Recente literatuur

Thierry Christiaens

Klinische Farmacologie

Heymans Instituut voor Farmacologie UGent

- Gerandomiseerde studies
  - Monoclonale AL voor migraine
  - Semaglutide voor obesitas, hoe lang effect?
  - Optimising Therapy to prevent avoidable hospital admissions in the multimorbid elderly OPERAM

- Niet gerandomiseerde studies
  - Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study
  - SABINA: An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries

Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial.

The Lancet Neurology 2017;16:425-34.

- Methods: This was a phase 2, randomised, double-blind, placebo-controlled, multicentre study of erenumab for adults aged 18-65 years with chronic migraine … Chronic migraine was defined as 15 or more headache days per month, of which eight or more were migraine days. Patients were randomly assigned (3:2:2) to subcutaneous placebo, erenumab 70 mg, or erenumab 140 mg, given every 4 weeks for 12 weeks…
- The primary endpoint was the change in monthly migraine days from baseline to the last 4 weeks of double-blind treatment (weeks 9-12). Safety endpoints were adverse events, clinical laboratory values, vital signs, and anti-erenumab antibodies…

Safety and efficacy of erenumab for preventive treatment of chronic migraine: a randomised, double-blind, placebo-controlled phase 2 trial.

The Lancet Neurology 2017;16:425-34.

- **Findings:** From April 3, 2014, to Dec 4, 2015, 667 patients were randomly assigned to receive placebo (n=286), erenumab 70 mg (n=191), or erenumab 140 mg (n=190).
- Erenumab 70 mg and 140 mg reduced *monthly migraine days* versus placebo (*both doses -6·6 days vs placebo -4·2 days*; *difference -2·5*, 95% CI -3·5 to -1·4, p<0·0001).
- Adverse events were reported in 110 (39%) of 282 patients, 83 (44%) of 190 patients, and 88 (47%) of 188 patients in the placebo, 70 mg, and 140 mg groups, respectively. ... *Serious adverse events were reported by seven (2%), six (3%), and two (1%)* patients, respectively; none were reported in more than one patient in any group or led to discontinuation.
- **Interpretation:** In patients with chronic migraine, erenumab 70 mg and 140 mg reduced the number of monthly migraine days with a safety profile similar to placebo, ... Further research is needed to understand long-term efficacy and safety of erenumab, and the applicability of this study to real-world settings.

Monoklonale antilichamen voor migraine profylaxe

Bedenkingen

- *zie ook* ***Folia augustus 2021*** (over alle RCT's van de 3 producten)
- Echte 'migrainekliniek' populatie, sterke selectie
- 12 weken is kort voor chronisch probleem zowel voor werkzaamheid als veiligheid
  (Folia "De bevindingen van enkele open-label studies met een opvolgingsduur van 1 tot 5 jaar zijn bemoedigend... ")
- Effect al bij al beperkt in absolute termen
- Veiligheid (op korte termijn) is OK;
  >< cases over hypertensie en *exclusies*: patiënten met voorgeschiedenis van myocardinfarct, beroerte, TIA, instabiele angina pectoris, …
- Prijs niet mis: ongeveer €500 per maand, een veelvoud is van de kostprijs van andere middelen voor migraineprofylaxe
- ➔Een subgroep van patiënten heeft allicht baat bij deze nieuwe medicatie, maar het is niet duidelijk waarin 'responders' verschillen van 'non-responders'.

Semaglutide: nieuwe behandeloptie bij obesitas? ➔ zie vorig FTB en Folia april 2021 ivm NEJM feb 2021 doi: 10.1056/NEJMoa2032183 .

- *STEP1-studie*: Deze studieresultaten kregen veel weerklank in de lekenpers, waar semaglutide wordt voorgesteld als een “gamechanger”
- ±2000 ptn, BMI>30 of >27+RF, geen DMt2,
  semaglutide 2,4mg 1x/w. vs Plac, 68 weken
- Aan het einde van de studie had meer dan 85% van de patiënten in de semaglutidegroep minstens 5% van hun oorspronkelijk gewicht verloren, en *50% van de patiënten had minstens 15% van hun gewicht verloren* (tegenover respectievelijk 30% en 5% van de patiënten met placebo)…
- Ernstige OE in de semaglutidegroep (10%) vs placebogroep (6%) en waren vooral van gastro-intestinale of hepatobiliaire aard; *aantal patiënten dat de behandeling stopzette wegens gastro-intestinale ongewenste effecten semaglutidegroep 4,5%, vs 0,8%* in de placebogroep).
- In hoeverre het gewichtsverlies behouden blijft na het stopzetten van **semaglutide** en of **semaglutide** op lange termijn ook een effect kan hebben op de complicaties van obesitas, is nog niet onderzocht.

Effect of Continued Weekly SC Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity. The STEP 4 Randomized Clinical Trial JAMA march2001.

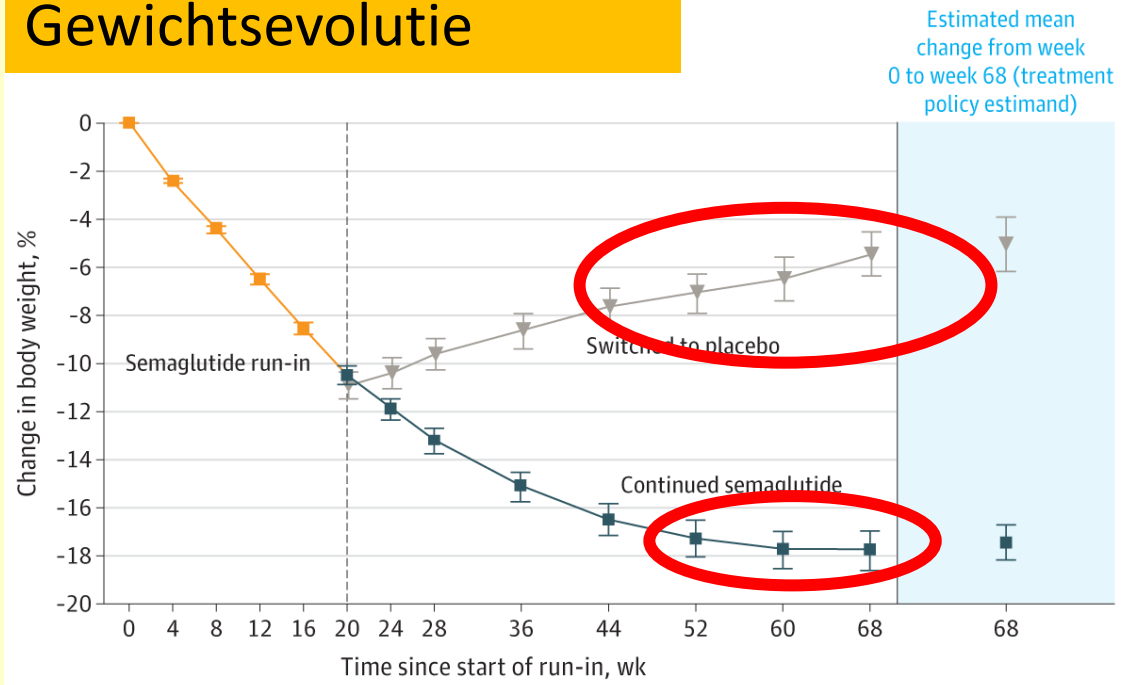
- OBJECTIVE To compare continued once-weekly treatment with SC semaglutide, 2.4mg, with switch to placebo for weight maintenance (both with lifestyle intervention) in adults with overweight or obesity after a 20-week run-in with subcutaneous semaglutide titrated to 2.4mg weekly.
- Intervention: … 803 participants (89.0%) who reached the 2.4-mg/wk semaglutide maintenance dose were randomized (2:1) to 48 weeks of continued subcutaneous semaglutide (n = 535) or switched to placebo (n = 268), plus lifestyle intervention in both groups
- NB alleen de succesvolle ptn geïncludeerd in deze studie

JAMA Network™

From: **Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial**

JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224

Gewichtsevolutie



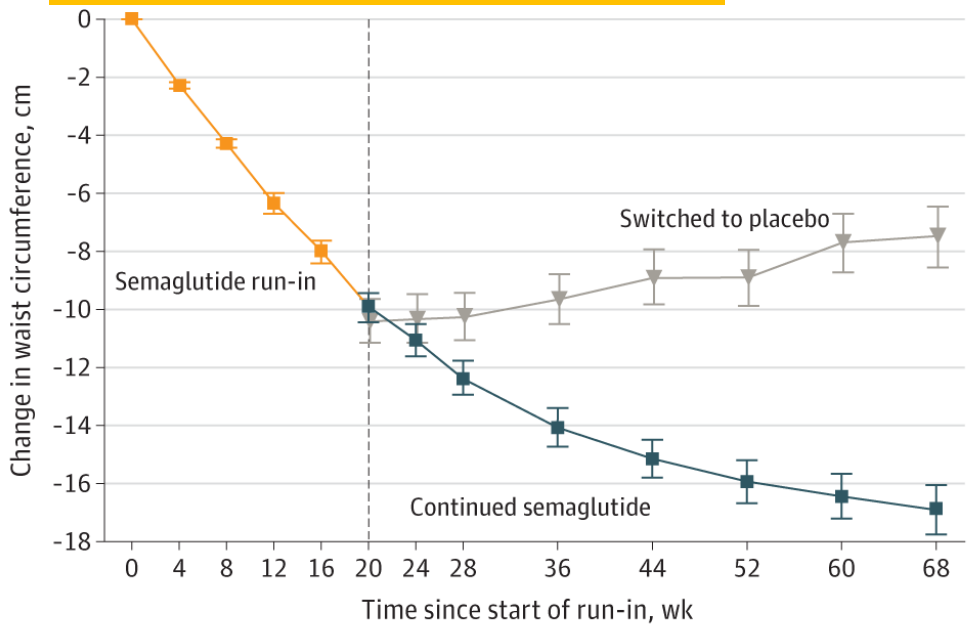
JAMA Network™

From: **Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial**

JAMA. 2021;325(14):1414-1425. doi:10.1001/jama.2021.3224

A

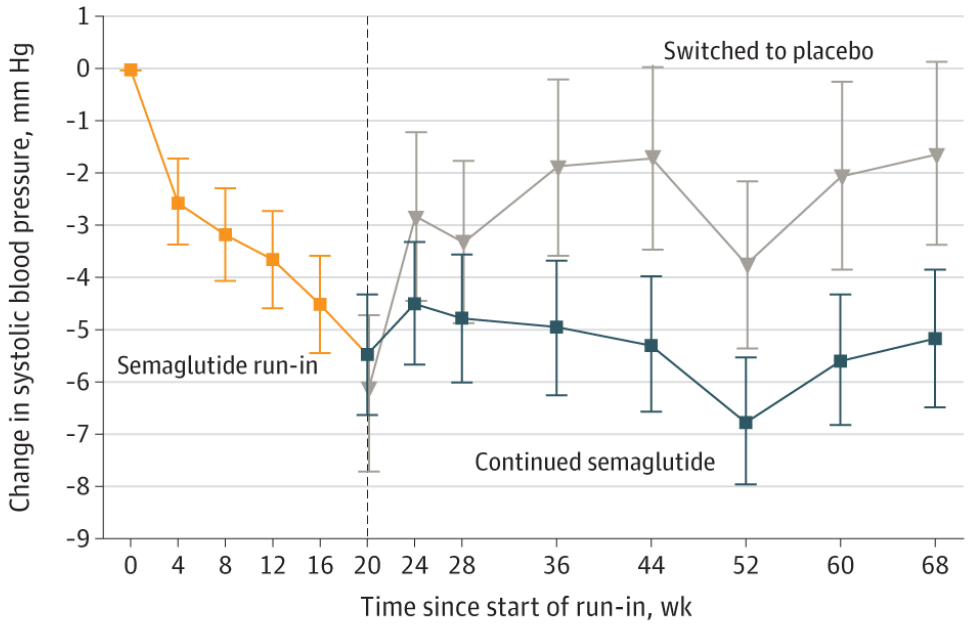
Buikomtrek



No. of participants							
Semaglutide run-in	803	801	803	802	800		
Continued semaglutide	535	527	531	525	523	521	515	518
Switched to placebo	268	266	264	258	259	254	245	248

B

Bloeddruk



No. of participants							
Semaglutide run-in	803	803	803	802	801		
Continued semaglutide	535	527	531	525	522	522	515	518
Switched to placebo	268	267	265	258	258	254	246	248

Effect of Continued Weekly SC Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity. The STEP 4 Randomized Clinical Trial JAMA march2001.

- CONCLUSIONS AND RELEVANCE Among adults with overweight or obesity who completed a 20-week run-in period with subcutaneous semaglutide, 2.4mg once weekly, maintaining treatment with semaglutide compared with switching to placebo resulted in continued weight loss over the following 48 weeks.

Bedenkingen

- G-daling houdt 1 jaar aan en stagneert dan?
- Stop = herwinnen G, volledig of vasthouden 5%?
- Levenskwaliteit (Step 1) SF-36 (physical functioning): +2 vs -0,6 (op 100 punten)
- Nu nog harde eindpunten verbeteren !
- Quid diabetici?

OPERAM: Optimising Therapy to prevent avoidable hospital admissions in the multimorbid elderly

https://pubmed.ncbi.nlm.nih.gov/34257088/

- **Objective:** To examine the effect of optimising drug treatment on drug related hospital admissions in older adults with multimorbidity and polypharmacy admitted to hospital.
- **Design:** Cluster randomised controlled trial.
- **Setting:** 110 clusters of inpatient wards within university based hospitals in four European countries (Switzerland, Netherlands, Belgium, and Republic of Ireland) defined by attending hospital doctors.

OPERAM: Optimising Therapy to prevent avoidable hospital admissions in the multimorbid elderly

https://pubmed.ncbi.nlm.nih.gov/34257088/

- **Objective:** To examine the effect of optimising drug treatment on drug related hospital admissions in older adults with multimorbidity and polypharmacy admitted to hospital.
- **Design:** Cluster randomised controlled trial.
- **Setting:** 110 clusters of inpatient wards within university based hospitals in four European countries (Switzerland, Netherlands, Belgium, and Republic of Ireland) defined by attending hospital doctors.
- **Participants:** 2008 older adults (≥70 years) with multimorbidity (≥3 chronic conditions) and polypharmacy (≥5 drugs used long term).
- **Intervention:** … usual care or a structured pharmacotherapy optimisation intervention performed at the individual level jointly by a doctor and a pharmacist, with the support of a clinical decision software system deploying the screening tool of older person's prescriptions and screening tool to alert to the right treatment (STOPP/START) criteria to identify potentially inappropriate prescribing.

Operam

- **Results:**
- 2008 older adults (median nine drugs) were randomised and enrolled in 54 intervention clusters (963 participants) and 56 control clusters (1045 participants) receiving usual care.
- In the intervention arm, 86.1% of participants (n=789) had inappropriate prescribing, with a mean of 2.75 (SD 2.24) STOPP/START recommendations for each participant.
- 62.2% (n=491) had ≥1 recommendation successfully implemented at two months, predominantly discontinuation of potentially inappropriate drugs.
- In the intervention group, 211 participants (21.9%) experienced a first drug related hospital admission compared with 234 (22.4%) in the control group.
- In the intention-to-treat analysis censored for death NS, first drug related hospital admission NS.
- *In the per protocol analysis, the hazard ratio for a drug related hospital admission was 0.91 (0.69 to 1.19).* The hazard ratio for first fall was 0.96 (0.79 to 1.15; 237 *v* 263 first falls) and for death was 0.90 (0.71 to 1.13; 172 *v* 203 deaths).

Operam

- **Conclusions:**
- Inappropriate prescribing was common in older adults with multimorbidity and polypharmacy admitted to hospital
  and was reduced through an intervention to optimise pharmacotherapy,
  but without effect on drug related hospital admissions.
- Additional efforts are needed to identify pharmacotherapy optimisation interventions that reduce inappropriate prescribing and improve patient outcomes.

Bedenkingen

- Zeer moeilijk om in deze multimorbide populatie duidelijk effect aan te tonen op harde einpunten binnen 12 m
- Participatie: ~20% sterfte; evaluatie interventie 726 op de 786 nog levenden
- Arts en apotheker, rol verpleegkundigen ?
- Enkel eenmalige medication review en alleen STOPP/START te weinig ?
  Regelmatig herhalen, betrekken nurses en meer aspecten meer effect?

- Gerandomiseerde studies
  - MA Delayed antibiotic prescribing for respiratory tract infections: individual patient data meta-analysis
  - Monoclonale AL voor migraine
  - GLP-1-analoog voor obesitas?
  - Optimising Therapy to prevent avoidable hospital admissions in the multimorbid elderly OPERAM
- Niet gerandomiseerde studies
  - SABINA
  - Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study

BMJ 2021;373:n991

- **Objective** To investigate whether the results of a rhythm control strategy differ according to the duration between diagnosis of atrial fibrillation and treatment initiation.

- **Design** & **Participants**
  Longitudinal observational cohort study. Population based cohort from the Korean National Health Insurance Service database.
  22 635 adults with atrial fibrillation and cardiovascular conditions, newly treated with rhythm control (antiarrhythmic drugs or ablation) or rate control strategies between 28 July 2011 and 31 December 2015.
  Of the study population, 12 200 (53.9%) were male, the median age was 70, and the median follow-up duration was 2.1 years.

- **Main outcome measure** A composite outcome of death from cardiovascular causes, ischaemic stroke, admission to hospital for heart failure, or acute myocardial infarction.

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study

BMJ 2021;373:n991

- **Results**
- Among patients with early treatment for atrial fibrillation (< one year since diagnosis), compared with rate control, rhythm control was associated with a lower risk of the primary composite outcome (weighted incidence rate per 100 person years 7.42 in rhythm control *v* 9.25 in rate control; hazard ratio 0.81, 95% confidence interval 0.71 to 0.93; P=0.002).

- No difference in the risk of the primary composite outcome was found between rhythm and rate control (weighted incidence rate per 100 person years 8.67 in rhythm control *v* 8.99 in rate control; 0.97, 0.78 to 1.20; P=0.76) in patients with late treatment for atrial fibrillation (initiated after one year since diagnosis). No significant differences in safety outcomes were found …

Treatment timing and the effects of rhythm control strategy in patients with atrial fibrillation: nationwide cohort study

BMJ 2021;373:n991

- **Conclusions** Early initiation of rhythm control treatment was associated with a lower risk of adverse cardiovascular outcomes than rate control treatment in patients with recently diagnosed atrial fibrillation. This association was not found in patients who had had atrial fibrillation for more than one year.

- Bedenkingen:
- Cohort = observationeel; hoofdvraag: ‘waarom heeft arts geopteerd voor rhythm versus rate ?’: mogelijkheid dat fittere ptn eerder ritme en slechter ingeschatte ptn eerder rate (selection bias)
- Koreaanse populatie versus Europese?
- ‘Recent VKF’ groep heeft baat met ritme controle op klinisch relevant eindpunt ; NNT~50 dus 1 event minder op 50 ptn. Soms vlot , soms zeer veel energie (herhaalde ZH opnames en verdovingen)

SABINA: An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries

Adv Ther. 2020; 37(3): 1124–1135.

Introduction

- Globally, individuals with asthma tend to overrely on short-acting β_2-agonists (SABAs) and underuse inhaled corticosteroids, thereby undertreating the underlying inflammation. Such relief-seeking behavior has been reinforced by long-standing treatment guidelines, which until recently recommended SABA-only use for immediate symptom relief. We aimed to describe the current burden of SABA use among European individuals with asthma within the SABA use IN Asthma (SABINA) program.

SABINA: An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries

Adv Ther. 2020; 37(3): 1124–1135.

Introduction

- Globally, individuals with asthma tend to overrely on short-acting β_2-agonists (SABAs) and underuse inhaled corticosteroids, thereby undertreating the underlying inflammation. Such relief-seeking behavior has been reinforced by long-standing treatment guidelines, which until recently recommended SABA-only use for immediate symptom relief. We aimed to describe the current burden of SABA use among European individuals with asthma within the SABA use IN Asthma (SABINA) program.

Methods

- Prescription and/or dispensing data during 2006–2017 from electronic medical records and/or national patient registries in the United Kingdom (UK), Germany, Italy, Spain, and Sweden were analyzed. Individuals aged at least 12 years old with a current asthma diagnosis and no other chronic respiratory conditions were included. Asthma treatment step and severity were based on treatment guidelines in use in each individual country. The proportion of individuals prescribed SABA was measured during a 12-month period. SABA overuse was defined as at least three SABA canisters per year.

SABINA: An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries

Adv Ther. 2020; 37(3): 1124–1135.

- **Results**
- More than one million individuals with asthma were included across five European countries...
  The prevalence of SABA overuse was 9% in Italy, 16% in Germany, 29% in Spain, 30% in Sweden, and 38% in the UK. In the UK, SABA overuse was greater in individuals with moderate-to-severe asthma versus individuals with mild asthma (58% versus 27%, respectively), while SABA overuse was similar in individuals with both mild (9–32%) and moderate-to-severe (8–31%) asthma in the other European countries.
- **Conclusions**
- The findings of this study from the SABINA program show that SABA overuse (at least three canisters per year) is common across Europe, despite the different healthcare and reimbursement policies of each country.

SABINA: An Overview of Short-Acting β2-Agonist Use in Asthma in European Countries

Adv Ther. 2020; 37(3): 1124–1135.

- **Bedenkingen**
- Tussen 1/4 en 1/3 patiënten overgebuik? Wat in België? (bij ons niet mogelijk egens geen link artsensoftware –Ernst astma- en apothekerssoftware
- (NB Italië enige met < 10 % , maar daar mogelijkheid OTC als ‘noodgeneesmiddel’ dat niet geregistreerd wordt)

- GINA richtlijnen in 2019 raden aan te starten met **combinatie SABA-Betamimeticum+ICS** ipv met SABA alleen. Op geen enkele studie gebaseerd maar wel op deze bezorgdheid: als ze overgebruiken hebben ze alvast ook ICS binnen. Maar geen bewijs dat dit effectief werkt
- >< als huisarts kennen we wel allemaal patiënten die 20-30 jaar 1 of 2 ‘Ventolintjes’ gebruiken per jaar. Nut om hieraan ook ICS toe te voegen: ?

Dank u

Vragen?