Farmacologia regolatoria – registrazione dei farmaci

- Base legale delle procedure registrative
  - Tipologia di domanda
    - Domanda completa
    - Domanda semplificata
- Procedure registrative
  - Procedura nazionale pura
  - Procedure europee
    - Mutuo riconoscimento
    - Decentrata
  - Procedura centralizzata
- Variazioni dell'AIC

Base legale delle procedure registrative

- Autorizzazione all'Immissione in Commercio (AIC)
- Direttiva 2001/83/CE
  - Tipologia completa (Art. 8, comma 3)
  - Tipologie semplificate
    - Medicinali generici (Art. 10)
    - Domanda bibliografica (Art. 10 bis)
    - Domanda per associazioni fisse (Art. 10 ter)
    - Domanda basata sul consenso all'uso del dossier (Art. 10 quater).

Tipologia completa Art. 8, comma 3 (in conformità all'Allegato I)

- Dati amministrativi
- Dati tecnici sul medicinale
- Dati relativi all'uso del medicinale
- Risultati delle prove farmaceutiche, precliniche e cliniche
- Riassunto delle Caratteristiche del Prodotto (RCP), Foglio Illustrativo (FI) e modello confezionamento.

Tipologia completa Art. 8, comma 3

- Dichiarazione conformità sperimentazioni cliniche eseguite fuori EU (direttiva 2001/20/CE)
- Certificazione responsabile FVG
- Descrizione sistema FVG e sistema gestione rischi
- Copia AIC ottenuta in altro Stato membro o in Paese terzo e eventuali dinieghi

Allegato I Direttiva 2001/83/CE

- Dossier di registrazione: insieme dei documenti e informazioni strutturati in conformità dell'Allegato I
- 5 moduli
  - Modulo 1: dati amministrativi
  - Modulo 2: riassunti qualità, non clinica e clinica
  - Modulo 3: informazioni chimiche, farmaceutiche, biologiche
  - Modulo 4: relazioni studi non clinici
  - Modulo 5: relazioni studi clinici

Formato comune a tutte le aree ICH

Common Technical Document (CTD)

- Il dossier di registrazione strutturato in 5 moduli prende il nome di *Common Technical Document*, CTD
- Il formato, contenuto e sistema di numerazione dei 5 moduli è definito nel volume 2B dell'EudraLex "*Presentation and Content of the Dossier*"
- Eudralex è la raccolta delle regole che governano i prodotti medicinali in EU

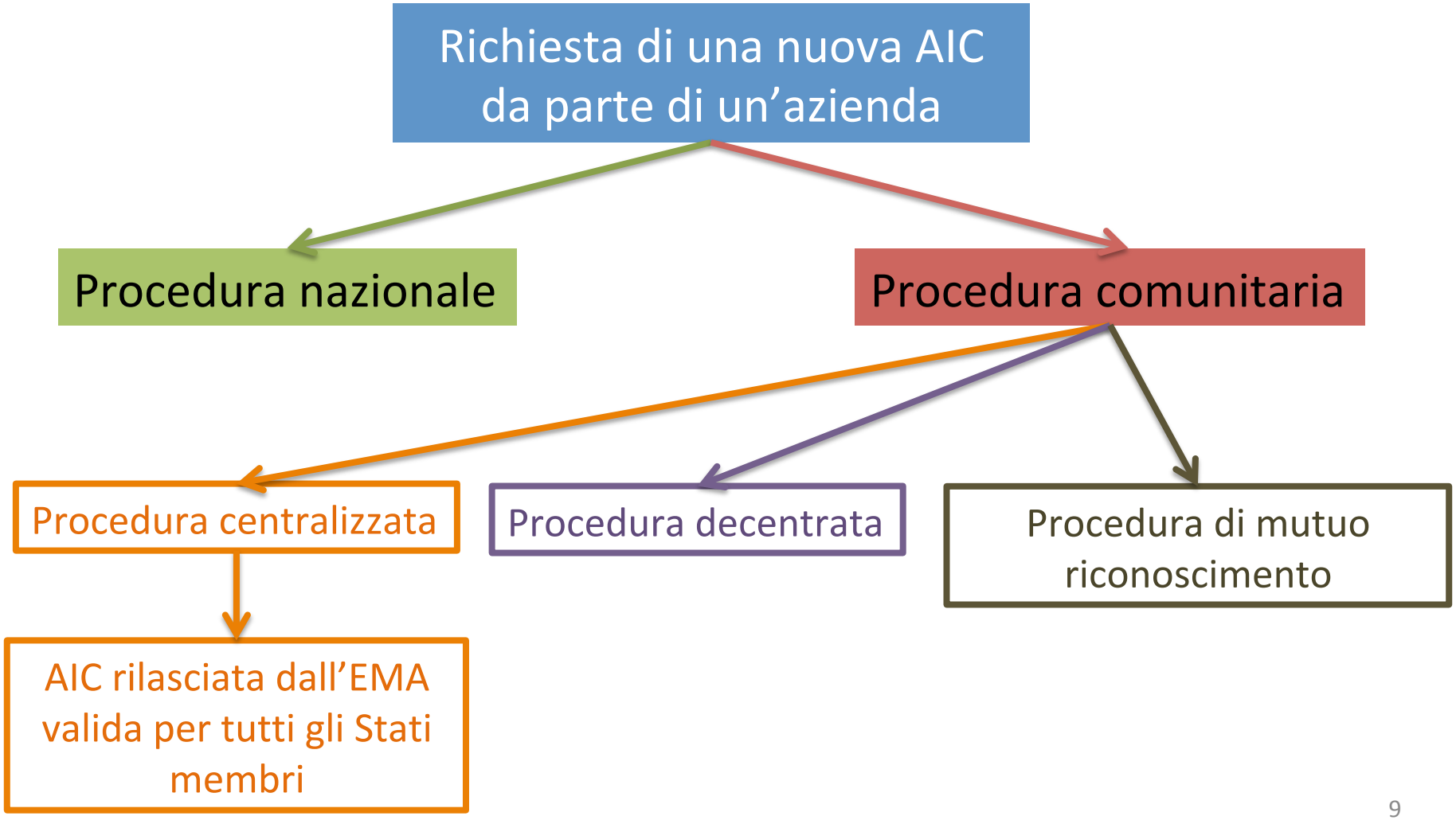
Requisiti per particolari categorie di medicinali

- Allegato I – Parte III definisce i requisiti specifici del dossier per:
  - Medicinali di origine biologica
    - Derivati dal plasma
    - Vaccini
  - Radiofarmaci e precursori
  - Medicinali omeopatici
  - Medicinali a base di erbe
  - Medicinali orfani

Requisiti per medicinali per terapie avanzate

- Allegato I – Parte IV definisce i requisiti specifici del dossier per:
  - Medicinali per terapia cellulare somatica
  - Medicinali per terapia genica
  - Prodotti ingegneria tessutale

Procedure per l'immissione in commercio dei nuovi farmaci



Direttiva 2001/83/EC

- AIC è rilasciata da Autorità Competente **nazionale**
- Recepita in Italia con Dlvo 219/2006
- Normativa di riferimento per procedure:
  - Nazionale pura
  - Europee (mutuo riconoscimento/decentrata)

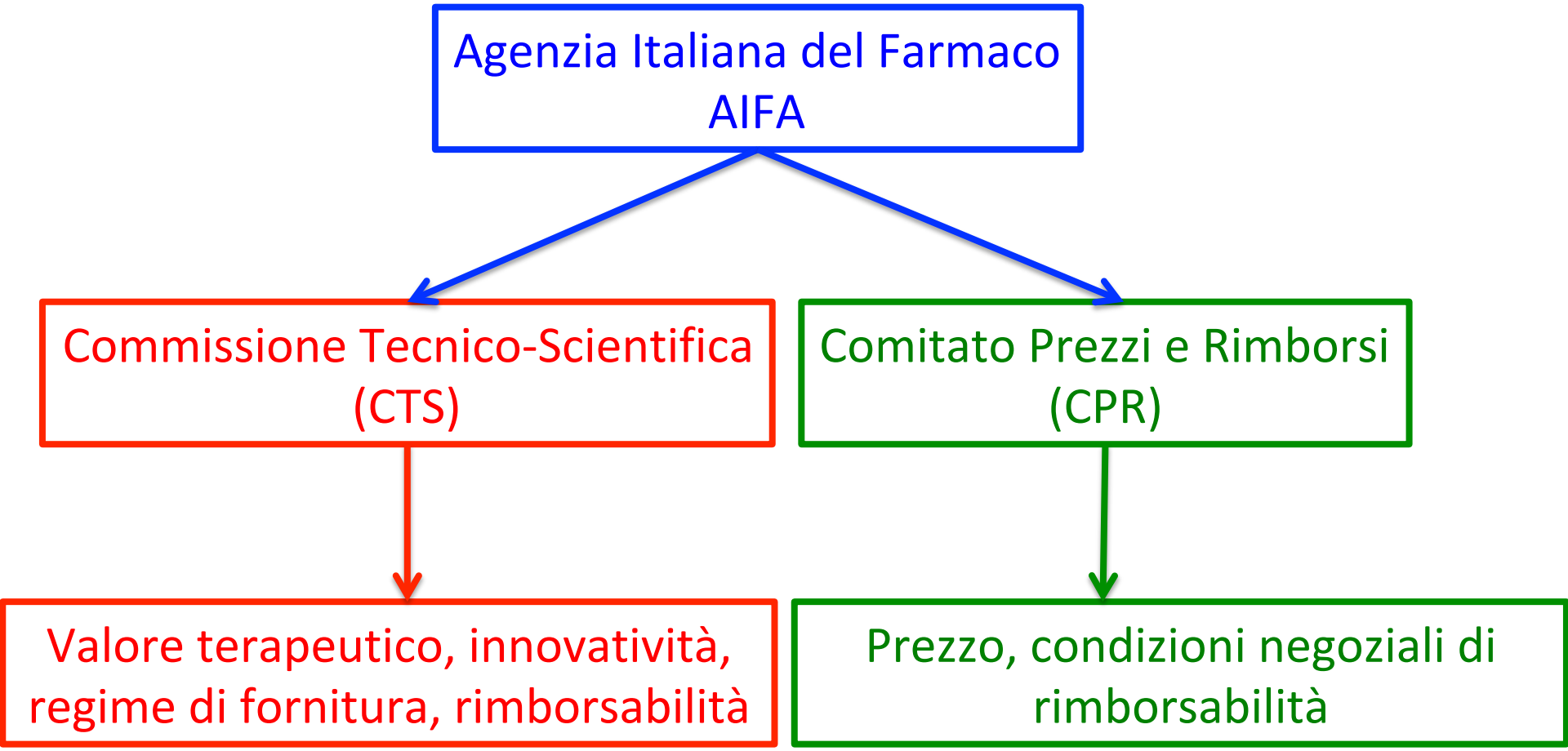
Regolamento 726/2004

- AIC è rilasciata da Autorità Competente **centrale** (Commissione Europea)
- Normativa di riferimento per la procedura centralizzata
- Direttamente applicabile in ciascuno degli Stati Membri

Procedura nazionale pura

- AIC valida esclusivamente sul territorio italiano
- Domanda presentata ad AIFA che la valuta con il supporto della Commissione Tecnico-Scientifica (CTS)
- AIC nazionale rilasciata da AIFA
- Non applicabile se:
  - I medicinali rientrano nello scopo obbligatorio della procedura centralizzata
  - Lo stesso dossier è già stato valutato o in corso di valutazione in altro stato membro (mutuo riconoscimento/decentrata)

Organismi di valutazione nazionali



AIFA
Agenzia Italiana del Farmaco

- Ente pubblico, sotto la direzione e la vigilanza del Ministero della Salute e dell'Economia
- Autorevolezza e autonomia supportate da due Commissioni tecnico-scientifiche composte da esperti (esterni) di comprovata e documentata esperienza nel settore:
  - Commissione Tecnico-Scientifica (CTS)
  - Comitato Prezzi e Rimborso (CPR)

AIFA
Agenzia Italiana del Farmaco

- Commissione Tecnico-Scientifica:
  - Attività connesse alle domande di AIC di nuovi medicinali (rischio/beneficio, costo/efficacia)
- Comitato Prezzi e Rimborso:
  - Attività connessa alla rimborsabilità dei farmaci

Sottomissione della domanda

- Il richiedente presenta ad AIFA una domanda corredata di tutte le informazioni e i documenti in accordo alla normativa (Direttiva 2001/83/CE recepita dal Dlvo 219/2006)
- AIFA adotta le proprie determinazioni entro 210 giorni dalla ricezione di una domanda valida

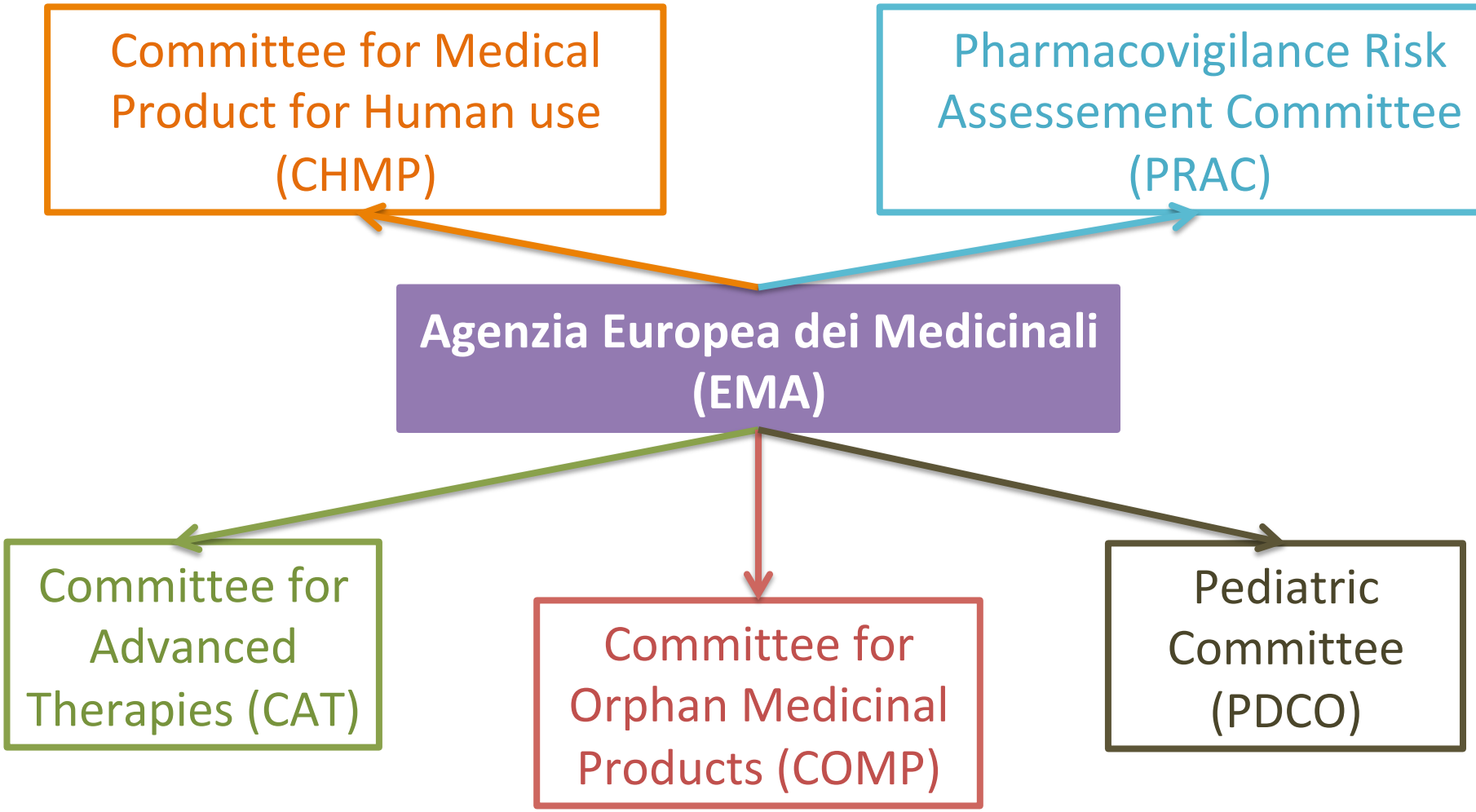
Sottomissione della domanda

- Validazione della domanda
- Istruttoria
- Parere della CTS ➔ *assessement report*
- Ratifica da parte del Consiglio di Amministrazione (Determinazione di AIC)
- Notifica al titolare, allegando RCP, FI, etichettatura
- L'estratto della Determinazione di AIC è pubblicato nella Gazzetta Ufficiale
- Prezzo e rimborsabilità

Sottomissione della domanda

- AIC in circostanze eccezionali rilasciata solo per ragioni obiettive e verificabili riportate nell'Allegato I, Parte II del Dlvo 219/2006
- Diniego dell'AIC:
  - Rapporto rischio/beneficio non favorevole
  - Efficacia terapeutica non sufficientemente documentata
  - Medicinale non presenta la composizione qualitativa e quantitativa dichiarata
  - Il richiedente può presentare opposizione

Organismo di valutazione europeo



Procedure registrative europee

- AIC nazionale in più Stati membri della CE, scelti dal richiedente
- Domanda basata sullo stesso dossier in ciascuno degli Stati membri in cui si vuole ottenere AIC
- Valutazione effettuata da Autorità Competente di uno Stato Membro di Riferimento (RMS) e riconosciuta da uno o più Stati membri interessati (Concerned Member States, CMSs)

Procedure registrative europee

- Procedura di mutuo riconoscimento (MRP)
- Procedura decentrata (DCP)

- Si differenziano per lo stato autorizzativo del medicinale al momento della domanda

Procedura di mutuo riconoscimento (MRP)

- Il medicinale ha già ottenuto l'AIC in uno Stato membro che assume il ruolo di Reference Member State (RMS)
- Il titolare sottomette la domanda negli Stati membri in cui vuole ottenere l'AIC – Concerned Member States (CMSs) – che riconoscono l'AIC già rilasciata da RMS
- Uso ripetuto della MRP

Procedura decentrata (DCP)

- Il medicinale non è mai stato autorizzato in nessun Stato membro
- Il richiedente sceglie lo Stato membro che avrà il ruolo di RMS
- La domanda è sottomessa contemporaneamente nel RMS e nei CMSs in cui vuole ottenere l'AIC

Procedura centralizzata

- Unica AIC comunitaria valida contemporaneamente in tutti gli Stati membri della CE
- Unica domanda di autorizzazione all'Agenzia Europea dei Medicinali (EMA)
- Valutazione tramite *Committee for Medicinal Products for Human Use* (CHMP) che tiene in considerazione le raccomandazioni del *Pharmacovigilance Risk Assessement Committee* (PRAC)
- AIC rilasciata da Commissione Europea in qualità di Autorità Competente centrale (*EC decision*)

Procedura centralizzata

- E’ obbligatoria per:
  - Medicinali derivanti da procedimenti biotecnologici
  - Medicinali per terapie avanzate:
    - Terapia cellulare somatica
    - Terapia genica
    - Prodotti ingegneria tissutale
  - Medicinali orfani
  - Medicinali contenenti una nuova sostanza attiva^ per il trattamento di: AIDS, cancro, disordini neurodegenerativi, diabete, malattie autoimmuni e altre disfunzioni immunitarie, malattie virali

^ non autorizzata nella CE alla data 20/11/2005 di entrata in vigore del regolamento 726/2004

Procedura centralizzata

- E’ opzionale per:
  - Qualsiasi altro medicinale che non rientra nelle categorie precedenti e **può** essere autorizzato secondo procedura centralizzata **se** soddisfa una delle seguenti condizioni:
    - Contiene una nuova sostanza attiva
    - Costituisce un’innovazione significativa sul piano terapeutico, scientifico o tecnico o il rilascio di un’autorizzazione centralizzata è nell’interesse dei pazienti

Procedura centralizzata

- Attività precedenti la sottomissione
  - *Scientific advice*
  - *Letter of intent*
- Esito della ammissibilità alla procedura centralizzata
  - Rapporteur/Co-Rapporteur
  - Product Team
  - CHMP
  - PRAC
- Presentazione della domanda
- Validazione della domanda
- Avvio della procedura: EMA assicura il rilascio di un parere entro 210 gg dall'inizio della procedura (esclusi i clock-stop)
- Valutazione
- Eventuale riesame: entro 15 gg comunicare l'intenzione, entro 60 gg richiedere il riesame

Procedura centralizzata

- A procedura conclusa la Commissione Europea adotta una decisione definitiva che viene pubblicata nella Gazzetta Ufficiale dell'Unione Europea ed include la data di autorizzazione e il numero di iscrizione nel registro comunitario

- In seguito all'adozione della EC Decision L'EMA pubblica l'EPAR (*Electronic Public Assessement Report*) sul proprio sito web

- L'EPAR è il CHMP *Assessment Report* privo delle informazioni commerciali a carattere riservato e contiene un sommario comprensibile per il pubblico

- Prima della commercializzazione in Italia, deve essere stabilito il regime di fornitura, il prezzo e le condizioni per la eventuale rimborsabilità a carico del SSN

Classi di rimborsabilità del Sistema Sanitario Nazionale (SSN)

	Classi di rimborsabilità
Fascia A	Rimborsati dal SSN con o senza Nota AIFA^ (con o senza Piano Terapeutico)
Fascia H	Rimborsati dal SSN e dispensabili in ambito ospedaliero o in strutture assimilabili
Fascia C	Non rimborsati dal SSN
Fascia C non negoziata (Cnn)	Medicinali automaticamente inseriti in questa classe dopo aver ricevuto l'AIC in attesa della negoziazione di prezzo/ rimborso

^ le Note AIFA limitano la rimborsabilità di alcuni medicinali sulla base delle migliori prove di efficacia presenti in letteratura, in modo da garantirne un uso appropriato. La Nota consente il rimborso nelle sole condizioni rilevanti e per quei pazienti con maggiore necessità. Sono periodicamente revisionate per adattarsi alle nuove evidenze scientifiche

Sistemi di accesso accelerato – *unmet clinical needs*

Conditional marketing authorization (CMA) EMA

- Possibile finché non siano disponibili dati a conferma del rapporto beneficio/ rischio a supporto di una normale autorizzazione
- Validità annuale rinnovabile

Approval under exceptional circumstances EMA

- Farmaci per patologia molto rare

Breakthrough therapy FDA

- Quando le evidenze cliniche preliminari indicano un possibile sostanziale miglioramento di un endpoint clinicamente significativo (morbidità irreversibile, mortalità, sintomi gravi)

Adaptive licensing EMA & FDA

- Meccanismi graduali e progressivi di autorizzazione all'immissione in commercio di nuovi farmaci per importanti unmet medical needs
- Periodica rivalutazione del profilo beneficio/rischio nella fase post-marketing.

Meccanismi di accesso rapido attivi in EU o USA

Meccanismi di accesso rapido	
Accelerated Approval (AA)	FDA/USA
Priority review	FDA/USA
Fast track	FDA/USA
Breakthrough therapy	FDA/USA
Conditional Marketing Authorization (CMA)^	EMA/EU
Approval under exceptional circumstances	EMA/EU
Accelerated assessement	EMA/EU
Adaptive licensing	EMA/FDA

^ utilizzata da BioNTech e Pfizer per la domanda di autorizzazione per il vaccino COVID-19 mRNA BNT162b2 presentata all'EMA

EMA's human medicines committee (CHMP) and its experts have been working intensively over the past weeks to evaluate data submitted by BioNTech and Pfizer in the context of the conditional marketing authorisation (CMA) application for BNT162b2, a COVID-19 mRNA vaccine.

EMA, its European experts and the European Commission are working towards the first marketing authorisation of a COVID-19 vaccine, with all the safeguards, controls and obligations that a CMA imposes, including:

- full prescribing information and package leaflet with detailed instructions for safe use;
- a robust risk-management and safety monitoring plan;
- manufacturing controls including batch controls for vaccines and conditions for storage;
- an investigation plan for use in children;
- legally binding post-approval obligations (i.e. conditions) and a clear legal framework for evaluation of emerging efficacy and safety data.

A marketing authorisation ensures that COVID-19 vaccines meet the same high EU standards as for all vaccines and medicines. It will be valid in all EU Member States at the same time enabling all Member States to benefit from the joint work done at EU level and allowing them to start rolling out their vaccination campaigns at the same time.

EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

EMA recommends first COVID-19 vaccine for authorisation in the EU

News 21/12/2020

EMA has recommended granting a conditional marketing authorisation for the vaccine Comirnaty, developed by BioNTech and Pfizer, to prevent coronavirus disease 2019 (COVID-19) in people from 16 years of age. EMA's scientific opinion paves the way for the first marketing authorisation of a COVID-19 vaccine in the EU by the European Commission, with all the safeguards, controls and obligations this entails.

EMA's human medicines committee (CHMP) has completed its rigorous evaluation of Comirnaty, concluding by consensus that sufficiently robust data on the quality, safety and efficacy of the vaccine are now available to recommend a formal conditional marketing authorisation. This will provide a controlled and robust framework to underpin EU-wide vaccination campaigns and protect EU citizens.

"Our thorough evaluation means that we can confidently assure EU citizens of the safety and efficacy of this vaccine and that it meets necessary quality standards. However, our work does not stop here. We will continue to collect and analyse data on the safety and effectiveness of this vaccine to protect people taking the vaccine in the EU."

A very large clinical trial showed that Comirnaty was effective at preventing COVID-19 in people from 16 years of age.

The trial involved around 44,000 people in total. Half received the vaccine and half were given a dummy injection. People did not know whether they received the vaccine or the dummy injection.

Efficacy was calculated in over 36,000 people from 16 years of age (including people over 75 years of age) who had no sign of previous infection. The study showed a 95% reduction in the number of symptomatic COVID-19 cases in the people who received the vaccine (8 cases out of 18,198 got COVID-19 symptoms) compared with people who received a dummy injection (162 cases out of 18,325 got COVID-19 symptoms). This means that the vaccine demonstrated a 95% efficacy in the clinical trial.

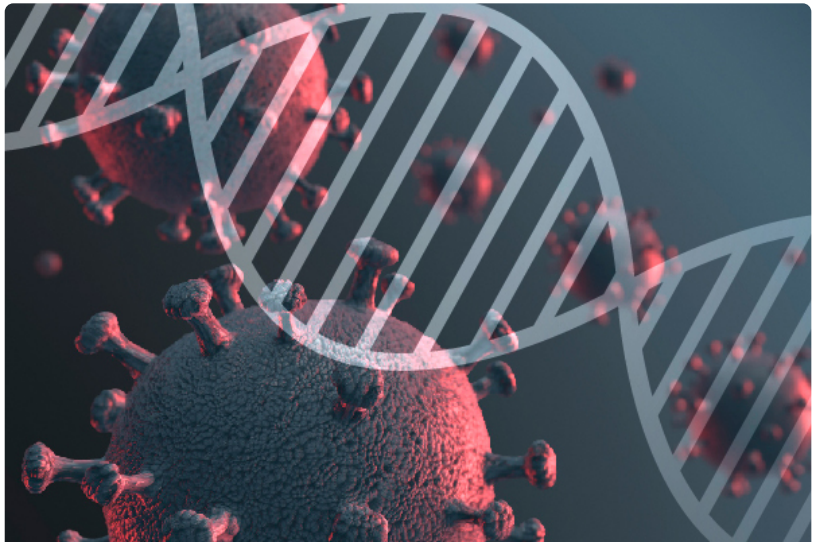
Comirnaty is given as two injections into the arm, at least 21 days apart. The most common side effects with Comirnaty were usually mild or moderate and got better within a few days after vaccination. They included pain and swelling at the injection site, tiredness, headache, muscle and joint pain, chills and fever. The safety and effectiveness of the vaccine will continue to be monitored as it is used across the Member States, through the EU pharmacovigilance system and additional studies by the company and by European authorities.

Where to find more information

The product information approved by the CHMP for Comirnaty contains prescribing information for healthcare professionals, a package leaflet for members of the public and details of conditions of the vaccine's authorisation.

An assessment report, with details of EMA's evaluation of Comirnaty, and the full risk management plan will be published within days. Clinical trial data submitted by the company in the application for marketing authorisation will be published on the Agency's Clinical data website in due course.

Save the date - Conferenza stampa congiunta del Direttore Generale e del Presidente dell'AIFA



Martedì 22 dicembre alle 16.30 Nicola Magrini e Giorgio Palù, Direttore Generale e Presidente dell'Agenzia Italiana del Farmaco, terranno una conferenza stampa congiunta sul tema dei vaccini COVID-19.

La conferenza sarà trasmessa in diretta sul canale YouTube dell'AIFA e potrà essere seguita attraverso il link https://youtu.be/TKlyg47KPgA .

Variazioni dell'AIC

- Il titolare deve:
  - Assicurare la conformità ai termini e contenuti dell'AIC
  - Tenere conto dei progressi scientifici e tecnici nei metodi di produzione e di controllo
  - Informare l'Autorità Competente di ogni nuovo dato che può implicare modifiche delle informazioni/documenti presentati a supporto della domanda di AIC

Variazioni dell'AIC

- Riferimenti normativi:

Procedura AIC	Normativa
Centralizzata	Regolamento 1234/2008
Mutuo riconoscimento/Decentrata	Regolamento 1234/2008
Nazionale pura	Determina AIFA 18 dicembre 2009 Dal 1 gennaio 2010 AIFA applica il Regolamento 1234/2008 anche alle variazioni nazionali

Il regolamento 1234/2008 riporta la definizione generale delle diverse tipologie di variazioni e la loro classificazione (negli allegati del regolamento)

Variazioni dell'AIC

- Le variazioni sono classificate in funzione del livello di rischio per la salute pubblica e dell'impatto sulla qualità, sicurezza ed efficacia del medicinale
- Il regolamento 1234/2008 riporta la definizione, la classificazione e gli esempi pratici delle diverse tipologie di variazioni

Classificazione delle variazioni

- Impatto:
  - Minimo o nullo
    - Variazioni minori
  - Significativo
    - Variazioni maggiori
    - Estensioni

LINK UTILI

- Sito EMA, sezione dedicata alle procedure regolatorie per i medicinali per uso umano https://www.ema.europa.eu/en/human-medicines-regulatory-information
- Sito CMDh, sezione dedicata ai medicinali per uso umano http://www.hma.eu/cmdh.html
- Sito commissione Europea, sezione dedicata all'EudraLex https://ec.europa.eu/health/documents/eudralex_en

Trial clinico
- un esempio -

JAMA | **Original Investigation**

Effect of High-Dose Omega-3 Fatty Acids vs Corn Oil on Major Adverse Cardiovascular Events in Patients at High Cardiovascular Risk
The STRENGTH Randomized Clinical Trial

Stephen J. Nicholls, MBBS, PhD; A. Michael Lincoff, MD; Michelle Garcia, RN, BSN, CCRC; Dianna Bash, BSN; Christie M. Ballantyne, MD; Philip J. Barter, MBBS, PhD; Michael H. Davidson, MD; John J. P. Kastelein, MD, PhD; Wolfgang Koenig, MD; Darren K. McGuire, MD, MHSc; Dariush Mozaffarian, MD, DrPH; Paul M Ridker, MD; Kausik K. Ray, MBChB, MD, MPhil; Brian G. Katona, PharmD; Anders Himmelmann, MD, PhD; Larrye E. Loss, PharmD, MBA; Martin Rensfeldt; Torbjörn Lundström, MD, PhD; Rahul Agrawal, MD; Venu Menon, MD; Kathy Wolski, MPH; Steven E. Nissen, MD

IMPORTANCE It remains uncertain whether the omega-3 fatty acids eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) reduce cardiovascular risk.

OBJECTIVE To determine the effects on cardiovascular outcomes of a carboxylic acid formulation of EPA and DHA (omega-3 CA) with documented favorable effects on lipid and inflammatory markers in patients with atherogenic dyslipidemia and high cardiovascular risk.

DESIGN, SETTING, AND PARTICIPANTS A double-blind, randomized, multicenter trial (enrollment October 30, 2014, to June 14, 2017; study termination January 8, 2020; last patient visit May 14, 2020) comparing omega-3 CA with corn oil in statin-treated participants with high cardiovascular risk, hypertriglyceridemia, and low levels of high-density lipoprotein cholesterol (HDL-C). A total of 13 078 patients were randomized at 675 academic and community hospitals in 22 countries in North America, Europe, South America, Asia, Australia, New Zealand, and South Africa.

INTERVENTIONS Participants were randomized to receive 4 g/d of omega-3 CA (n = 6539) or corn oil, which was intended to serve as an inert comparator (n = 6539), in addition to usual background therapies, including statins.

MAIN OUTCOMES AND MEASURES The primary efficacy measure was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina requiring hospitalization.

RESULTS When 1384 patients had experienced a primary end point event (of a planned 1600 events), the trial was prematurely halted based on an interim analysis that indicated a low probability of clinical benefit of omega-3 CA vs the corn oil comparator. Among the 13 078 treated patients (mean [SD] age, 62.5 [9.0] years; 35% women; 70% with diabetes; median low-density lipoprotein [LDL] cholesterol level, 75.0 mg/dL; median triglycerides level, 240 mg/dL; median HDL-C level, 36 mg/dL; and median high-sensitivity C-reactive protein level, 2.1 mg/L), 12 633 (96.6%) completed the trial with ascertainment of primary end point status. The primary end point occurred in 785 patients (12.0%) treated with omega-3 CA vs 795 (12.2%) treated with corn oil (hazard ratio, 0.99 [95% CI, 0.90-1.09]; *P* = .84). A greater rate of gastrointestinal adverse events was observed in the omega-3 CA group (24.7%) compared with corn oil–treated patients (14.7%).

CONCLUSIONS AND RELEVANCE Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

TRIAL REGISTRATION ClinicalTrials.gov Identifier: NCT02104817

Question In statin-treated patients with high cardiovascular risk, high triglycerides, and low HDL cholesterol levels, does adding a carboxylic acid formulation of omega-3 fatty acids (eicosapentaenoic acid and docosahexaenoic acid) to background therapy improve cardiovascular outcomes?

Domanda alla quale lo studio vuole rispondere

Tipo di studio

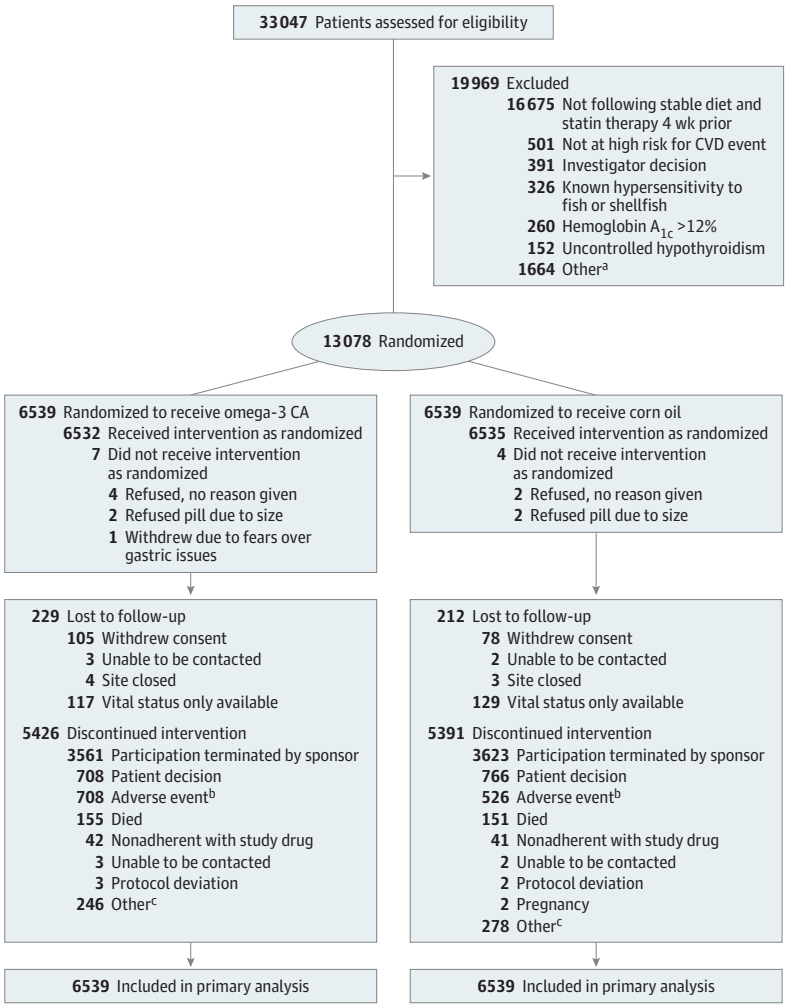
End-point composito

Numero di registrazione del trial

JAMA. 2020;324(22):2268-2280. doi:10.1001/jama.2020.22258
Published online November 15, 2020.

Flow diagram del trial in accordo alle raccomandazioni CONSORT

Figure 1. Recruitment, Randomization, and Patient Flow in the STRENGTH Clinical Trial



CA indicates carboxylic acid formulation; CVD, cardiovascular disease.

[a] Other reasons for not meeting inclusion/exclusion criteria include not meeting age requirement; elevated liver enzymes; use of fibrates, bile acid sequestrants, or niacin within 4 weeks of randomization; not following a stable diet; poorly controlled hypertension; and occurrence of myocardial infarction or coronary bypass graft surgery within 30 days of randomization.

[b] Adverse events leading to study drug discontinuation by system organ class (omega-3 CA/corn oil; multiple events are possible): gastrointestinal (403/202), neoplasms (81/78), cardiac (39/46), nervous system (36/42), infections (32/30), skin (24/20), kidney/urinary (16/25), investigations (21/14), metabolic disorders (18/17), musculoskeletal (14/18), hepatobiliary (13/14), injury (11/13), vascular (13/11), respiratory (13/10), and psychiatric (11/7).

[c] Other reasons abstracted from free text (omega-3 CA/corn oil): investigator decision (22/22), patient decision (26/33), potential lost to follow-up (113/129), reached end point (18/18), moved (31/36), social reasons (7/13), comorbid condition (11/8), pill burden (5/10), study terminated (9/4), and site closed (4/5).

Table 1. Patient Characteristics and Medication Use in a Trial of Omega-3 Fatty Acids to Reduce Major Adverse Cardiovascular Events

	No. (%)	
	Omega-3 CA (n = 6539)	Corn oil (n = 6539)
Age, mean (SD), y	62.5 (9.0)	62.5 (9.0)
Sex		
Male	4250 (65.0)	4260 (65.1)
Female	2289 (35.0)	2279 (34.9)
Body mass index, mean (SD)	32.2 (5.7)	32.2 (5.6)
Race		
White	5341 (81.7)	5382 (82.3)
Asian	698 (10.7)	657 (10.0)
Black	180 (2.8)	166 (2.5)
Other[a]	320 (4.9)	334 (5.1)
Ethnicity: Hispanic or Latino	264/4647 (5.7)	268/4675 (5.7)
Comorbidities		
Established CVD at baseline	3638 (55.6)	3678 (56.2)
Coronary disease	3009 (46.0)	3026 (46.3)
Cerebrovascular disease	536 (8.2)	512 (7.8)
Peripheral vascular disease	227 (3.5)	257 (3.9)
Aortic disease	214 (3.3)	244 (3.7)
Diabetes at baseline[b]	4608 (70.5)	4562 (69.8)
Hypertension	5732 (87.7)	5688 (87.0)
eGFR,[c] mean (SD), mL/min/1.73 m^2	77.2 (19.9)	77.5 (19.7)
Medication use		
RAAS blockers	5315 (81.3)	5310 (81.2)
Antiplatelet agents	4623 (70.7)	4700 (71.9)
β-Blockers	4347 (66.5)	4348 (66.5)
High-intensity statin	3255 (49.8)	3273 (50.1)
Other statin	3284 (50.2)	3266 (49.9)
Ezetimibe	234 (3.6)	245 (3.7)

Abbreviations: CA, carboxylic acid formulation; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; RAAS, renin-angiotensin aldosterone system.

[a] The "other" category included American Indian or Alaska Native; Native Hawaiian or other Pacific Islander; multiple races; and unknown.

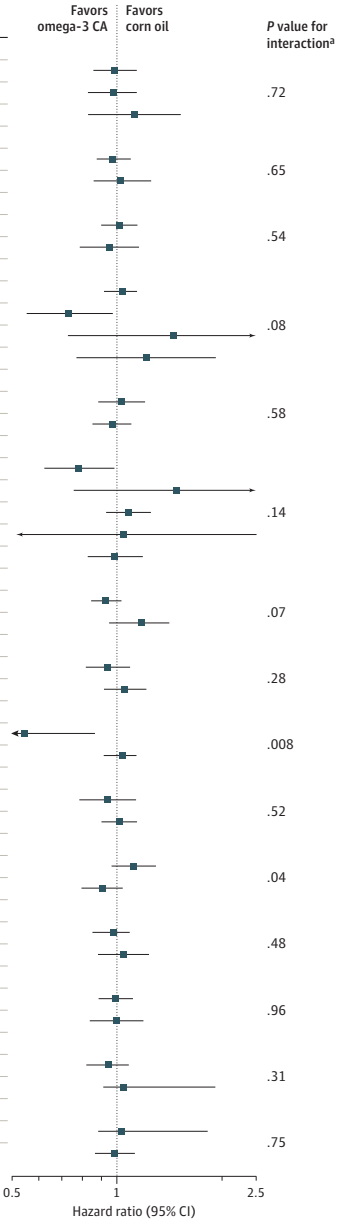
[b] Diabetes on or before the first dose of study medication, defined by patient self-report, chart review, or use of diabetes medications.

[c] Estimated glomerular filtration rate was estimated using the CKD-EPI formula: eGFR = 141 × min(SCr/κ, 1)α × max(SCr /κ, 1) − 1.209 × 0.993Age × 1.018 [if female] × 1.159 [if Black]; where k = 0.7 for females or 0.9 for males and α = −0.329 for females or −0.411 for males.

Le caratteristiche dei pazienti

Figure 3. Effect of Omega-3 CA on the Primary Composite Cardiovascular End Point in Prespecified Subgroups

Subgroup	Omega-3 CA			Corn oil			Absolute rate difference	Hazard ratio (95% CI)	*P* value for interaction[a]
	No. of events	Total person-years	Events per 100 person-years	No. of events	Total person-years	Events per 100 person-years			
Age at baseline, y									
<65	391	12721	3.07	390	12493	3.12	-0.05	0.98 (0.85-1.13)	.72
65-75	305	7642	3.99	327	7964	4.11	-0.12	0.97 (0.83-1.14)	
>75	89	1545	5.76	78	1463	5.33	0.43	1.12 (0.82-1.51)	
Diabetes on or before the first dose of study medication									
Yes	565	15452	3.67	576	15345	3.75	-0.08	0.97 (0.87-1.09)	.65
No	220	6456	3.41	219	6576	3.33	0.08	1.02 (0.85-1.24)	
Sex									
Men	583	14132	4.13	579	14163	4.09	0.04	1.01 (0.90-1.13)	.54
Women	202	7776	2.60	216	7758	2.78	-0.18	0.94 (0.78-1.14)	
Race									
White	644	18085	3.56	644	18246	3.53	0.03	1.02 (0.91-1.13)	.08
Asian	81	2234	3.63	103	2028	5.08	-1.45	0.72 (0.54-0.96)	
Black	22	579	3.80	14	540	2.59	1.21	1.44 (0.73-2.81)	
Other	38	996	3.81	33	1073	3.08	0.73	1.20 (0.76-1.91)	
BMI at baseline									
<30	309	8341	3.70	297	8126	3.66	0.04	1.03 (0.88-1.20)	.58
≥30	475	13552	3.51	496	13780	3.60	-0.09	0.97 (0.85-1.10)	
Region									
Asia	134	3457	3.88	166	3364	4.93	-1.05	0.78 (0.62-0.98)	.14
Australia and New Zealand	21	441	4.76	14	442	3.17	1.59	1.48 (0.75-2.90)	
Europe	384	11755	3.27	359	11771	3.05	0.22	1.07 (0.93-1.24)	
Latin America	11	474	2.32	11	506	2.17	0.15	1.03 (0.45-2.37)	
North America	235	5781	4.06	245	5838	4.20	-0.14	0.98 (0.82-1.18)	
Established CVD at baseline									
Yes	569	11695	4.87	610	11751	5.19	-0.32	0.94 (0.84-1.05)	.07
No	216	10214	2.11	185	10169	1.82	0.29	1.16 (0.95-1.41)	
Statin use at baseline									
High intensity	371	10905	3.40	393	10944	3.59	-0.19	0.94 (0.81-1.08)	.28
Other	414	11003	3.76	402	10976	3.66	0.10	1.04 (0.91-1.20)	
Ezetimibe at baseline									
Yes	29	795	3.65	49	768	6.38	-2.73	0.54 (0.34-0.86)	.008
No	756	21114	3.58	746	21152	3.53	0.05	1.02 (0.92-1.13)	
eGFR at baseline, mL/min BSA									
<60	223	4185	5.33	231	4047	5.71	-0.38	0.94 (0.78-1.13)	.52
≥60	562	17716	3.17	564	17869	3.16	0.01	1.01 (0.90-1.13)	
hsCRP at baseline, mg/dL									
<0.2	381	10483	3.63	348	10702	3.25	0.38	1.11 (0.96-1.28)	.04
≥0.2	404	11425	3.54	447	11218	3.98	-0.44	0.90 (0.79-1.03)	
Non-HDL-C at baseline, mg/dL									
<140	505	14394	3.51	516	14169	3.64	-0.13	0.97 (0.85-1.09)	.48
≥140	280	7515	3.73	279	7752	3.60	0.13	1.04 (0.88-1.23)	
Triglycerides at baseline, mg/dL									
<300	562	15905	3.53	566	15794	3.58	-0.05	0.99 (0.88-1.11)	.96
≥300	223	6003	3.71	229	6127	3.74	-0.03	0.99 (0.83-1.19)	
VLDL									
<46	347	10373	3.35	368	10283	3.58	-0.23	0.94 (0.81-1.08)	.31
≥46	414	10844	3.82	403	10934	3.69	0.13	1.04 (0.91-1.91)	
Apolipoprotein CIII									
<16	346	9980	3.47	338	9890	3.42	0.05	1.02 (0.88-1.81)	.75
≥16	433	11634	3.72	446	11802	3.78	-0.06	0.98 (0.86-1.12)	



BSA, body surface area; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; and VLDL, very low-density lipoprotein. SI conversion factors are in Table 4.

[a] *P* value estimated using a Cox proportional hazards model with factors for treatment, established cardiovascular status at baseline, region, subgroup (only if not one of the covariates), and treatment × subgroup interaction in the model.

I risultati

Il ruolo del Data Monitoring Committee

Early Trial Termination

On January 8, 2020, when 1384 primary end points had been recorded in 13 078 randomized patients, the independent DMC recommended termination of the trial due to a low probability of demonstrating a clinical benefit of omega-3 CA compared with corn oil. This decision was based on the data crossing the futility boundary prespecified in the group sequential monitoring plan in conjunction with an increased risk of atrial fibrillation (oral communication, DMC chair Mark Pfeffer, MD, PhD, to executive committee chair Steven E. Nissen, MD, August 2020). The executive steering committee and sponsor accepted this recommendation and terminated the trial on this date, and patients were recommended to stop study medication. End-of-study visits were scheduled for all patients, with the last patient visit completed by May 14, 2020. The executive steering committee and others involved in the conduct of the trial remained blinded to treatment allocation and results until the conclusion of the trial and finalization of the database.

I limiti rilevati dagli stessi autori dello studio

Limitations

This study has several limitations. First, all patients were at high risk of future cardiovascular events, and background statin therapy was required. Whether benefits might be observed in a lower-risk primary prevention population remains uncertain. Second, this trial evaluated the effect of administration of 4-g/d of a combination of EPA and DHA in fixed proportion. While different doses and proportions were not evaluated, elevations in plasma concentrations of both EPA and DHA were achieved, yet no cardiovascular benefit was observed. Third, no large clinical trial has evaluated the effect of purified DHA at any dose on cardiovascular outcomes.

Conclusions

Among statin-treated patients at high cardiovascular risk, the addition of omega-3 CA, compared with corn oil, to usual background therapies resulted in no significant difference in a composite outcome of major adverse cardiovascular events. These findings do not support use of this omega-3 fatty acid formulation to reduce major adverse cardiovascular events in high-risk patients.

Le conclusioni

ARTICLE INFORMATION

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Other - Conceptual framework of data presentation: Ray.

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Role of the Funder/Sponsor: The sponsor, AstraZeneca Inc, participated actively in designing the study in collaboration with the steering committee, developing the protocol, which was written by the steering committee, and provided logistical support during the trial, in terms of site management in collaboration with C5Research.The sponsor maintained the trial database. After completion of the trial, as specified in the study contract, a complete copy of the database was transferred to C5Research, where statistical analyses were performed by an independent statistician, Kathy Wolski, MPH. The Executive Steering Committee made the decision to publish the manuscript and takes responsibility for the completeness and accuracy of the data. The manuscript was drafted by the first author, with input from all authors. The sponsor was permitted to review the manuscript and make suggestions, but the final decisions on content were performed by the Executive Committee. The results reported in the manuscript are the results of the analyses performed by Kathy Wolski. While the steering committee and coordinating center had confidentiality agreements with the sponsor, the study contract specified that a copy of the study database be provided to C5Research for independent analysis. While employees of the sponsor are coauthors of the manuscript, they provided review of the drafts. The academic authors had unrestricted rights to publish the results. The manuscript was modified after consultation with coauthors. The final decision on content was exclusively retained by the academic authors.

Investigator Listing: A complete list of all executive committee members, steering committee members, DSMB members, and all participating investigators appears in Supplement 3.

Meeting Presentation: Presented at the American Heart Association Scientific Sessions, online November 15, 2020.

Data Sharing Statement: See Supplement 4.

E per la trasparenza, le informazioni su:

- **Conflitti di interesse**
- **Fonti di finanziamento**
- **Sponsor**