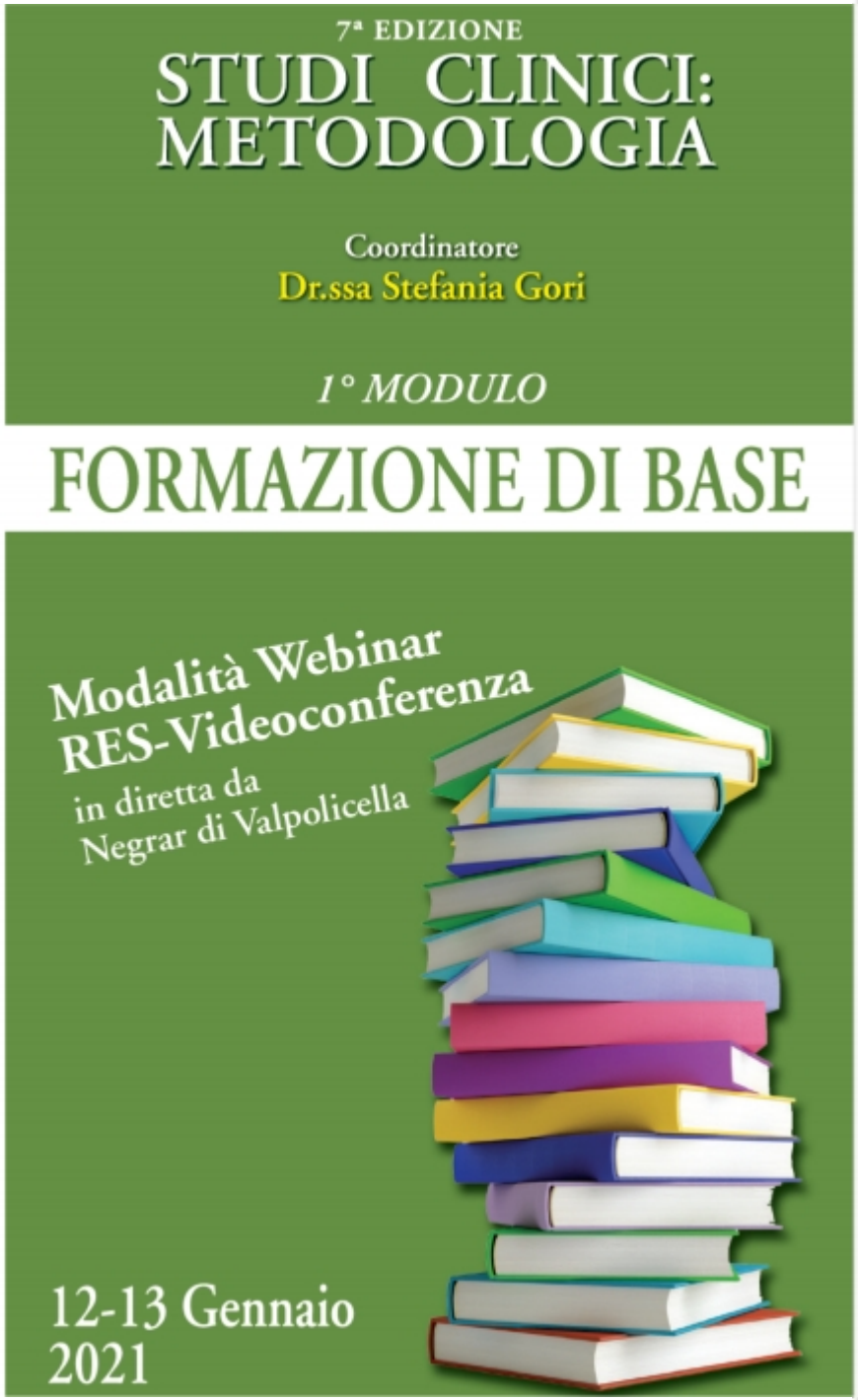
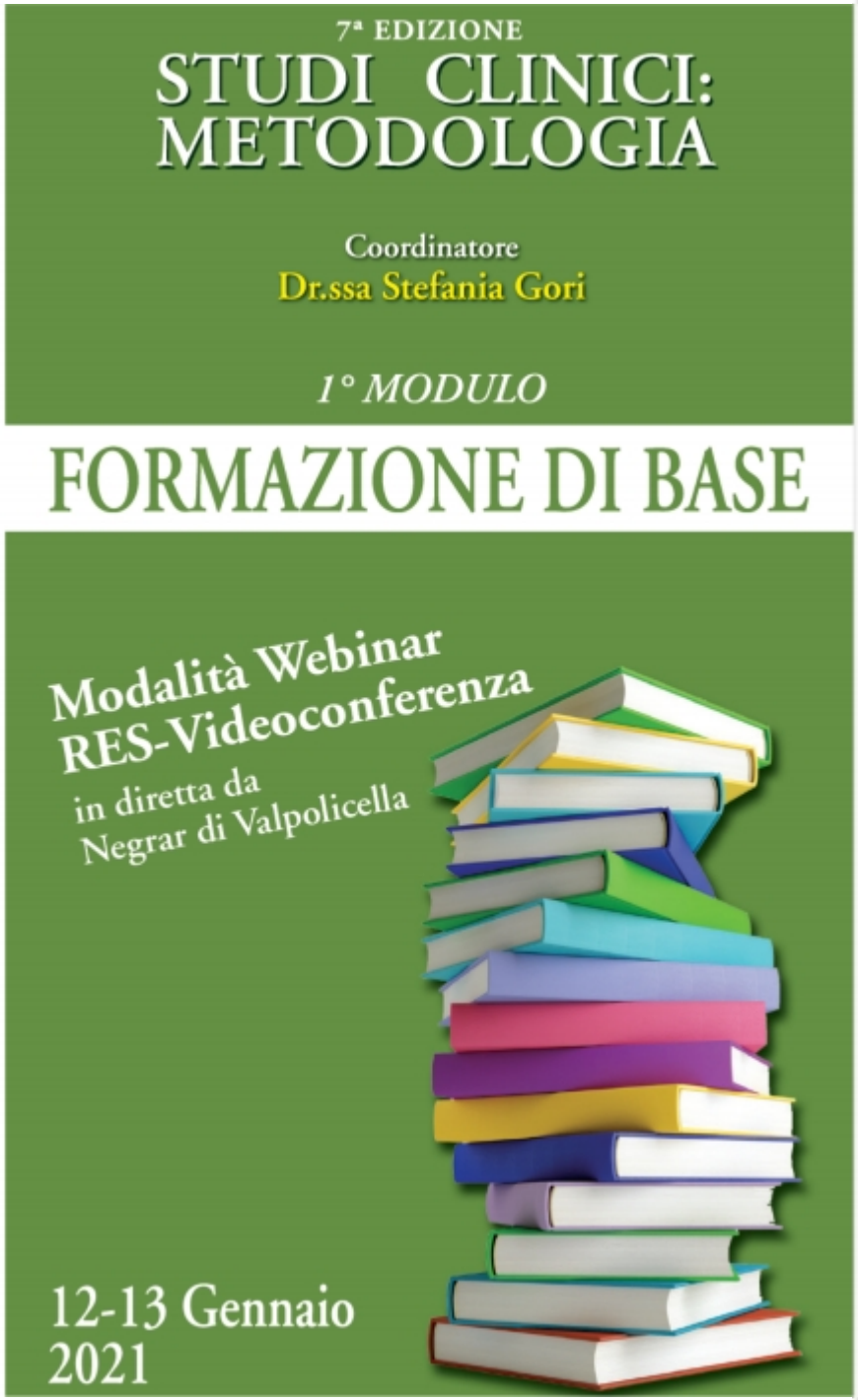


STUDI CLINICI: METODOLOGIA

Formazione di base

Marta Bonotto
Udine



STUDI CLINICI: METODOLOGIA

Quesito clinico

Per i ricercatori QUESITO CLINICO è l'IDEA

Ciò che si vuole trovare

Ciò a cui si vuole dare una risposta

QUESITO CLINICO come primum movens

C'è un quesito per ogni "gusto"...

Eziologia/ rischio	Individuare le responsabilità di un fattore nel determinismo di una condizione di rischio: "Qual è la responsabilità eziologica del fattore di rischio X nell'insorgenza della condizione Y?"
Diagnosi	Definire la *performance* di un test diagnostico: "Quale è l'accuratezza del test diagnostico X, rispetto al *gold-standard* Y, nella diagnosi della condizione Z?"
Prognosi	"Qual è la storia naturale della condizione X e la potenza dei fattori prognostici?"
Terapia/ trattamento/ intervento	Valutare l'efficacia di un intervento assistenziale di natura tecnica, relazionale o educativa: "Quale è l'efficacia del trattamento X (preventivo, terapeutico o riabilitativo) rispetto al trattamento Y, nella condizione Z?"

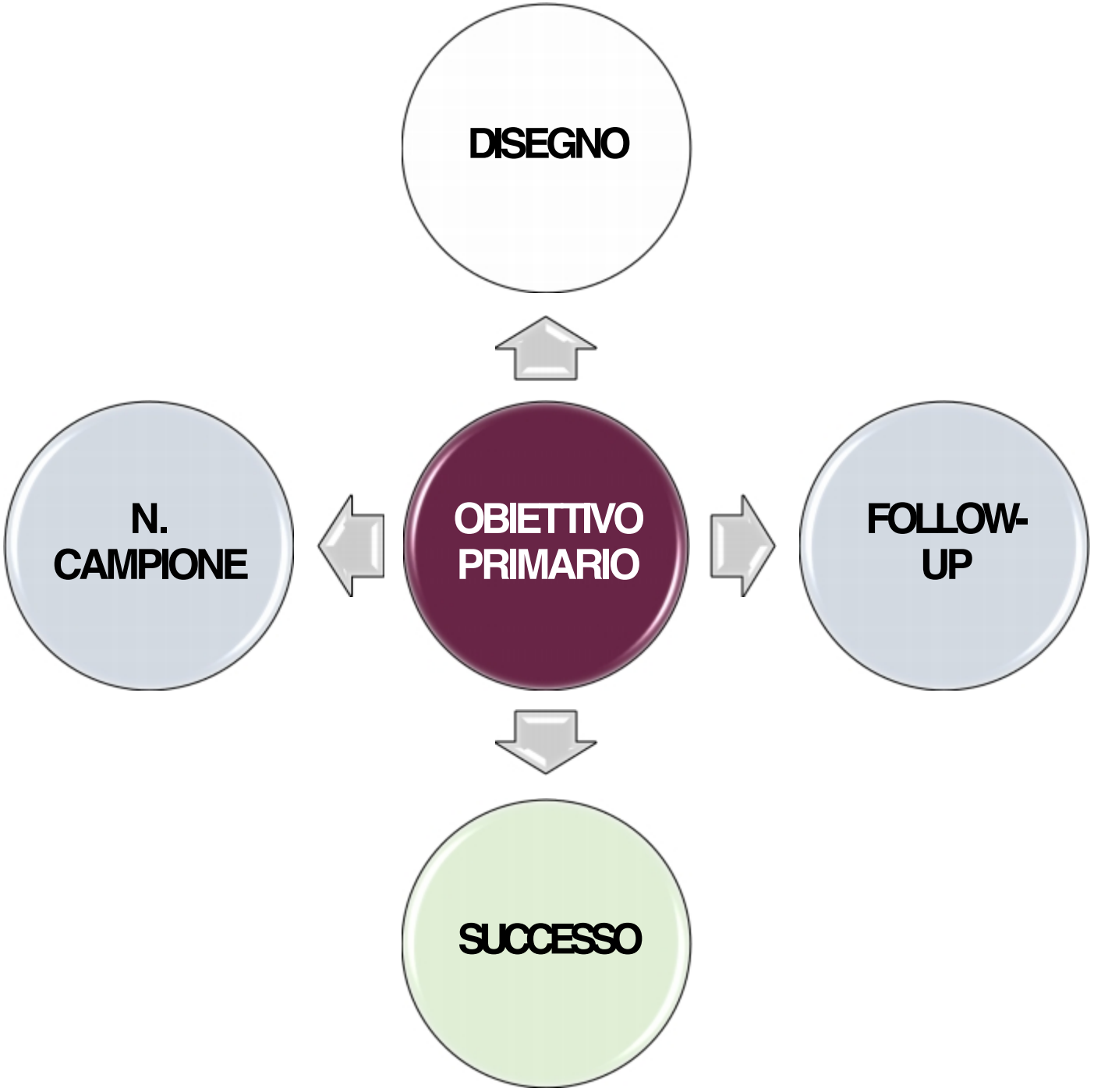
Quesito cui gli sperimentatori sono piu interessati a rispondere, e al quale lo studio vuole dare una risposta

OBIETTIVO PRIMARIO

OBIETTIVI SECONDARI

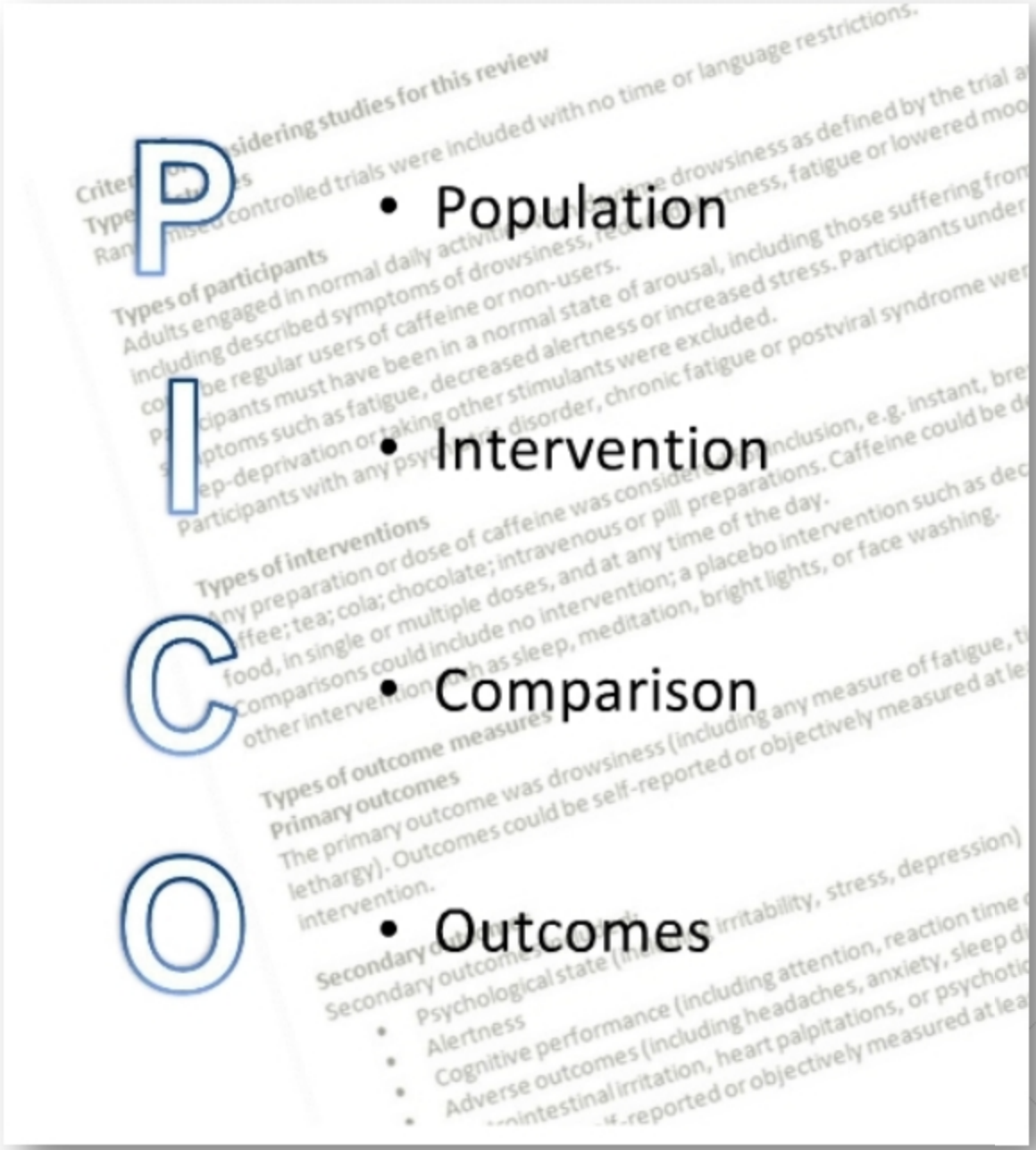
altri quesiti di interesse, in qualche modo correlati al quesito primario

L'obiettivo primario non soffre la solitudine


DISEGNO
N. CAMPIONE
OBIETTIVO PRIMARIO
FOLLOW-UP
SUCCESSO

…esempio...

L'utilizzo di un percorso di cure riabilitative di tipo multidisciplinare nell'anziano con frattura del femore può ridurre l'incidenza dei tassi di mortalità e morbilità, diminuire i tempi di degenza e il rischio di riammissioni e migliorare la performance nella attività quotidiane?


P
• Population
I
• Intervention
C
• Comparison
O
• Outcomes
GRADE

…esempio...

L'u$lizzo di un percorso di cure riabilita$ve di $po mul$disciplinare nell'anziano con fra7ura del femore può ridurre l'incidenza dei tassi di mortalità e morbilità, diminuire i tempi di degenza e il rischio di riammissioni e migliorare la performance nella a=vità quo$diane?

…esempio…

L'utilizzo di un percorso di cure riabilitative di tipo multidisciplinare nell'anziano con frattura del femore può ridurre l'incidenza dei tassi di mortalità e morbilità, diminuire i tempi di degenza e il rischio di riammissioni e migliorare la performance nella attività quotidiane?

Metodologia PICO		
P	*patient* (paziente)	età superiore ai 65 anni con frattura del femore
I	*intervention* (intervento)	percorso di riabilitazione multidisciplinare
C	*comparison* (controllo)	percorso di riabilitazione non multidisciplinare
O	*outcomes* (risultati)	mortalità, complicazioni, durata del ricovero, riammissione, attività quotidiane

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ABSTRACT

BACKGROUND

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials), Département Hospitalo-Universitaire FIRE (Fibrose, Inflammation, and Remodeling), Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Université Paris-Diderot, INSERM Unité 1148, Paris (P.G.S.); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London (P.G.S.); the Department of Medicine, University of Maryland School of Medicine, Baltimore (M.M.); the Utah Lipid Center, Salt Lake City (E.A.B.); the Office of Health Promotion and Disease Prevention, Department of Medicine,

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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.

ORIGINAL ARTICLE

Fracture Prevention with Zoledronate in Older Women with Osteopenia

Ian R. Reid, M.D., Anne M. Horne, M.B., Ch.B., Borislav Mihov, B.Phty., Angela Stewart, R.N., Elizabeth Garratt, B.Nurs., Sumwai Wong, B.Sc., Katy R. Wiessing, B.Sc., Mark J. Bolland, Ph.D., Sonja Bastin, M.B., Ch.B., and Gregory D. Gamble, M.Sc.

ABSTRACT

BACKGROUND

Bisphosphonates prevent fractures in patients with osteoporosis, but their efficacy in women with osteopenia is unknown. Most fractures in postmenopausal women occur in those with osteopenia, so therapies that are effective in women with osteopenia are needed.

METHODS

We conducted a 6-year, double-blind trial involving 2000 women with osteopenia (defined by a T score of –1.0 to –2.5 at either the total hip or the femoral neck on either side) who were 65 years of age or older. Participants were randomly assigned to receive four infusions of either zoledronate at a dose of 5 mg (zoledronate group) or normal saline (placebo group) at 18-month intervals. A dietary calcium intake of 1 g per day was advised, but calcium supplements were not provided. Participants who were not already taking vitamin D supplements received cholecalciferol before the trial began (a single dose of 2.5 mg) and during the trial (1.25 mg per month). The primary end point was the time to first occurrence of a nonvertebral or vertebral fragility fracture.

Perché la P?

Perché la P?

Il quesito come *primum movens*

Metodologia PICO		
P	*patient* (paziente)	età superiore ai 65 anni con frattura del femore
I	*intervention* (intervento)	percorso di riabilitazione multidisciplinare
C	*comparison* (controllo)	percorso di riabilitazione non multidisciplinare
O	*outcomes* (risultati)	mortalità, complicazioni, durata del ricovero, riammissione, attività quotidiane

Quesito di ricerca

L'utilizzo di un percorso di cure riabilitative di tipo multidisciplinare nell'utente anziano con frattura del femore può ridurre l'incidenza dei tassi di mortalità e morbilità, diminuire i tempi di degenza e il rischio di riammissioni e migliorare la performance nelle attività di vita quotidiana?

ORIGINAL ARTICLE

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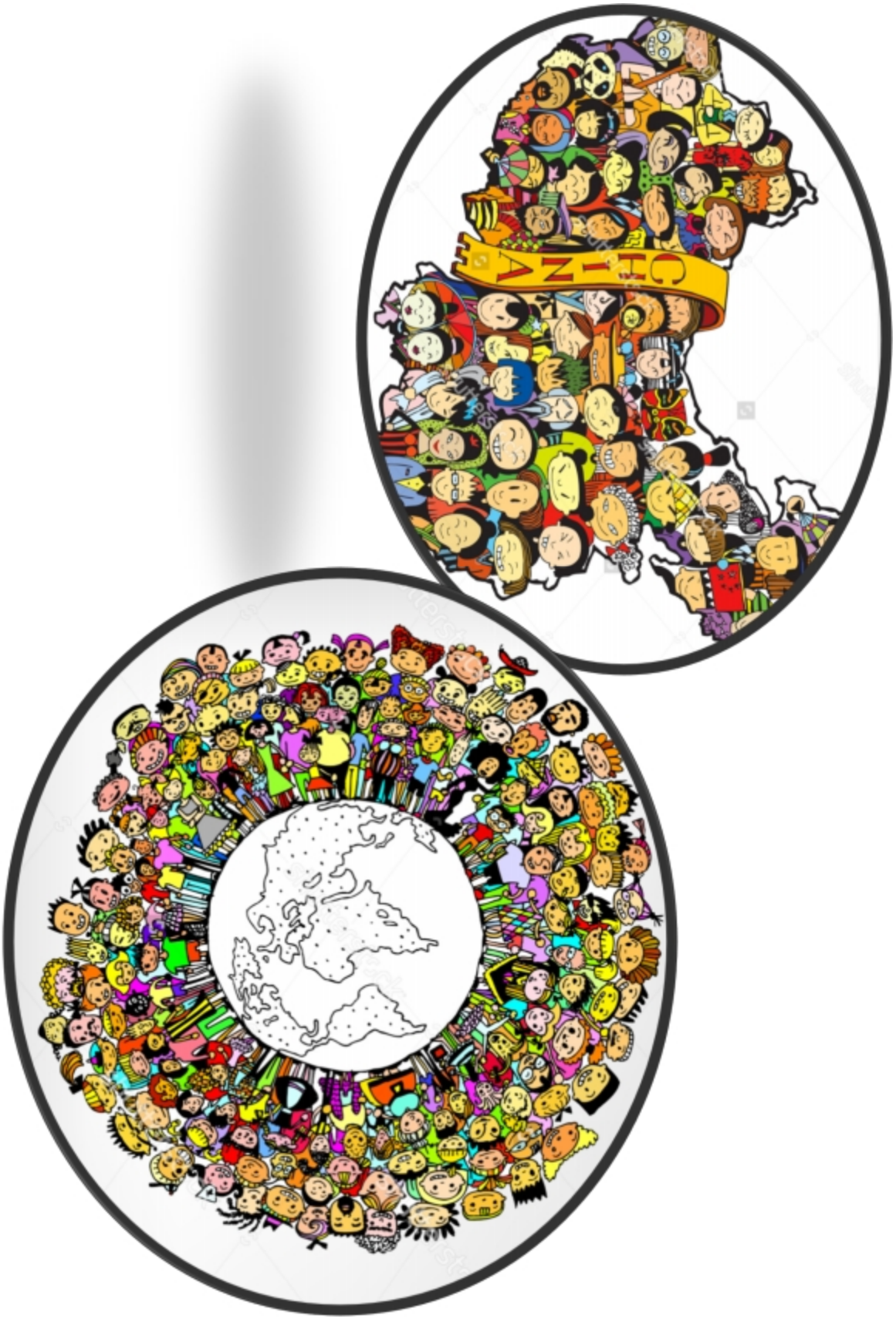


The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 NOVEMBER 8, 2018 VOL. 379 NO. 19

A Trial of a Triple-Drug Treatment for Lymphatic Filariasis

Christopher L. King, M.D., Ph.D., James Suamani, B.S., Nelly Sanuku, B.S., Yao-Chieh Cheng, B.S., Samson Satofan, Brooke Mancuso, M.S.P.H., Charles W. Goss, Ph.D., Leanne J. Robinson, Ph.D., M.P.H., Peter M. Siba, Ph.D., Gary J. Weil, M.D., and James W. Kazura, M.D.

ABSTRACT

BACKGROUND

The World Health Organization has targeted lymphatic filariasis for global elimination by 2020 with a strategy of mass drug administration. This trial tested whether a single dose of a three-drug regimen of ivermectin plus diethylcarbamazine plus albendazole results in a greater sustained clearance of microfilariae than a single dose of a two-drug regimen of diethylcarbamazine plus albendazole and is noninferior to the two-drug regimen administered once a year for 3 years.

METHODS

In a randomized, controlled trial involving adults from Papua New Guinea with *Wuchereria bancrofti* microfilaremia, we assigned 182 participants to receive a single dose of the three-drug regimen (60 participants), a single dose of the two-drug regimen (61 participants), or the two-drug regimen once a year for 3 years (61 participants). Clearance of microfilariae from the blood was measured at 12, 24, and 36 months after trial initiation.

From the Center for Global Health and Diseases, Case Western Reserve University School of Medicine (C.L.K., Y.-C.C., B.M., J.W.K.), and the Veterans Affairs Medical Center (C.L.K.), Cleveland; Papua New Guinea Institute of Medical Research, Goroka (J.S., N.S., S.S., L.J.R., P.M.S.); and the Division of Biostatistics (C.W.G.) and Department of Medicine, Infectious Diseases Division (G.J.W.), Washington University School of Medicine, St. Louis. Address reprint requests to Dr. King at the Center for Global Health and Diseases, Case Western Reserve University, Biomedical Research Bldg. 421, 2109 Adelbert Rd., Cleveland, OH 44106, or at cxk21@case.edu.

This is the *New England Journal of Medicine*

ORIGINAL REPORTS | Gastrointestinal Cancer

Phase I/II Trial to Evaluate the Efficacy and Safety of Nanoparticle Albumin-Bound Paclitaxel in Combination With Gemcitabine in Patients With Pancreatic Cancer and an ECOG Performance Status of 2

Teresa Macarulla, MD, PhD[1]; Roberto Pazo-Cid, MD, PhD[2]; Carmen Guillén-Ponce, MD, PhD[3]; Rafael López, MD, PhD[4]; Ruth Vera, MD, PhD[5]; Margarita Reboredo, MD[6]; ...

Show More

https://doi.org/10.1200/JCO.18.00089

Abstract

Purpose

Gemcitabine plus nanoparticle albumin-bound (NAB) paclitaxel (GA) significantly improved survival compared with gemcitabine alone in patients with metastatic pancreatic ductal adenocarcinoma (PDAC) and a Karnofsky performance status (PS) of 70% or greater. Because of the low number of patients with reduced PS, the efficacy of this regimen in fragile patients remains unclear. This study aimed to evaluate the efficacy and tolerability of different GA dosing regimens in patients with a poor PS.

PANCREOX: A Randomized Phase III Study of Fluorouracil/Leucovorin With or Without Oxaliplatin for Second-Line Advanced Pancreatic Cancer in Patients Who Have Received Gemcitabine-Based Chemotherapy

Sharlene Gill, Yoo-Joung Ko, Christine Cripps, Annie Beaudoin, Sukhbinder Dhesy-Thind, Muhammad Zulfiqar, Pawel Zalewski, Thuan Do, Pablo Cano, Wendy Yin Han Lam, Scot Dowden, Helene Grassin, John Stewart, and Malcolm Moore

A B S T R A C T

Purpose

The standard of care for second-line therapy in patients with advanced pancreatic cancer after gemcitabine-based therapy is not clearly defined. The CONKO-003 phase III study reported a survival benefit with second-line fluorouracil (FU) and oxaliplatin using the oxaliplatin, folinic acid, and FU (OFF) regimen.[1] PANCREOX was a phase III multicenter trial to evaluate the benefit of FU and oxaliplatin administered as modified FOLFOX6 (mFOLFOX6; infusional fluorouracil, leucovorin, and oxaliplatin) versus infusional FU/leucovorin (LV) in this setting.

Patients and Methods

Patients with confirmed advanced pancreatic cancer who were previously treated with gemcitabine therapy and with an Eastern Cooperative Oncology Group performance status of 0-2 were eligible. A total of 108 patients were randomly assigned to receive biweekly mFOLFOX6 or infusional FU/LV until progression. Progression-free survival (PFS) was the primary end point.

Results

Baseline patient characteristics were similar in both arms. No difference was observed in PFS (median, 3.1 months *v* 2.9 months; $P = .99$). Overall survival (OS) was inferior in patients assigned to mFOLFOX6 (median, 6.1 months *v* 9.9 months; $P = .02$). Increased toxicity was observed with the addition of oxaliplatin, with grade 3/4 adverse events occurring in 63% of patients who received mFOLFOX6 and 11% of those who received FU/LV. More patients in the mFOLFOX6 arm withdrew from study due to adverse events than in the FU/LV arm (20% *v* 2%), whereas the use of post-progression therapy was significantly higher in the FU/LV arm (25% *v* 7%; $P = .015$). No significant differences were observed in time to deterioration on the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Core 30 global health scale.

Conclusion

No benefit was observed with the addition of oxaliplatin, administered as mFOLFOX6, versus infusional FU/LV in patients with advanced pancreatic cancer previously treated with first-line gemcitabine.

J Clin Oncol 34:3914-3920.

VOLUME 34 · NUMBER 23 · AUGUST 10, 2016

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Metastatic Pancreatic Cancer: American Society of Clinical Oncology Clinical Practice Guideline

Davendra P.S. Sohal and Alok A. Khorana, Cleveland Clinic, Cleveland, OH; Pamela B. Mangu, American Society of Clinical

Davendra P.S. Sohal, Pamela B. Mangu, Alok A. Khorana, Manish A. Shah, Philip A. Philip, Eileen M. O'Reilly, Hope E. Uronis, Ramesh K. Ramanathan, Christopher H. Crane, Anitra Engebretson, Joseph T. Ruggiero, Mehmet S. Coour. Michelle Lau. Susan Urba. and Daniel Laheru

Clinical Question 2: What Is the Appropriate First-Line Treatment of Patients With Metastatic Pancreatic Cancer?

Recommendation 2.1. Leucovorin, fluorouracil, irinotecan, and oxaliplatin (FOLFIRINOX) is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, favorable comorbidity profile, patient preference and support system for aggressive medical therapy, and access to chemotherapy port and infusion pump management services (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.2. Gemcitabine plus nanoparticle albumin-bound (NAB) -paclitaxel is recommended for patients who meet all of the following criteria: ECOG PS 0 to 1, relatively favorable comorbidity profile, and patient preference and support system for relatively aggressive medical therapy (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: strong).

Recommendation 2.3. Gemcitabine alone is recommended for patients who have either an ECOG PS 2 or a comorbidity profile that precludes more-aggressive regimens and who wish to pursue cancer-directed therapy. The addition of either capecitabine or erlotinib to gemcitabine may be offered in this setting (Type: evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: moderate).

Perché la C?

Perché la C?

Perché la C?

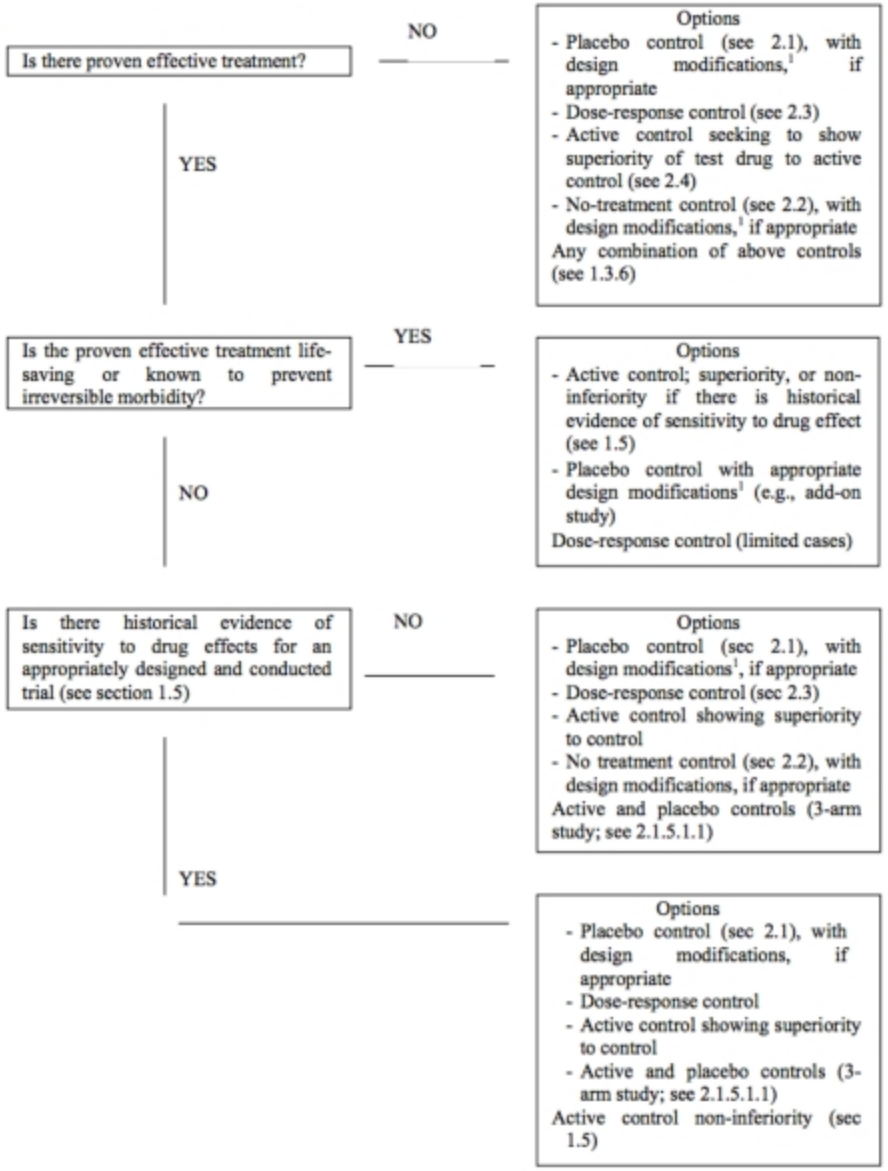
Choice of Control Group

- The selection of an appropriate control group is a critical decision which impacts on the scientific validity and ethical acceptability of a clinical investigation.
- The proper control group allows for discrimination between patient outcomes caused by the test treatment, and outcomes caused by other factors such as the natural progression of the disease, observer or patient expectations, or other treatments.

Perché la C?

FIGURE 1: CHOOSING THE CONCURRENT CONTROL FOR DEMONSTRATING EFFICACY

This figure shows the basic logic for choosing the control group; the decision may depend on the available drugs or medical practices in the specific region.



http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002925.pdf

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cardiometabolic Risks and Severity of Obesity in Children and Young Adults

Asheley C. Skinner, Ph.D., Eliana M. Perrin, M.D., M.P.H., Leslie A. Moss, M.H.A., C.H.E.S., and Joseph A. Skelton, M.D.

ABSTRACT

BACKGROUND

The prevalence of severe obesity among children and young adults has increased over the past decade. Although the prevalence of cardiometabolic risk factors is relatively low among children and young adults who are overweight or obese, those with more severe forms of obesity may be at greater risk.

Table 1. Definitions of Abnormal Values for Risk-Factor Variables.*

Variable	Age Range	No. of Participants Evaluated	Definition of Abnormal Value
	yr		
Total cholesterol	3–19	6876	≥200 mg/dl
HDL cholesterol	3–19	6873	<35 mg/dl
Systolic BP	8–19	6412	≥95th percentile
Diastolic BP	8–19	6412	≥95th percentile
LDL cholesterol	3–19	2464	≥130 mg/dl
Triglycerides	3–19	2537	≥150 mg/dl
Glycated hemoglobin	12–19	4237	>5.7%
Glucose	12–19	1991	≥100 mg/dl

Table 4. Risk Ratios for Cardiovascular Risk Factors by Sex and Weight Category.*

Risk-Factor Variable and Weight Category	All Participants		Female Participants		Male Participants	
	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value	Risk Ratio (95% CI)	P Value
Total cholesterol						
Overweight	0.70 (0.58–0.85)	<0.001	0.79 (0.58–1.07)	0.12	0.63 (0.49–0.82)	<0.001
Class I obesity	Reference		Reference		Reference	
Class II obesity	1.12 (0.88–1.45)	0.34	1.17 (0.78–1.77)	0.45	1.09 (0.78–1.54)	0.60
Class III obesity	1.29 (0.92–1.80)	0.14	1.08 (0.56–2.00)	0.80	1.41 (0.93–2.15)	0.10
HDL cholesterol						
Overweight	0.55 (0.44–0.69)	<0.001	0.46 (0.33–0.65)	<0.001	0.60 (0.43–0.85)	0.004
Class I obesity	Reference		Reference		Reference	
Class II obesity	1.65 (1.31–2.01)	<0.001	1.06 (0.70–1.60)	0.78	2.00 (1.45–2.74)	<0.001
Class III obesity	1.89 (1.35–2.66)	<0.001	1.19 (0.66–2.12)	0.56	2.36 (1.55–3.58)	<0.001
LDL cholesterol						
Overweight	0.67 (0.48–0.93)	0.02	0.66 (0.41–1.06)	0.08	0.69 (0.42–1.12)	0.13
Class I obesity	Reference		Reference		Reference	
Class II obesity	0.92 (0.57–1.48)	0.19	1.04 (0.51–2.18)	0.90	0.80 (0.42–1.52)	0.50
Class III obesity	0.79 (0.44–1.43)	0.59	0.85 (0.38–1.89)	0.68	0.75 (0.32–1.78)	0.51

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitchin, M.D., Judith Absalon, M.D., Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M.D., Gonzalo Pérez Marc, M.D., Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.Sc., Kena A. Swanson, Ph.D., Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren V. Kalina, Ph.D., David Cooper, Ph.D., Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., Haylene Nell, M.D., Axel Schaefer, M.D., Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D., Philip R. Dormitzer, M.D., Ph.D., Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D., for the C4591001 Clinical Trial Group*

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and the resulting coronavirus disease 2019 (Covid-19) have afflicted tens of millions of people in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal efficacy trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to receive two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (30 μg per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified RNA vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2 full-length spike protein. The primary end points were efficacy of the vaccine against laboratory-confirmed Covid-19 and safety.

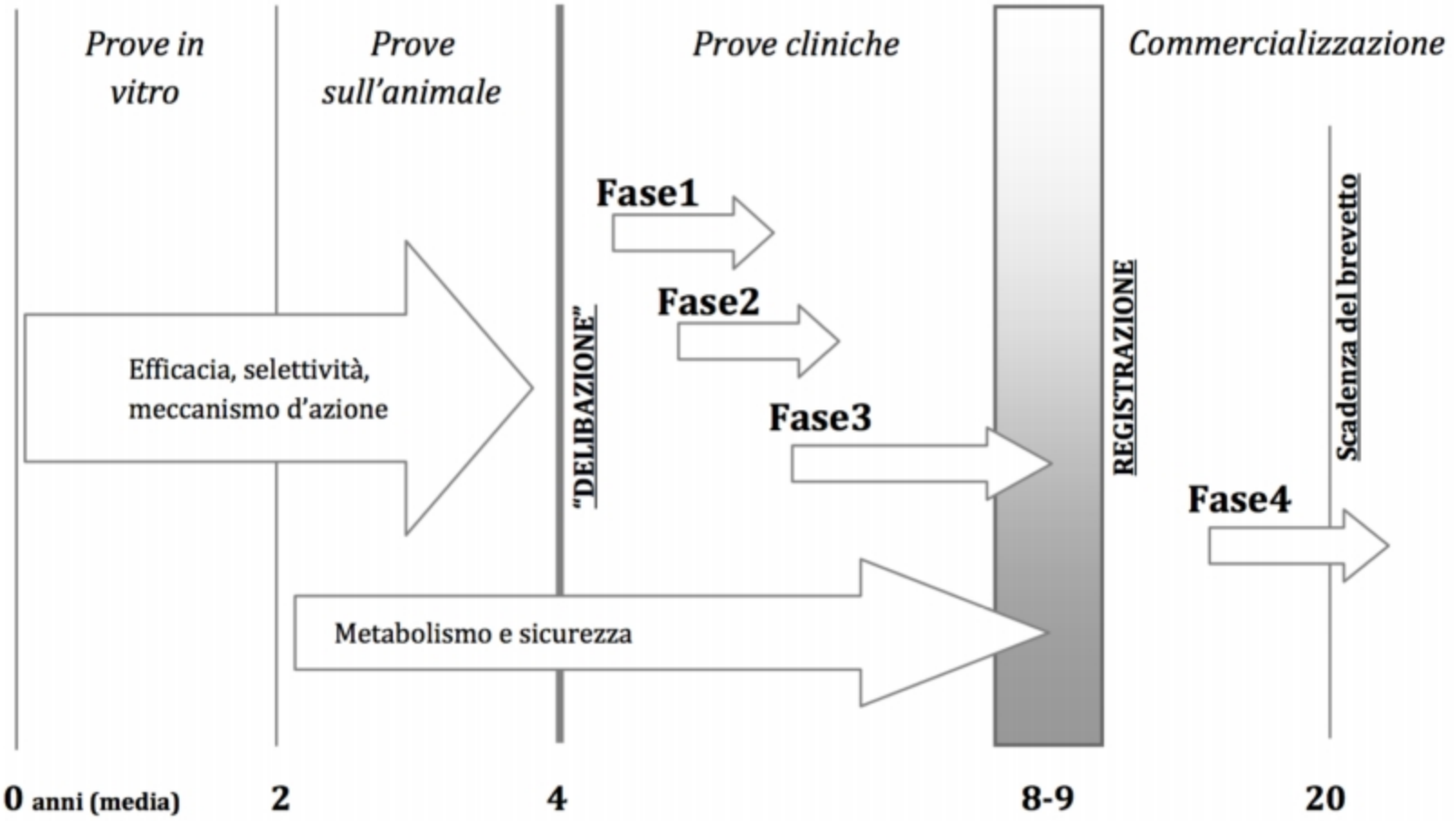
The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Absalon at Pfizer, 401 N. Middletown Rd., Pearl River, NY 10965, or at judith.absalon@pfizer.com.

*A complete list of investigators in the C4591001 Clinical Trial Group is provided in the Supplementary Appendix, available at NEJM.org.

Drs. Polack and Thomas contributed equally to this article.

This article was published on December 10, 2020, and updated on December 16, 2020, at NEJM.org.

Quale O?


Prove in vitro
Prove sull'animale
Prove cliniche
Commercializzazione
Fase1
Fase2
Fase3
Fase4
Efficacia, selettività, meccanismo d'azione
"DELIBAZIONE"
REGISTRAZIONE
Scadenza del brevetto
Metabolismo e sicurezza
0 anni (media)
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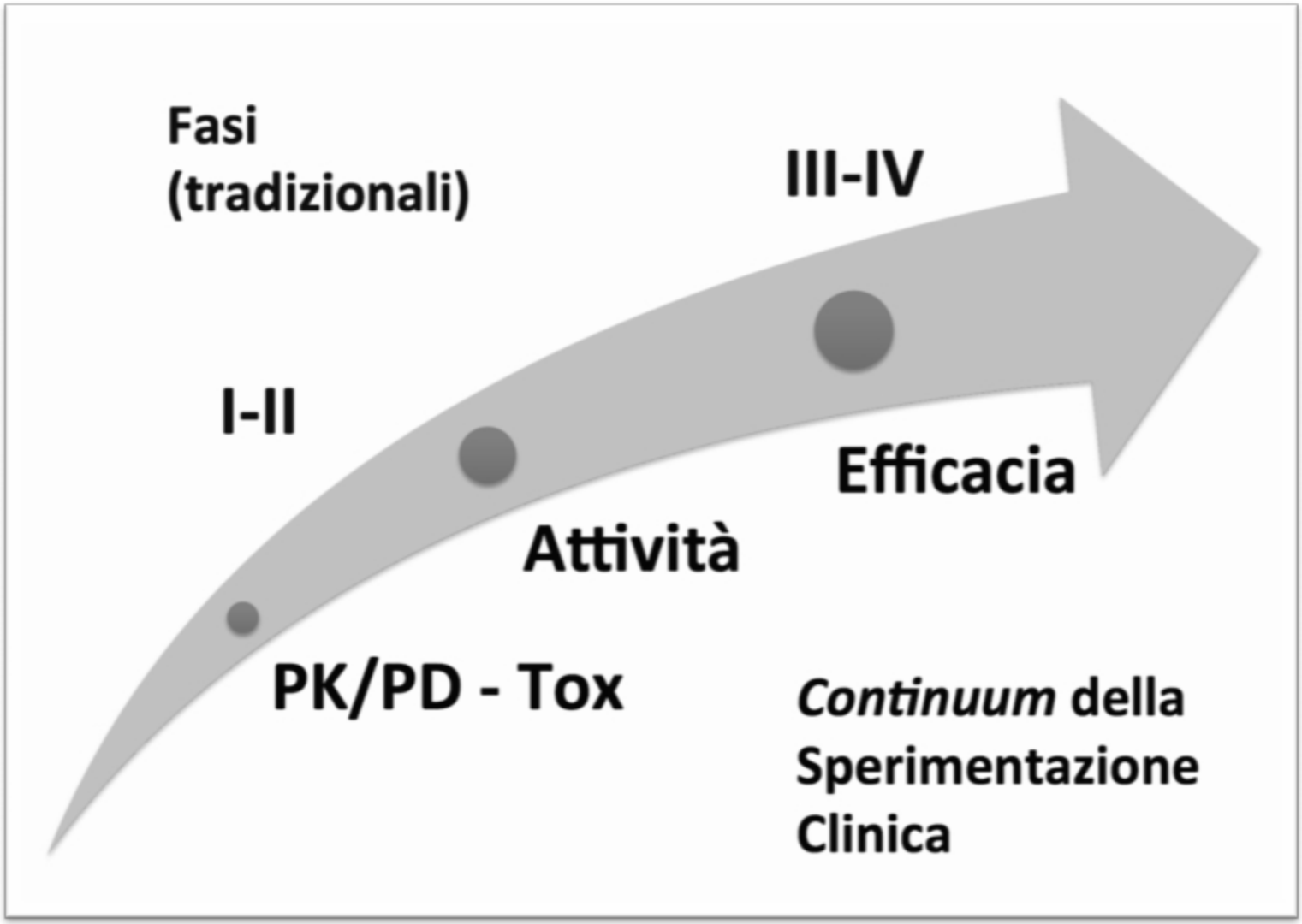
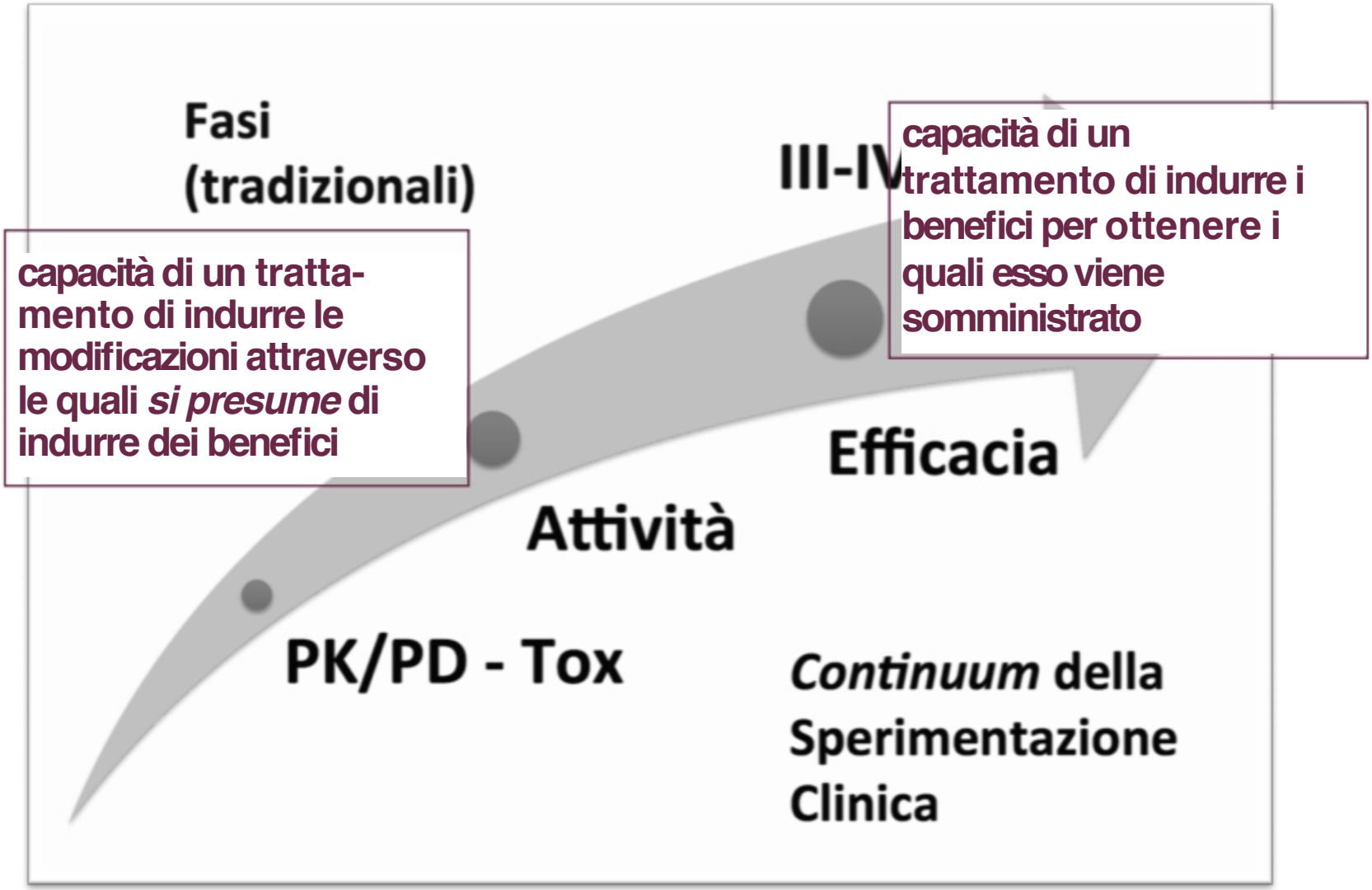
Quale O?


Fasi
(tradizionali)
III-IV
I-II
Efficacia
Attività
PK/PD - Tox
Continuum della
Sperimentazione
Clinica

Quale O?


Fasi
(tradizionali)
III-IV
capacità di un trattamento di indurre i benefici per ottenere i quali esso viene somministrato
capacità di un tratta-mento di indurre le modificazioni attraverso le quali *si presume* di indurre dei benefici
Efficacia
Attività
PK/PD - Tox
Continuum della Sperimentazione Clinica

Quale O?

	Attività	
diuretico	riduzione P.A.	riduzione malatt. C.V.
antidiab. orale	riduz. glicemia	riduz. mortalità
a.infiammat.	az. a.aggregante	riduzione malatt. C.V.
citotossico	riduz. tumorale	riduz. mortalità
citostatico	controllo malattia	riduz. mortalità

Efficacia

Quale O?

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

ABSTRACT

BACKGROUND

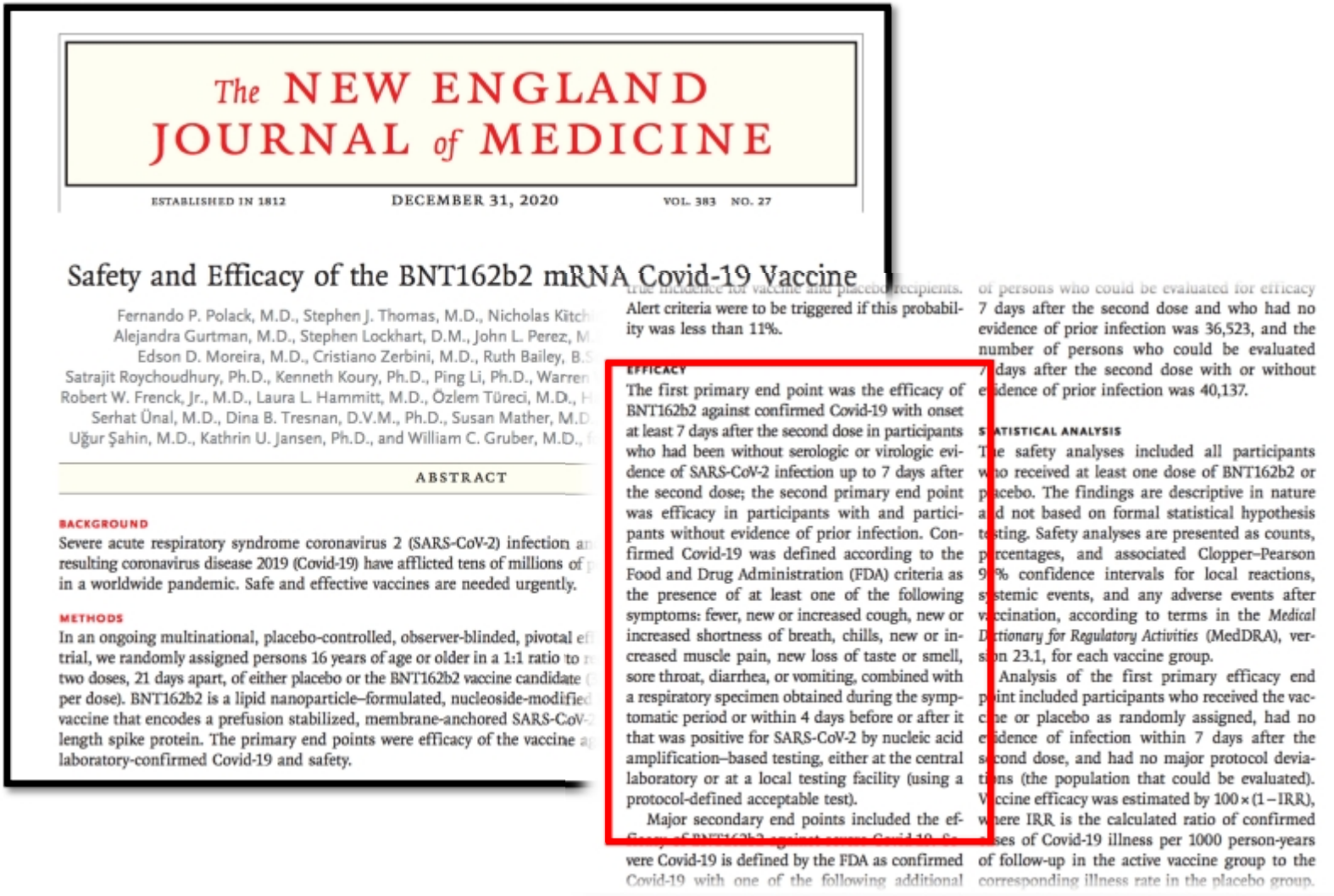
Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

METHODS

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

From Brigham and Women's Hospital Heart and Vascular Center and Harvard Medical School, Boston (D.L.B.); FACT (French Alliance for Cardiovascular Trials), Département Hospitalo-Universitaire FIRE (Fibrose, Inflammation, and Remodeling), Assistance Publique–Hôpitaux de Paris, Hôpital Bichat, Université Paris-Diderot, INSERM Unité 1148, Paris (P.G.S.); National Heart and Lung Institute, Imperial College, Royal Brompton Hospital, London (P.G.S.); the Department of Medicine, University of Maryland School of Medicine, Baltimore (M.M.); the Utah Lipid Center, Salt Lake City (E.A.B.); the Office of Health Promotion and Disease Prevention, Department of Medicine, Emory University School of Medicine

Quale O?



The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 DECEMBER 31, 2020 VOL. 383 NO. 27

Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine

Fernando P. Polack, M.D., Stephen J. Thomas, M.D., Nicholas Kitch
Alejandra Gurtman, M.D., Stephen Lockhart, D.M., John L. Perez, M
Edson D. Moreira, M.D., Cristiano Zerbini, M.D., Ruth Bailey, B.S
Satrajit Roychoudhury, Ph.D., Kenneth Koury, Ph.D., Ping Li, Ph.D., Warren
Robert W. Frenck, Jr., M.D., Laura L. Hammitt, M.D., Özlem Türeci, M.D., H
Serhat Ünal, M.D., Dina B. Tresnan, D.V.M., Ph.D., Susan Mather, M.D
Uğur Şahin, M.D., Kathrin U. Jansen, Ph.D., and William C. Gruber, M.D.,

ABSTRACT

BACKGROUND

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection a
resulting coronavirus disease 2019 (Covid-19) have afflicted tens of m
in a worldwide pandemic. Safe and effective vaccines are needed urgently.

METHODS

In an ongoing multinational, placebo-controlled, observer-blinded, pivotal ef
trial, we randomly assigned persons 16 years of age or older in a 1:1 ratio to r
two doses, 21 days apart, of either placebo or the BNT162b2 vaccine candidate (
per dose). BNT162b2 is a lipid nanoparticle–formulated, nucleoside-modified
vaccine that encodes a prefusion stabilized, membrane-anchored SARS-CoV-2
length spike protein. The primary end points were efficacy of the vaccine a
laboratory-confirmed Covid-19 and safety.

true incidence for vaccine and placebo recipients. Alert criteria were to be triggered if this probability was less than 11%.

EFFICACY

The first primary end point was the efficacy of BNT162b2 against confirmed Covid-19 with onset at least 7 days after the second dose in participants who had been without serologic or virologic evidence of SARS-CoV-2 infection up to 7 days after the second dose; the second primary end point was efficacy in participants with and participants without evidence of prior infection. Confirmed Covid-19 was defined according to the Food and Drug Administration (FDA) criteria as the presence of at least one of the following symptoms: fever, new or increased cough, new or increased shortness of breath, chills, new or increased muscle pain, new loss of taste or smell, sore throat, diarrhea, or vomiting, combined with a respiratory specimen obtained during the symptomatic period or within 4 days before or after it that was positive for SARS-CoV-2 by nucleic acid amplification–based testing, either at the central laboratory or at a local testing facility (using a protocol-defined acceptable test).

Major secondary end points included the efficacy of BNT162b2 against severe Covid-19. Severe Covid-19 is defined by the FDA as confirmed Covid-19 with one of the following additional

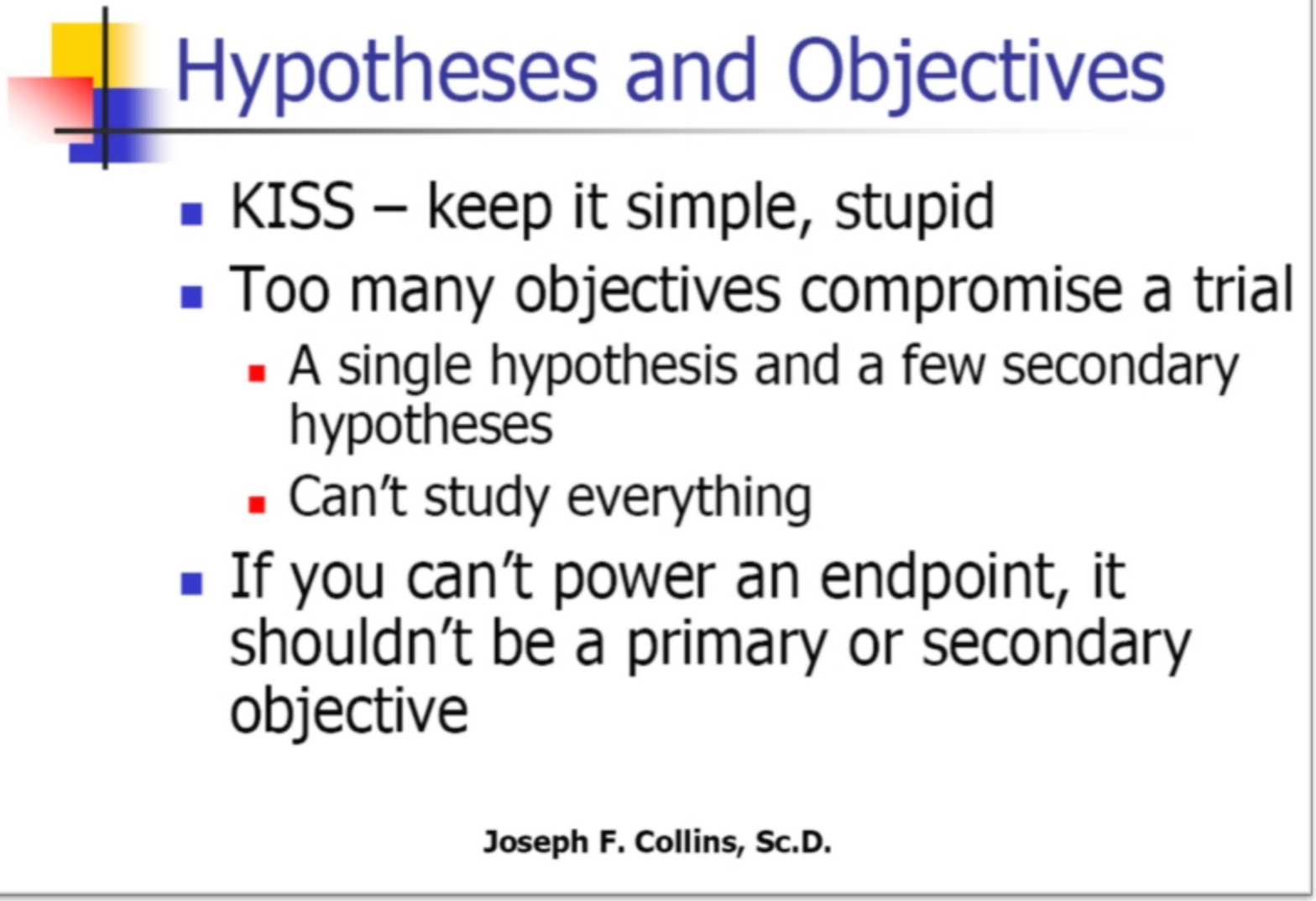
of persons who could be evaluated for efficacy 7 days after the second dose and who had no evidence of prior infection was 36,523, and the number of persons who could be evaluated 7 days after the second dose with or without evidence of prior infection was 40,137.

STATISTICAL ANALYSIS

The safety analyses included all participants who received at least one dose of BNT162b2 or placebo. The findings are descriptive in nature and not based on formal statistical hypothesis testing. Safety analyses are presented as counts, percentages, and associated Clopper–Pearson 95% confidence intervals for local reactions, systemic events, and any adverse events after vaccination, according to terms in the *Medical Dictionary for Regulatory Activities* (MedDRA), version 23.1, for each vaccine group.

Analysis of the first primary efficacy end point included participants who received the vaccine or placebo as randomly assigned, had no evidence of infection within 7 days after the second dose, and had no major protocol deviations (the population that could be evaluated). Vaccine efficacy was estimated by 100×(1−IRR), where IRR is the calculated ratio of confirmed cases of Covid-19 illness per 1000 person-years of follow-up in the active vaccine group to the corresponding illness rate in the placebo group.

OBIETTIVO PRIMARIO

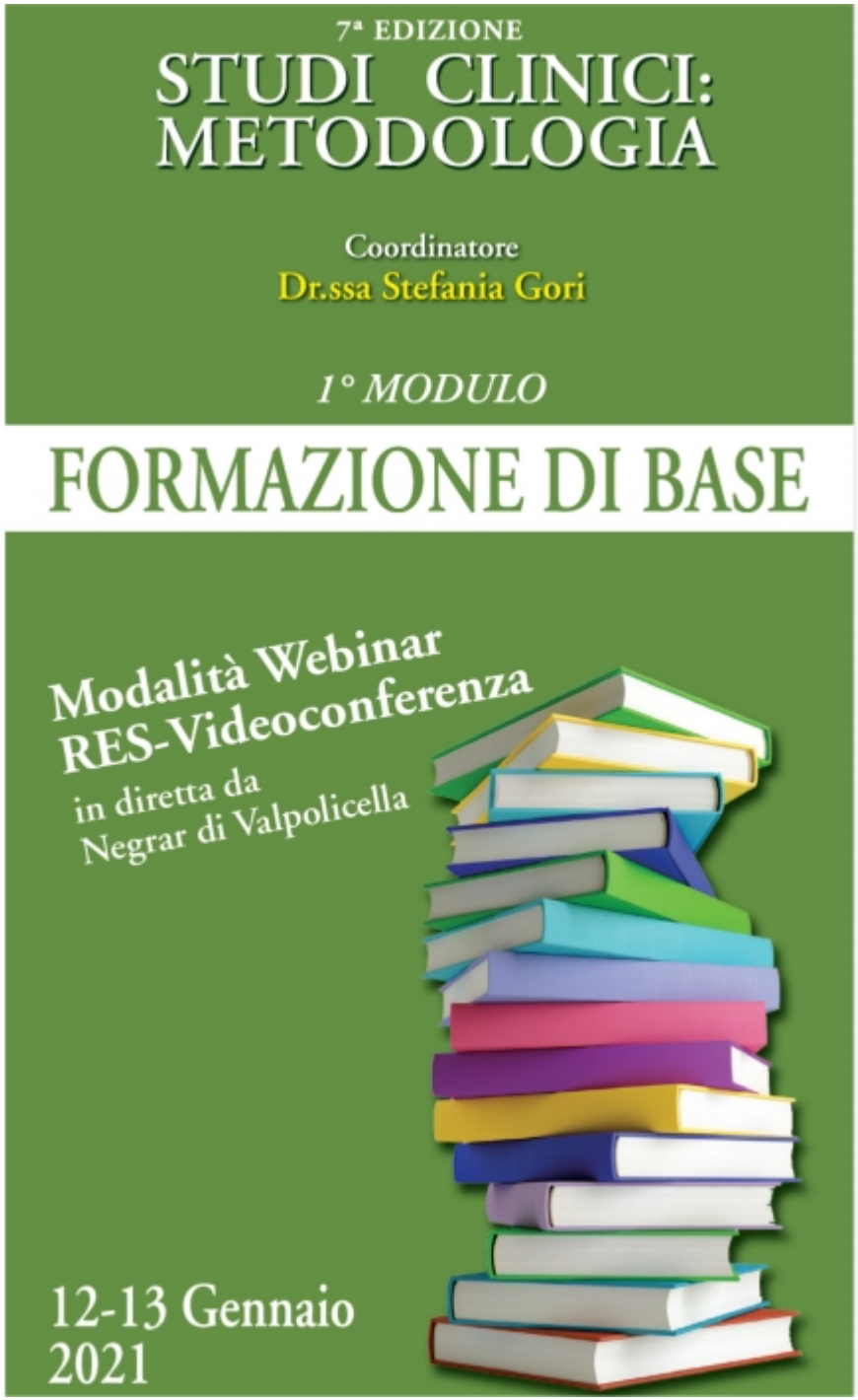


OBIETTIVO PRIMARIO

Hypotheses and Objectives

- KISS – keep it simple, stupid
- Too many objectives compromise a trial
  - A single hypothesis and a few secondary hypotheses
  - Can't study everything

- Common error – Sinking ship: Avoid overloading the study with too many objectives and too much data collection

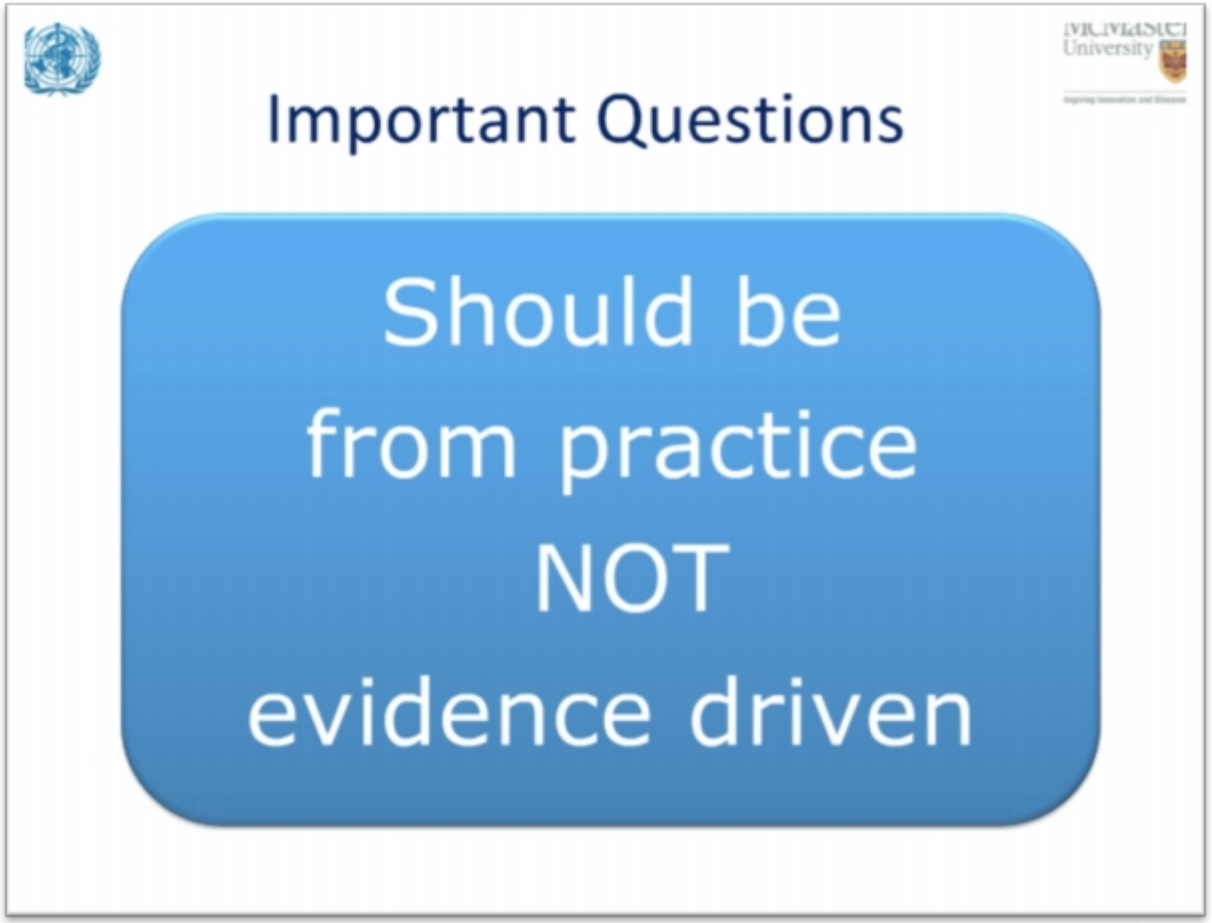


STUDI CLINICI: METODOLOGIA

Plausibilità e rilevanza dello studio

RAZIONALE

Fa#ori da considerare sull'opportunità di una sperimentazione clinica



RAZIONALE

Fa#ori da considerare sull'opportunità di una sperimentazione clinica

1. Gravità dell'affezione/problema
2. Efficacia delle terapie disponibili
3. Tossicità (scomodità) delle terapie disponibili rispetto a quelle alternative
4. Presumibile superiorità delle terapie sperimentali

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Knott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group*

N Engl J Med 2012;366:109-19

APPROXIMATELY 20% OF ALL BREAST CANcers have gene amplification or overexpression (or both) of human epidermal growth factor receptor 2 (HER2),[1] a tyrosine kinase transmembrane receptor, resulting in a more aggressive phenotype and a poor prognosis.

Treatment with the anti-HER2 humanized monoclonal antibody trastuzumab in addition to chemotherapy, as compared with chemotherapy alone, significantly improves progression-free and overall survival among patients with HER2-positive metastatic breast cancer.

However, in most patients with HER2-positive metastatic breast cancer, the disease progresses,[8] highlighting the need for new targeted therapies for advanced disease.

Pertuzumab prevents HER2 from dimerizing with other ligand-activated HER receptors, most notably HER3.

Because pertuzumab and trastuzumab bind to different HER2 epitopes and have complementary mechanisms of action, these two agents, when given together, provide a more comprehensive blockade of HER2 signaling and result in greater antitumor activity than either agent alone in HER2-positive tumor models.

The Clinical Evaluation of Pertuzumab and Trastuzumab (CLEOPATRA) study assessed the efficacy and safety of pertuzumab plus trastuzumab plus docetaxel, as compared with placebo plus trastuzumab plus docetaxel, as first-line treatment for patients with HER2-positive metastatic breast cancer.

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Presumibile superiorità delle terapie sperimentali

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