

# Una svolta nella ricerca biomedica e clinica: l'etica della comunicazione.

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## Examples of Medical Reversal

### 1. Nutrition

- ✓ **The gluten story: from gluten supplemented pasta to gluten-free cereals for everybody**

### 2. Drugs

- Collapse of estrogenic substitution therapy in menopause.
- **The aspirin affair: from foe to friend of the heart.**

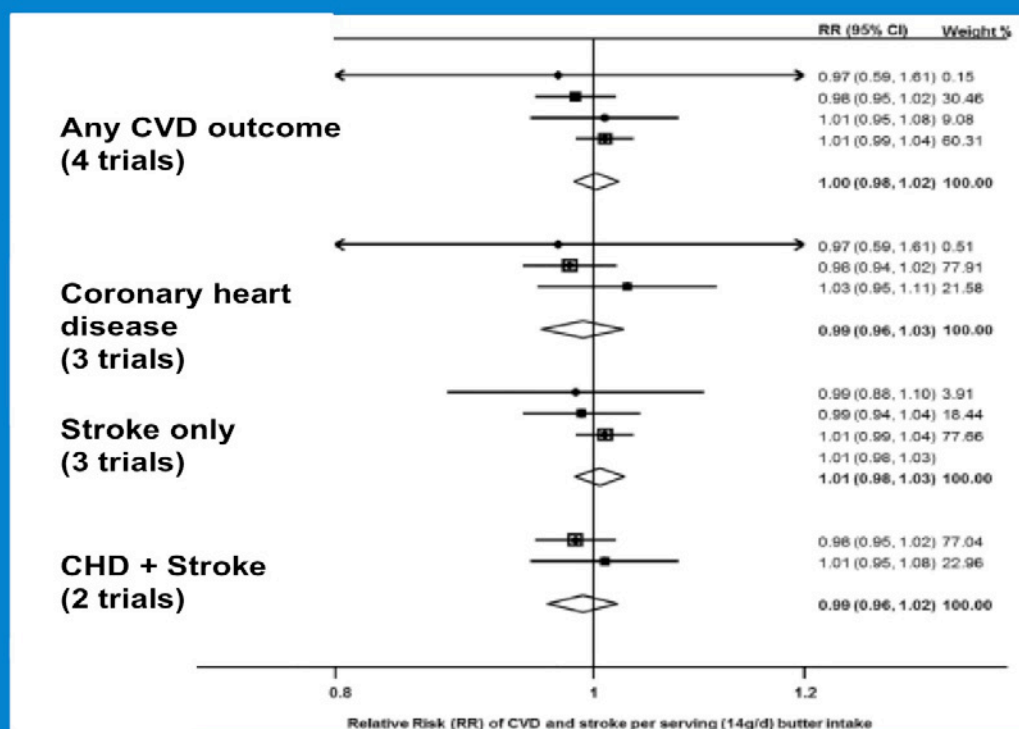
### 3. Other therapeutic procedures

- Angioplasty-stent obsolete in stable angina: medical therapy better (*Boden WE et al NEJM 2007*).
- Closure of a patent foramen ovale, or of left auricola in AF: whether and when?

## A complicated affair: the Fat Wars

- Even the axiomatic association between dietary and circulating lipids and atherosclerosis (CVD) is today challenged.
- Saturated fats (SFA), despite demonization, are still an essential component of human tissues and cells.
- SFA increase LDL chol, but reduce the total number of LDL particles, that could balance the effect on CVD (*Prado CB et al, J Clin Lipidol 2011*)
- Contradictory role of stearic acid (*Hunter JE et al, Ann J Clin Nutr 2010*)
- **Are Dairy Fats different?** In a large study a higher intake of dairy SFA was associated with a lower CV risk in comparison with meat SFA (*MESA study, Am J Clin Nutr 2012*)
- Dairy fats appear to be neutral for CVD and probably also good for diabetes

## Moderate butter consumption (referred to one serving, 14g/d) and risk of cardiovascular events



Pimpin L et al. PLOS One, 2016

## THE PURE STUDY

- High intake of saturated, monounsaturated fatty acids, and animal proteins was associated with increased survival
- High total carbohydrates were associated with high mortality. However, fruits, legumes and raw vegetables were protective.
- 
- It is suggested that added sugars and refined grains are likely responsible of this association (*C.E. Ramsden, Lancet Aug 29, 2017*)

**Comments:** The PURE study included 18 Countries, 14 of which were of low-or low to middle income. There were only 4 European Countries (eastern)

- The endpoint “total mortality is subject to a high number of variables, from genetics to socio-economic level, lifestyle and nutritional habits.
- **These result cannot be transferred to Western populations!**

Lo studio PURE rimette in discussione la patogenesi dell'Aterosclerosi?

**CONTRORDINE: bistecche, formaggi e grassi NON FANNO MALE!** (da *Repubblica Salute 29 agosto 2017*)

PURE study challenges the definition of a healthy diet: but key questions remain  
(*The Lancet; Aug 29, 2017*)

**PURE shakes up nutritional field: finds high Fat intake beneficial!** (*Medscape sept 1, 2017*)

## Re-defining hypertension after the new ACC/AHA Guidelines (November 2017)

In the morning of November 14, 2017, a considerable number of U.S. adults (12%) woke up as “unaware Hypertensives”.

The new classification emphasizes the individual assessment of global CV risk (> 10% in 10 years)

Persons with BP levels of syst 120 to 129 and diast less than 80 are no longer considered “normal”. They have “elevated blood pressure” ( a new disease)

Persons who have syst 130 to 139 with diast 80 to 89 are labeled as **1° stage hypertensive**. They should receive non pharmacological treatment unless they have a global CV risk > 10% in 10 yrs. In this case they should receive monotherapy.

Persons with 140/90 or more are labeled “stage 2 hypertensives”, and receive full or combined therapy (beta-blockers non first-line) calibrated according to BP levels and global CV risk.

## Considerations about the new Hypertension Guidelines 2017

1. **Problems of communication: indeed a new level of disease is created affecting people previously defined as healthy.**
2. **Excessive medicalisation of population, increasing costs , in the search for an unattainable zero risk?**
3. **Isolated systolic hypertension not considered**
4. **Therapeutic goals prescribed are no different in young and elderly patients and the new normal values may cause side effects**
5. **Beta blockers are beneficial in pts with high heart rate**

*(from Bakris G, Sorrentino M. NEJM Jan 17, 2018)*

## Value and limitations of RCTs and meta-analyses

- RCTs are effective tools supplying dependable knowledge useful in clinical settings.
- *But trials or meta-analyses can hardly cover the complexity of single cases, and their results are not always transferable to “real world patients”.*
- Attempts at increasing the translational value of trials are being introduced, as Bayesian approach, and other adaptive changes.
- **Anyway, RCT results are subject to change, repositioning, and sometimes overturnings (reversals) because of genetic and environmental factors (timing, geography, supporting care, social level (Yusuf, NEJM 2016). Multicountry megatrials sometimes questioned.**

## Communication with the patient

- ✓ “Uncertainty is our fellow traveler in research”. (Bruno de Finetti, 1906-1985). But, how to share this concept with patients?
- ✓ What we must transfer, is rather that our medical choices “represent the best dependable knowledge available at the given time”.
- ✓ Thus, the patient will be informed, able to actively participate in choices, and may share main decisions (even share scientific data).

## How do patients perceive the concepts of risk and probability?



- Perception of probability figures varies according to the mode of expression, and is also greatly influenced by personal or familiar experiences: **subjective probability** (Kahneman D, 2011).

## Communication with media and health managers



- With some exceptions, media search for “breaking news, “discoveries”.
- Health managers also expect stable information that can be translated into health services and be evaluated in money. They should indeed accept the concept of “temporary validity of medical truth”.

## Usefulness of what seems useless in scientific research

- Biomedical research cannot be easily judged on the basis of its direct and practical impact. (Examples: Doppler, Boltzmann)  
(from *L'utilità dell'inutile*. Nuccio Ordine, ed Bompiani/Giunti, 2013)
- Conversely: clinical research is expected to be directly useful
- However, a good part of available clinical research, is less useful than expected (*Joannidis JPA. PLOS medicine, 2016*)
- Sources of uselessness are not simply the results, but rather design, context, ways of information, external validity, population differences, etc
- The present **information overload** is therefore dangerous as it equally disseminates useful and useless data (**fake news**).

## La scienza, anche la più teorica, riserva sempre grandi sorprese.

### Due esempi significativi

1. **Ludwig Boltzmann** (Vienna 1844-Duino 1906) un matematico, affermò che il calore è prodotto da moto vorticoso e collisioni delle particelle elementari. Fu contestato e isolato; si uccise. La sua geniale teoria fu poi confermata, con forti conseguenze scientifiche e pratiche (tra cui il nostro piccolo forno a micro-onde)
2. **Christian Doppler** (Salisburgo 1803-Venezia 1853) descrisse il cambiamento di colore delle stelle secondo i loro movimenti. Più di un secolo dopo, il suo "Effetto Doppler" traslato dalla luce al suono, genera un esame diagnostico oggi praticato da milioni di persone.

## Uncertainty or Complexity?

- The concepts of risk, probability, and uncertainty cannot be conveyed to patients, health managers, and media.
- First we should define our clinical choices as “the most validated and dependable choice at the time”.
- We should make the counterparts understand that scientific notions are dynamic in natura and depend upon time, context, populations and social-psychologic status.
- Simplifications should be avoided, looking for a new language, apt to making people understand the **complexity** of the problems we are dealing with.

## How to reconcile uncertainty and complexity, with the pragmatic and empathic attitude of the Clinician

- **Uncertainty and complexity in the era of precision medicine!** We need a new language (*Hartzband NEJM, 2011*)
- Besides “hard events”, subjective ailments should be re-evaluated.
- Listening does not mean to accept free “narrative medicine”, the patient should receive guided questions
- Avoid just hearing without listening (*Drazen JM, NEJM 2016*)
- Technological fragmentation, is dangerous, as it leads to substitution of the **real patient** by the “**digital patient**”.



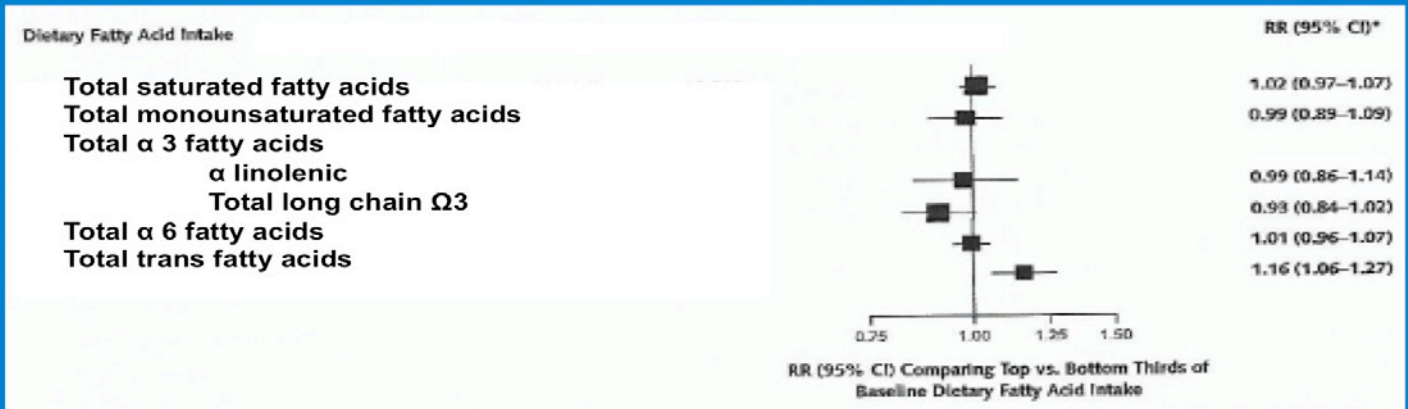
# Tornare all'origine delle parole della medicina

- **Asclepio** (latino Esculapio): un semidio figlio di Apollo: è l'iniziatore della medicina.
- **Chirone**, il centauro che aveva allevato Asclepio, è l'iniziatore della Chirurgia
- **Asclepio** riceve in dono da Atena la testa mozzata di Medusa, da cui sgorga sangue, da una parte venefico e dall'altra salvifico
- **Pharmakon**: vuol dire sia medicamento che veleno
- **Medico**: non significa solo "chi cura", ma che "si prende cura": una disposizione d'animo.
- **Terapia**: servizio, assistenza reciproca.

*Curi U, Le parole della Cura, 2017*

**GRAZIE !**

## Dietary intake of fatty acids and coronary events (observational , prospectives studies)



Chowdhury R et al. Ann Int Med, 2014  
De Sousa RJ. BMJ, 2015

## Does uncertainty depend on not being medicine an “exact science”?

### *But how “exact” are exact sciences today?*

- ✓ According to quantistic theory the Universe is composed by particles in perpetual motion and collisions and their velocity and position are indeterminable (**Heisenberg**). The universe is unstable and responds to probability and random effects.
- ✓ Thus, **uncertainty and probability rule the Universe, not only medical science!**

# Tolerating uncertainty as the initial step towards advancement of science and medicine: the next medical revolution?



Medical scientists and doctors should never be dogmatic!

## La fondamentale ambivalenza della Ricerca Clinica

- Tenta di applicare metodi matematici (statistici) rigorosi al fine di quantificare fenomeni essenzialmente qualitativi, complessi e variabili.
- Difficile pertanto trasferire correttamente i dati della ricerca alla valutazione diagnostica e terapeutica della singola persona.
- La ricerca clinica sembra quindi irriducibile alle cosiddette “hard sciences”. Di qui la sopravvalutazione dei “hard endpoints” e la sottovalutazione della soggettività e qualità della vita.

(in parte da Curi U. *Le parole della cura*. Cortina Ed. Milano, 2017)

## Karl Popper e Daniel Kahnemann

- *K. Popper, filosofo della scienza, afferma che il risultato sperimentale deve essere non solo ripetibile, ma anche “falsificabile” se mutano le condizioni di base. La scienza avanza a forza di smentite, ripensamenti, anche capovolgimenti.*
- *D. Kahnemann, psicologo, introduce il concetto di “probabilità soggettiva”. La percezione del valore della probabilità è fortemente influenzata dalla storia umana di chi la percepisce.*

## The FAT WARS

### La controversia:

- Nel 1982 il MRFIT study conferma le certezze del rapporto colesterolo/aterosclerosi (*JAMA 1982*)
- Nel 2014 una metanalisi non trova alcuna evidenza che un consumo basso di acidi grassi saturi, e alto di polinsaturi, riducano il rischio relativo di malattia coronarica. (*Chowdbury R. Ann Int Med 2014*)
- Nel 2015 un'altra metanalisi di studi prospettici nega il rapporto tra introito di acidi grassi saturi e la mortalità vascolare/coronarica. (*De Souza RJ, BMJ 2015*)
- La molteplicità dei fattori di mortalità CV è un fattore confondente (*Curdiff DK, Cureus 2016*)
- Grande evidenza viene data invece agli acidi grassi trans, margarine, prodotti da forno (*Kummerow PA. 2009-2017*)
- Contemporaneamente, vengono scagionati almeno in parte gli acidi grassi saturi dei latticini (dairy foods) giudicati “neutri” riguardo alle malattie cardiovascolari (*De Oliveira OMC, A, J Clin Nutr 2013/2017*)