
CLOSING IN ON THE SILVER BULLET
The Cancer Silver Bullet

100% Lethal to cancer cells

100% Harmless to patient cells

Step 1: identify a gene that is absolutely required for cancer cell survival but not for patient cell survival

Step 2: destroy or turn off the gene
What Makes a Cell Malignant?

• genetic/epigenetic mutations
• suppression of apoptosis
• enhancement of cell growth/division
Accumulation of Mutations → Malignancy

Accumulation of Mutations → Oncogenic Addiction

• loss of redundant metabolic pathways required for cell survival
• remaining pathway dependent upon one or two genes (addiction)
• increased number of mutations \(\rightarrow\) Increased oncogene addiction
Proposed Role of MCM9 Helicase Activity in MMR

Mismatch introduced by replication error

Mismatch recognized by MutS, allowing recruitment of MutL and MCM9; MCM9 helicase catalyzes the removal of mismatch-containing strand

Repair synthesis through the action of replication factors, including RFC*, PCNA, Pol δ and RPA

* Proteins found associated with MCM9

MMR = Mismatch Repair

Multiple gene products (proteins) required for repair

Over time, failure of mismatch repair leads to sequences of repeating bases in the DNA called **microsatellites.**
Microsatellite instability (MSI) is the condition of genetic hypermutability (predisposition to mutation) that results from impaired DNA mismatch repair (MMR). The presence of MSI represents phenotypic evidence that MMR is not functioning normally.
Many cancers (e.g. Lynch Syndrome) are characterized by high levels of MSI indicative of defects in MMR.

Hypermutation caused by defective MMR plays a role in the malignant behavior of a cell.

There are multiple mechanisms of MMR and as a developing cancer cell loses these due to mutations, it may become highly dependent upon a residual functioning MMR gene.

Oncogene Addiction: In general, many cancers are critically dependent upon certain genes for survival while the surrounding normal tissue is not.
Looking for oncogenic addiction target genes
• targeted 18,009 genes in 339 cancer cell lines
• turned off each gene individually and observed for effect on cell growth/survival
• result: high sensitivity, specificity and precision in classifying essential and non-essential genes in cancer cell lines
Dark Bar: genes essential for cancer and adjacent normal tissue
Light Bar: genes essential for cancer only
WRN Helicase

- diverse roles in DNA repair, replication, transcription and telomere maintenance

- Cancer cell WRN-dependency (oncogenic addiction) correlated with the number of microsatellite deletions within a MSI cell line (biomarker)

- Knockout of WRN gene in identified cancer cell lines
  a) impaired cell growth
  b) caused DNA breaks/chromosome fragmentation
In Microsatellite Instability cancers (very common) the frequency of the Microsatellite Instability (easily measured) correlates with the degree to which mismatch repair is impaired and the likelihood of there being oncogenic addiction to the WRN Helicase gene product.

*Silver Bullet Target*
CONCLUSION

Using the currently available genetic/biochemical toolbox researchers can:

• test hundreds of cancer cell lines for
• thousands of essential cancer genes and also
• determine which of these genes are not essential for normal tissue (The Silver Bullet Target)

Next Step: refine the individual bullets for these targets (develop drugs which specifically turn off the Silver Bullet Target genes)
# 9
ECSTASY & PTSD
Post-Traumatic Stress Disorder

- 8% lifetime incidence in US population
- 35% of PTSD patients have debilitating symptoms not responsive to treatment
- 27-40% therapy dropout rate, often due to worsening of symptoms, hospitalization
- after the most effective therapies (cognitive processing therapy; prolonged exposure therapy)
- 60–72% of veterans still meet PTSD diagnostic criteria
New Idea: drug administration during therapy to decrease dropout, failure, avoidance

Two randomized, controlled pilot studies suggested safety and efficacy of MDMA (Ecstasy)

“Trauma theorists have asserted that emotional engagement is necessary for processing traumatic experiences and, under the influence of MDMA, people are able to remain emotionally connected while working with difficult traumatic material.”

Ot’alora G M. Psychopharmacology 2018
3,4-methylenedioxymethamphetamine (MDMA)-assisted psychotherapy for post-traumatic stress disorder in military veterans, firefighters, and police officers: a randomised, double-blind, dose-response, phase 2 clinical trial

Michael C Mithoefer, Ann T Mithoefer, Allison A Feduccia, Lisa Jerome, Mark Wagner, Joy Wymer, Julie Holland, Scott Hamilton, Berra Yazar-Klosinski, Amy Emerson, Rick Doblin

Mithoefer MC et al. Lancet Psychiatry 2018

3,4-Methylenedioxymethamphetamine-assisted psychotherapy for treatment of chronic posttraumatic stress disorder: A randomized phase 2 controlled trial

Marcela Ot’alora G1, Jim Griqsby2, Bruce Poulter1,

Ot’alora G M et al. Journal of Psychopharamamocology 2018
Mithoefer

- veterans, firefighters, police officers with chronic PTSD
- failed Cognitive Behavioral Therapy, Eye Movement Desensitization Reprocessing, Prolonged Exposure, Group and Individual Psychotherapy

Ot’alora

- mixed group: childhood abuse; combat; assaults, etc.
- failed Cognitive Behavioral Therapy, Eye Movement Desensitization Reprocessing, Prolonged Exposure, Group Psychotherapy

All psychiatric drugs were tapered and stopped prior to trial
PRIMARY OUTCOME: change in CAPS-IV score

CAPS-IV Categories of Questions
- Re-experiencing symptoms
- Avoidance symptoms
- Negative alterations in cognition and mood
- Alterations in arousal and reactivity

Secondary Endpoints:
- Beck Depression Inventory
- Pittsburgh Sleep Quality Index
- Global Assessment of Functioning
- Dissociative Experiences Scale II
- Post-Traumatic Growth Inventory
Experimental Intervention

Active Control: 30-40 mg MDMA
Intervention: 75-125 mg MDMA

2 or 3 eight-hour psychotherapy sessions after receiving study drug

Frequent telephone follow-up and 90-minute therapy sessions without drug between drug sessions
<table>
<thead>
<tr>
<th>Primary efficacy variable, PP set</th>
<th>40 mg MDMA (n=6)</th>
<th>100 mg MDMA (n=9)</th>
<th>125 mg MDMA (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CAPS-IV total score, mean (SD)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>84.6 (9.0)</td>
<td>94.4 (20.2)</td>
<td>91.6 (19.7)</td>
</tr>
<tr>
<td>Post 2 blinded sessions</td>
<td>80.6 (18.8)</td>
<td>70.0 (28.2)</td>
<td>54.6 (31.9)</td>
</tr>
<tr>
<td>Change</td>
<td>-4.0 (11.9)</td>
<td>-24.4 (24.2)</td>
<td>-37.0 (20.9)</td>
</tr>
<tr>
<td>p Value</td>
<td>-</td>
<td>0.10</td>
<td>0.01</td>
</tr>
<tr>
<td>Primary efficacy measure</td>
<td>30 mg MDMA plus psychotherapy (n=7)</td>
<td>75 mg MDMA plus psychotherapy (n=7)</td>
<td>125 mg MDMA plus psychotherapy (n=12)</td>
</tr>
<tr>
<td>--------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
<td>--------------------------------------</td>
</tr>
<tr>
<td>Mean CAPS-IV total score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>87.4 (14.1)</td>
<td>82.4 (17.3)</td>
<td>89.7 (17.3)</td>
</tr>
<tr>
<td>After two experimental sessions of MDMA</td>
<td>76.0 (23.4)</td>
<td>24.1 (17.2)</td>
<td>45.3 (33.8)</td>
</tr>
<tr>
<td>Change†</td>
<td>-11.4 (12.7)</td>
<td>-58.3 (9.8)</td>
<td>-44.3 (28.7)</td>
</tr>
<tr>
<td>p value‡</td>
<td>NA</td>
<td>0.0005</td>
<td>0.004</td>
</tr>
</tbody>
</table>
# 10

ω-3 FATTY ACIDS and ISCHEMIC HEART DISEASE
ω−3 Fatty Acids Involved in Human Physiology

α-linolenic acid (ALA) in walnut, flaxseed, hemp oils

Eicosapentaenoic acid (EPA) in fish, squid, krill

docosahexaenoic acid (DHA) in fish, squid, krill

Added to statin therapy to reduce cardiovascular events
Human Metabolism

ALA  →  EPA  →  DHA
Effects of n–3 Fatty Acid Supplements in Diabetes Mellitus

Associations of Omega-3 Fatty Acid Supplement Use With Cardiovascular Disease Risks
Meta-analysis of 10 Trials Involving 77,917 Individuals

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer
CONCLUSIONS
Supplementation with n−3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo. (Funded by the National Institutes of Health and others; VITAL ClinicalTrials.gov number, NCT01169259.)

CONCLUSIONS
Among patients with diabetes without evidence of cardiovascular disease, there was no significant difference in the risk of serious vascular events between those who were assigned to receive n−3 fatty acid supplementation and those who were assigned to receive placebo. (Funded by the British Heart Foundation and others;)

Findings  This meta-analysis of 10 trials involving 77,917 participants demonstrated that supplementation with marine-derived omega-3 fatty acids for a mean of 4.4 years had no significant association with reductions in fatal or nonfatal coronary heart disease or any major vascular events.
Yokoyama M et al. Lancet 2007

Japan EPA Lipid Intervention Study (JELIS)

- open label, randomized
- 1800 mg eicosapentaenoic acid (EPA)
- 18,645 subjects followed for 4.6 years
- 19% relative reduction in major coronary events
Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Bhatt DL et al. NEJM 2019
Icosapent ethyl

Eicosapentaenoic
We already have very potent statins!

Why do we need to be studying fatty acids?
Figure 2. Kaplan-Meier Cumulative Incidence Curves for the Composite End Point of Cardiovascular Death, Myocardial Infarction, or Stroke in the Entire Population With 4-Year Follow-up and Key Subgroups

<table>
<thead>
<tr>
<th>No. at risk</th>
<th>Time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Total population</td>
<td>45227</td>
</tr>
<tr>
<td>Ischemic event at baseline</td>
<td>21890</td>
</tr>
<tr>
<td>Stable atherosclerosis</td>
<td>15264</td>
</tr>
<tr>
<td>Risk factors only</td>
<td>8073</td>
</tr>
</tbody>
</table>

Only first events are included. CV indicates cardiovascular; MI, myocardial infarction.
BLUES: TG 200-499 mg/dl  Orange: TG < 150 mg/dl
Nichols GA. Diabetes Obesity Metabolism 2018
REDUCE-IT

- prospective, randomized, double-blind, placebo-controlled trial
- icosapent ethyl 2gm bid vs. placebo
- subjects: age > 45 yrs with known CAD
  - age > 50 yrs with DM plus another CAD risk factor
- LDL 40 – 100 on statin therapy
- TG 150 - 499
# Table 1. Characteristics of the Patients at Baseline.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Icosapent Ethyl (N = 4089)</th>
<th>Placebo (N = 4090)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR) — yr</td>
<td>64.0 (57.0–69.0)</td>
<td>64.0 (57.0–69.0)</td>
</tr>
<tr>
<td>≥65 yr — no. (%)</td>
<td>1857 (45.4)</td>
<td>1906 (46.6)</td>
</tr>
<tr>
<td><strong>Male sex — no. (%)</strong></td>
<td>2927 (71.6)</td>
<td>2895 (70.8)</td>
</tr>
<tr>
<td><strong>White race — no. (%)</strong></td>
<td>3691 (90.3)</td>
<td>3688 (90.2)</td>
</tr>
<tr>
<td><strong>Body-mass index;</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>30.8 (27.8–34.5)</td>
<td>30.8 (27.9–34.7)</td>
</tr>
<tr>
<td><strong>Cardiovascular risk stratum — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary-prevention cohort</td>
<td>2892 (70.7)</td>
<td>2893 (70.7)</td>
</tr>
<tr>
<td>Primary-prevention cohort</td>
<td>1197 (29.3)</td>
<td>1197 (29.3)</td>
</tr>
<tr>
<td><strong>Diabetes — no. (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1</td>
<td>27 (0.7)</td>
<td>30 (0.7)</td>
</tr>
<tr>
<td>Type 2</td>
<td>2367 (57.9)</td>
<td>2363 (57.8)</td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>1695 (41.5)</td>
<td>1694 (41.4)</td>
</tr>
</tbody>
</table>
Composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina.

Hazard Ratio 0.75
p < 0.001

Bhatt DL et al.
New Engl J Med 2019
Other agents that also lower triglyceride levels, including other n−3 fatty acids, extended release niacin, fenofibrate, and cholesteryl ester transfer protein inhibitors have not been shown to reduce cardiovascular events. Why does icosapent ethyl work?

• anti-inflammatory effects
• membrane stabilization
• plaque stabilization
• anti-oxidant effects