Medical research in the "real world": Advantages, challenges, difficulties and gains.

Luiz Miguel Santiago
MD, PhD
Medical research in the "real world": Advantages, challenges, difficulties and gains.

• Disclosure:

• MSD
• Tecnimedede
• Angellini
• Merck
Why and what about investigating in the General Practice setting?

The need to have answers and to what questions?

My interests or... the clinical and the social problems?

And is it a translational investigation?

And “my investigation” or a broadly oriented one?
Why and what about in the General Practice setting?

doi: 10.3109/13814780903452184
European research agenda for General Practice/Family Medicine

• Primary Care Management
• Person-centred care
• Specific problem solving skills
  - Diagnosis
  - Therapy
  - Chronic care / disease management
  - Decision making
  - Quality of care
  - Educational research
European research agenda for General Practice/Family Medicine

- Comprehensive approach
- Community orientation
- Holistic approach
And what about the support to investigate

• The investigational structure.

• The investigational support: money, time.

• The release of investigational results: Thesis? Papers? Presentations?
What are we investigating in Portugal?

• In fact we do a lot...

• We have more than 5000 GP/FD

• There are: 20 PhD GP/FD

• All thesys in populational issues.
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EDITORIAL
- Tangibilidade da complexidade
  Touching complexity in family medicine
  Paulo Brito
- Terapias alternativas precisam de uma ciência alternativa
  Alternative medicine requires alternative science
  David Marçal

REVISÕES
- O papel do exercício físico na prevenção das quedas nos idosos: uma revisão baseada na evidência
  The role of physical exercise in the prevention of falls in the elderly: an evidence-based review
  Patrícia Cunha, Luísa Costa Pinheiro
- Diabetes mellitus e cancro colorectal: uma revisão baseada na evidência
  Diabetes mellitus and colorectal cancer: an evidence-based review
  Samantha Estevão Oliveira, Isabel Machado, Alfredo João Pereira, Marlene Barros

RELATOS DE CASOS
- Apenas mais um acidente do trabalho? Relato de um caso clínico de coreia de Huntington
  Just another work accident? A case report of Huntington chorea
  Hugo Taveira Cunha, Filipa Borges Lopes
- A linha tênue entre a demência e depressão no idoso: relato do caso
  Distinguishing dementia from depression in the elderly: a case report
  João Pinto Carneiro, Helena Cabral

ARTIGOS BREVES
- Quando o apoio às colinas se trata de síndrome de Diogenes: a propósito de um caso clínico
  The Diogenes syndrome: a case report
  Alireza Oliveira, Sophia Sousa, Susana Paiva
- Líquen plano: a história de uma cooperação de sucesso
  Lichen planus: a case of successful teamwork
  Sofia Sousa e Silva, Catarina Meireles, Fátima Costa, Susana Correia
- Fenômeno de Raynaud do mamilo em mulheres a amamentar: relato de três casos clínicos
  Raynaud’s phenomenon of the nipple in breastfeeding women: a report of three cases
  Arnaldos Abrantes, Dusan Djokovic, Catarina Bastos, Patrícia Veiga

FORMAÇÃO
- Diagrama de Stacey: um exercício formativo em medicina geral e familiar
  The Stacey Diagram: a formative exercise in family medicine
  Filipe Manuel, Eurico Carreira, Vítor Ramos

CLUBE DE LEITURA
What about numbers: Portuguese Journal of General Practice.

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Since 2011: n=24

Profesional motivation: 3
Alcohol
Chronic disease integrated management
Asthma/COPD
Quality of prescription
GP/FM practice
Tobacco
Arterial Hypertension
PhD students

Ana Luisa Neves (FMUP)  Inês Rosendo (FMC)
Ana Quelhas (FMUP)      Joana Gomes (FMUP)
António Lourenço (ENSP)  Joana Silva Monteiro (UM)
Avelina Moniz (ENSP)     João Sarmento (ENSP)
Catarina Matias (UBI)   Liliana Constantino (UBI)
Cláudia Bulhões (UM)    Luis Monteiro (UBI)
Dagmara Paiva (FMUP)    Margarida Mesquita (ENSP)
Daniel Pinto (FCM)      Miguel Julião (FML):
David Rodrigues (FCM)  Paula Broeiro (ENSP)
Denise Alexandra (FML)  Rosa Gallego (FML):
Filipe Prazeres (UBI)   Susana Farinha (ENSP)
Frederico Rosário (FML) Teresa Ventura (FCM)
                      Tiago Sousa Veloso (FMUP)
GD/FM portuguese PhD

Alberto Pinto Hespanhol
André Biscaia
Armando Brito de Sá
Berta Nunes
Bruno Heleno
Carlos Martins
Cristina Ribeiro
Dina Gaspar
Hernâni Caniço
Isabel Santos

José Frey Ramos
José Mendes Nunes
Liliana Laranjo
Luciana Couto
Luís Alves
Luís Rebelo
Luiz Santiago
Vasco Maria
Zaida Azeredo
Paulo Santos
The Themes

Condições do exercício da clínica geral no norte de Portugal
Satisfação profissional do médicos de família portugueses
A decisão em medicina geral e familiar
O corpo e a saúde numa aldeia rural: a construção social da doença e da saúde no processo de reprodução
A Medicina geral e familiar e a abordagem do consumo de álcool
Motivação profissional em contexto de educação: O internato médico de medicina geral e familiar
O doente com patologia múltipla em medicina geral e familiar: comorbilidade de quatro doenças crónicas
Capacitação dos doentes e gestão da asma: um estudo em medicina geral e familiar
Ética e cuidados de saúde primários
Abordagem da angina de peito em medicina geral e familiar
Sintomas somatoformes em Medicina Geral e Familiar
Factores de influência na prescrição em clínica geral no norte de Portugal
O doente com artrite reumatóide e o seu contexto familiar
Medicamentos e corpo. Consumidores de fármacos: o que pensam e o que sabem
Estudos de imunidade celular em hepatopatias medicamentosas
Biodinâmica e saúde
Prejuízos programas de rastreio.
Seguimento de utentes após prescrição de ECG em medicina geral e familiar
Estudo Prevenção. PT: Actividades de Prevenção nos Cuidados de Saúde Primários Portugueses
Desenvolvimento de um registo pessoal de saúde com um módulo de autogestão na diabetes
Determinantes sócio-económicos dos comportamentos e atitudes associados à saúde cardiovascular
Person-centred care

Definition of the research domain according WONCA

1. Adopting a person-centred approach in dealing with patients and problems
2. Establishing an effective doctor-patient relationship respecting the patient’s autonomy
3. Communicating, setting priorities and acting in partnership
4. Providing longitudinal continuity of care
Focus of future research

1. Better understanding and clearly defining (components of) person-centeredness

2. Developing additional instruments to describe and measure the complex aspects and outcomes

3. Patient and doctor perceptions, perspectives and preferences on person-centeredness, communication, involvement and shared decision making (including social, cultural and environmental circumstances affecting these preferences)

4. Evaluating effectiveness of a person-centred approach with regard to relevant clinical health outcomes and outcome measures such as satisfaction, knowledge, quality of life

5. Effective methods of (future) GP training to practice a person-centred approach and the sustainability of training/education effects
The problem of Person Centered Medicine

• Lets take cardio-vascular health.
• Encouragement of the use of Framingham or Score to calculate CV Risk.
• Only for high risk in Primary Prevention: statins or anti-AHT treatment.

• Still...
Blood-Pressure Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Cholesterol Lowering in Intermediate-Risk Persons without Cardiovascular Disease

Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease
CONCLUSIONS
Therapy with candesartan at a dose of 16 mg per day plus hydrochlorothiazide at a dose of 12.5 mg per day was not associated with a lower rate of major cardiovascular events than placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)

CONCLUSIONS
Treatment with rosuvastatin at a dose of 10 mg per day resulted in a significantly lower risk of cardiovascular events than placebo in an intermediate-risk, ethnically diverse population without cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; HOPE-3 ClinicalTrials.gov number, NCT00468923.)

CONCLUSIONS
The combination of rosuvastatin (10 mg per day), candesartan (16 mg per day), and hydrochlorothiazide (12.5 mg per day) was associated with a significantly lower rate of cardiovascular events than dual placebo among persons at intermediate risk who did not have cardiovascular disease. (Funded by the Canadian Institutes of Health Research and AstraZeneca; ClinicalTrials.gov number, NCT00468923.)
Conclusion: Hypertension control is significantly associated with target organ damage, taking at least one anti-hypertensive drug at night and not taking non-steroidal anti-inflammatory drugs simultaneously.
Hypertension: avoid olmesartan pending its withdrawal
Olmesartan exposes patients to increased, and sometimes severe, gastrointestinal adverse effects. It is in the best interest of patients not to use it. Olmesartan, commercialised for hypertension, is no more effective than the other sartans or than ACEs (angiotensin-converting enzyme inhibitors) against the cardiovascular complications of hypertension.

Since mid-2012, excessive, sometimes severe, gastrointestinal adverse effects (enteropathies) with diarrhoea, sometimes intense abdominal pains, weight loss, etc. have been observed particularly with olmesartan, compared with other sartans or ACEs.

A French study carried out in 2014 revealed 10 times more hospitalisations for enteropathy with olmesartan than with other sartans or ACEs.

In February 2015, the pharmacovigilance committee of the French health products agency (ANSM) voted unanimously to withdraw olmesartan-based drugs from the market. In April 2015, the Transparency Committee proposed stopping their reimbursement because of this risk, "after a period of one year" – a very generous period for the pharmaceutical companies.
Statins stimulate atherosclerosis and heart failure: pharmacological mechanisms

http://dx.doi.org/10.1586/17512433.2015.1011125

In contrast to the current belief that cholesterol reduction with statins decreases atherosclerosis, we present a perspective that statins may be causative in coronary artery calcification and can function as mitochondrial toxins that impair muscle function in the heart and blood vessels through the depletion of coenzyme Q10 and ‘heme A’, and thereby ATP generation.
Statins inhibit the synthesis of vitamin K2, the cofactor for matrix Gla-protein activation, which in turn protects arteries from calcification. Statins inhibit the biosynthesis of selenium containing proteins, one of which is glutathione peroxidase serving to suppress peroxidative stress.
An impairment of selenoprotein biosynthesis may be a factor in congestive heart failure, reminiscent of the dilated cardiomyopathies seen with selenium deficiency.
Thus, the epidemic of heart failure and atherosclerosis that plagues the modern world may paradoxically be aggravated by the pervasive use of statin drugs.
We propose that current statin treatment guidelines be critically reevaluated.
Statins are the most commonly prescribed drugs for the treatment of dyslipidemia. They are also recommended in primary and secondary prevention of cardiovascular disease. ... statins interfere with the synthesis of isoprenoid intermediates, which may explain many of their pleiotropic properties, including their antioxidant effects. Oxidative stress ... an imbalance between the synthesis of reactive oxygen species and their elimination by antioxidant defense systems ... Reactive oxygen species interfere ... contributing to the contractile dysfunction, myocardial hypertrophy and fibrosis observed in the pathophysiology of heart failure.

By regulating several molecular pathways that control nicotinamide adenine dinucleotide phosphate oxidase and endothelial nitric oxide synthase activity, statins help restore redox homeostasis...

The results of observational studies and clinical trials with statins in heart failure have not been consensual. ...
Specific problem solving skills

Definition of the research domain

Specific problem solving skills, according to the WONCA Europe definition, include the ability to

1. Relate decision making processes to the prevalence and incidence of illness in the community
2. Selectively gather, interpret and apply information from history-taking, physical examination and investigations, in collaboration with the patient
3. Adopt incremental investigation, using time as a tool and to cope with uncertainty
4. Manage conditions which present early or in an undifferentiated way
5. Make effective and efficient use of diagnostic and therapeutic interventions, both in urgent or chronic conditions
COX-1 and COX-2 selectivity of NSAIDs: CV and GI Risks

Increasing CV Risk?

Increasing GI Risk?

Warner TD, Mitchell JA. The FASEB Journal 2004;18:790-804. Reproduced with permission of FEDN OF AM SOCIETIES FOR EXPERIMENTAL BIO (FASEB) in the format Presentation via Copyright Clearance Center
A case–control study was conducted using the PHARMO Record Linkage System, a Dutch population-based registry. Cases were patients hospitalized with a primary diagnosis of PE and were matched to controls without a history of PE. Study population 4433 cases and 16 802 controls.

Conclusions: Use of NSAIDs is associated with an increased risk of symptomatic PE. This association may be partially explained by underlying medical conditions, as suggested by a similarly increased thrombotic risk in patients receiving acetaminophen and tramadol.
Diabetes
People with type 2 diabetes treated with insulin plus concomitant metformin had a reduced risk of death and MACE compared with people treated with insulin monotherapy. There was no statistically significant difference in the risk of cancer between people treated with insulin as monotherapy or in combination with metformin.

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Diagnosis

1. Studies on diagnostic reasoning in an unselected primary care setting, starting from complaints
2. Diagnostic/predictive values of history taking, simple clinical examination or sophisticated diagnostic test
3. Step-wise or incremental diagnostic approach, incl. red-flag issues
4. Severity scores and their practical and clinical consequences
Figure 1 Defining expert generalist practice [26,27].

Variable components:
- Consultation skills
- Continuity of care
- Doctor-patient relationship

Constant components:
- Principle of PDM*
- Practice of IM*

Delivering care for:
- Undifferentiated problems
- First contact care
- Complex problems
- Widest range of problems

*PDM = Person-centred Decision Making; IM = Interpretive Medicine

Protocol dictated care: a ‘technical bypass’?²
Guidelines
Ups and downs of evidence and practice guidelines

An analysis of the 363 articles in the (NEnglJMed – Mayo Clinics Proceedings 2013), 146 (40.2%) found the practice ineffective compared with a previous standard or its omission: reversal - when a current medical practice was found to be inferior to a lesser or previous standard.
Ups and downs of evidence and practice guidelines

How can we acknowledge and accept the fact that nearly half of the actions that we are taking today could be wrong?

With evidence that does not stand the test of time and practice guidelines rife with expert opinions, it’s no wonder that family physicians no longer know what to believe!
Is evidence-based medicine overrated in family medicine? **YES**

EBM: A philosophy of clinical medicine.  

**But overrated because of:**

1. **Vagueness and incompleteness** in its formulation *(Evidence = Truth)*;

2. **Incongruence** with the realities of family medicine *(many encounters in family practice do not yield clean, searchable questions)*;  

**Multimorbidity!**
http://www.alltrials.net

European Clinical Trials Directive
Identifying analgesic trials listed on multiple registries and pairing trials with results is challenging.

World Health Organization International Clinical Trials Registry Platform (ICTRP): 447 unique trials were identified, with 86 trials listed on more than one registry: Overall, only 46% of all trials had results available.

Trials on ClinicalTrials.gov are significantly more likely to have available results.
In the process of drafting and implementing clinical guidelines:

It is not always clear how panellists are selected leaving open the possibility that bias is introduced from the start if likeminded experts are chosen.

Despite evidence-based medicine places expert’s opinion in the lowest rank, paradoxically, guidelines are usually written by people who have worked and carried out some meaningful research in the field.
• ... Intellectual conflicts of interest and we can never be sure about equal weight given to people from other disciplines with experience in methodology.

• Second, disease definition has been a matter of debate in cases in which numerical thresholds are considered (ie, hyperlipidemia, osteoporosis, hypertension)
Lower and lower thresholds for diagnosis and treatment are being proposed without considering the potential harms of overdiagnosis and increasing the target population for pharmacological or surgical treatment.

Most of these ‘widening the spectrum of disease guidelines’ were written by panellists disclosing financial ties to pharmaceutical companies.
Research Misconduct Identified by the US Food and Drug Administration Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature, by Charles Seife

OBJECTIVES To identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature.

CONCLUSIONS AND RELEVANCE When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct.