Towards evidence-based practice via practice-based evidence: the Italian experience

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**Background.** Research is a fundamental tool for GPs’ clinical practice. Independent research should be the answer to important questions on population needs not yet answered. To have a democratic approach, the results of the studies should be available not only to GPs but also to patients participating to the research. Research has also a formative value for investigators: a process of learning by doing. Risk and Prevention Study is a model of the ‘Italian experience’ in doing research in primary health care.

**Objective.** To describe the collaboration between Centro Studi e Richerche in Medicina Generale and Mario Negri Institute in producing observational and experimental research in the setting of family medicine such the Risk and Prevention Study.

**Methods.** Risk and Prevention Study has two main aims and two different methods: the first, to establish the effectiveness of an intensive recommended treatment and lifestyle advice in cardiovascular (CV) prevention is an observational design. The second, the efficacy of n-3 polyunsaturated fatty acid in patients with CV risk is a randomized controlled trial design.

**Results.** The Risk and Prevention trial has enrolled up until now 860 Italian GPs and over 12,500 high CV risk patients that will be followed during 5 years. They will visit their GP at least once a year. The first year of follow-up of the study has been completed. Relatively few patients (2.5%) have withdrawn. The treatment was well tolerated.

**Conclusions.** Enrolment of large number of GPs in research appears feasible when an independent design with clear benefit for the patient’s needs is offered.

**Keywords.** Cardiovascular risk prevention, family medicine, randomized controlled trial.

**Introduction**

This paper has the aim to introduce the preliminary results of Risk and Prevention Study and will describe the experience of the joint group between Mario Negri Institute and Centro Studi e Richerche in Medicina Generale (CSeRMEG) that in the last 20 years has promoted some research in family medicine setting.

‘Mario Negri’ is an independent pharmacological research institute with a long-standing tradition in basic and clinical research and in organizing network of scientist from different specialists [the Gruppo Italiano per lo Studio della Sopravvivenza nell’Infarto miocardio (GISSI) studies and Primary Prevention Project (PPP) trial are the most remarkable achievements with the cardiologists and the GPs].

CSeRMEG is a small group of Italian GPs that is dealing mostly with the doctor–patient relationship, and since the beginning (1986) has believed that research is part of daily work for a family physician. The challenge is to consider research as an intrinsic and fundamental part of the clinical practice, not something optional or a side activity, to be referred to experts, but as a tool for the production of knowledge.

**Italian experience of Family Practice Research**

GPs are used in the daily practice to respond to the questions that patients bring, and when the current evidence is not enough to give an answer and uncertainty is present, research is the way to adopt a specific question.

Family Practice is the kingdom of uncertainty and questions are always present and there is a need to select the relevant problems and to find the ‘sense’ of
the research project in other words to ‘organize the curiosity’.

When a research protocol is written, two capital points should be taken into account:

- Why it is important to undertake this research?
- Who will benefit from this study?

Once this is clarified, three more items are important for integrating research in the physician daily agenda:

- Matching the needs of the patients: utilizing the setting of general practice to implement randomized controlled trials negotiating with ‘real patients’ (old people, women and polypathologies).
- Choose the problem in an historical context: for instance, after the thrombolysis has drastically decreased death due to cardiovascular (CV) diseases in hospital settings, the reduction of sudden death (that means before the patient arrive to hospital) became a relevant problem to be investigated.
- Democracy, that means that all the people participating to the research are author of the research (both GPs and patients) and that GPs and patients should know and be able to use all the results of the research. 3

Italian experience shows that learning by doing may bring interesting results also without University departments of General Practice that sometimes emphasize too much of the research methodology.

Independence

Independence and transparency are also important. A recent Italian law4 has changed the usual meaning of sponsor and states that

- The funding company shall not interfere in writing the research protocol and is not involved in the appointment of the members of the different research committees.
- Investigators maintain the ownership of the research data and have full control of all data procedures.
- Researchers may decide to modify the protocol during the research and stop the research in order to offer to the patients the best therapeutical choice.
- Researchers decide how to publish and how to spread the results of the trial without restriction from the funding company.

Once it is stated that both GPs and patients participating in the research are the authors of the research, informed consent can never be a bureaucratic exercise, but should become a shared research projects between GPs and patients, that means

- sharing uncertainty while planning how to overcome it;
- patients’ implicit acknowledgement that research is a setting of patient-oriented care;
- research results are communicated to the patients at its end (acknowledgment of patients as ‘author’ too!).

Pragmatic versus explanatory trials

Several features of pragmatic versus explanatory trials show why pragmatic trials are much more suitable for general practice.

Explanatory trials are aimed to further scientific knowledge, that is for example understanding the biological basis of the response to the treatment. Often they have surrogate end points that do not always prove to be really representative of the clinical end points.

Pragmatic trials also differ from explanatory trials in relation to patient selection. In explanatory trials, the population is carefully defined and homogenous, whereas in pragmatic trials patients are selected to reflect doctors’ and patients’ variability. Both in the PPP and in the Risk and Prevention Study trials, a mandatory definition was not given, for example, of hypertension, hypercholesterolaemia, diabetes or high risk: GPs were left free to include patients who were diagnosed based on their usual practice.

The two approaches to research will sometimes arrive at different conclusions about the benefit of a given treatment, either because a treatment which works in an ideal setting does not work in real life or because improvement in a biomedical end point in a well-selected population does not produce the expected health gain in the real practice.

Pragmatic trials:

- measure effectiveness—the benefit of a treatment in routine clinical practice (placebo and blindness, unlike randomization are not mandatory and sometime impossible to use);
- represent the patients to whom the treatment will be applied (this ensures generalizability);
- reflect variations between patients (and doctors too!) that occur in real clinical practice;
- are aimed to inform choices between treatments.

Risk and Prevention

The Risk and Prevention trial is a typical model of the collaboration between Mario Negri Institute and
different scientific societies of family physicians. It is one of the largest randomized controlled trial ever done in general practice.

Such a wide participation requires a lot of effort in recruiting doctors (most of them unskilled in doing research), a lot of meetings to explain the protocol and a lot of time before randomizations are fulfilled.

Collaboration with the Istituto Mario Negri has been the key to success. This means collaborating with a research institute that has, besides a well-known experience in projecting, organizing and doing research, a deep and long-standing awareness of strength and shortcomings of general practice, of its capabilities and needs of support.

The Risk and Prevention collaborative group is carried on by several different Italian scientific societies: CSeRMEG, ASSIMEFAC, FIMMG, CoS and AMISI with Mario Negri Institute.5–11

Currently in progress in Italy in the setting of general practice, it combines an epidemiological and an experimental approach in the same population (at high CV risk) in order to

- verify whether recommended treatments (the best evidence-based therapy) for CV prevention, aimed at optimizing CV prevention, are applicable and efficient in everyday practice, with annual control and a sort of ‘deal’ with the patient for the improvement of his lifestyle.
- evaluate the efficacy of n-3 polyunsaturated fatty acids (n-3 PUFAs) in reducing the incidence of CV events through a controlled, randomized, double-blind clinical trial.

Patients were eligible if they were considered at high CV risk because of multiple risk factors and previous manifestations of atherosclerotic disease. They were randomly allocated to receive 1 g a day of n-3 PUFA or the matching placebo capsules. After randomization, follow-up visits are scheduled every year for 5 years.

In 2004, the enrolment started and 1620 GPs attended the start-up course, 1486 agreed to participate and 860 have randomized patients (58% of those who agreed to participate).

Enrolled population

At the end of March 2006, 12 521 patients have been randomized, a mean of 14 per GP

These populations are characterized by:

61% of male and 39% of female
Mean age 64 years with 30% under 60, 40% between 60 and 70 years, 27% between 70 and 80 years and 3% over 80 years.

The inclusion criteria are as follows:

29% atherosclerotic pathology
48% diabetes + one more risk factor
21% more than four risk factors
1% other (GPs were allowed to include patients that they perceived at high risk)

These data are quite similar to data coming from an epidemiologic survey also called Risk and Prevention (set-up to check the feasibility of a randomized trial) for sex and age. However, the randomized trial enrolled more diabetics (48% versus 33%) and less atherosclerotic patients (29% versus 39%) compared to the epidemiologic survey.

Among the atherosclerotic patients (that are 29% of the randomized population), 40% had angina, 31% had a revascularization procedure, 26% had peripheral arteriopathy, 26% had a transient ischaemic attack and 15% a stroke.

Of the diabetic group (that are 48% of the randomized population), 79% had at least three or more associated risk factors, and these were 80% hypertension, 62% hypercholesterolaemia, 56% male, 53% obesity, 46% age over 65 years, 22% family history and 16% smoke.

Population characteristics

77.2% are married, 13.3% widow, 6.6% never married and 2.9% separated or divorced.
87.0% live with the family, 12.3% alone, 0.6% in institution.
50.2% have done only elementary school, 27.1% have done an inferior school, 17.7% have done secondary school and 4.8% have a University degree.
56.2% are retired, 24% of females and 14% of males are smokers.

Nutritional/health-related habits

90% of the patients answered to a questionnaire on nutritional habits:
37% declare to eat vegetables more than once daily, 34% once daily.
56% declare to eat fruits more than once daily, 29% once daily.
5.5% declare to eat fish more at least or more than three times a week, 26% twice a week, 43% once a week.
79% declare to use olive oil regularly, 12% often, 5% sometimes, 3% never.
41% practice daily physical exercise of different intensity (light, moderate and heavy) and among these 16% practice moderate to heavy intensity exercise daily.
15% are often involved in cultural activity, 25% sometimes and 58% never or rarely.
12% felt sad or depressed during the last year, 39% sometimes, 48% never or rarely.

Perception of the risk: only 2% of the patients believe they have very high CV risk, 14% high, 45% medium, 26% low and 11% very low (note: all of them were included because they are at high CV risk).

Prescriptions
Number of drugs: 4% do not take any drug, 14% one drug a day, 25% two drugs, 25% three drugs, 16% four drugs and 15% five or more drugs.

Antihypertensive agents: 5% of patients with hypertension do not take any drug, 30% take one drug, 35% take two drugs, 22% take three drugs and 8% more than three. The therapeutic class of the antihypertensive agents are as follows: 54% angiotensin converting enzyme inhibitors, 50% diuretics, 33% beta blockers, 23% sartans, 23% calcium channel blockers, 8% alpha blockers and 25% central inhibitors.

Antidiabetic drugs: 22% of patients with diabetes do not take any drug, 42% take one drug, 30% take two drugs and 6% take more than two. The therapeutic class of the antidiabetic agents are 30% biguanides, 25% sulphanilurea, 27% association between biguanides and sulphanilurea, 2% acarbose, 0.5% glitazones and 11% insulin.

Antilipaemic drugs: 44% of patients with hypercholesterolaemia do not take any drug, 55% take one drug and 0.3% take two drugs.

Therapeutic assessment
Hypertension control: 89% of males and 90% of females have drug treatment for hypertension, but 59% of males and 65% of females have a systolic blood pressure equal or below 140 mmHg and 31% of males and 29% of females have a diastolic blood pressure equal or below 90 mmHg.

Diabetes control: 71% of males and 73% of females have a drug treatment for diabetes, but 36% of males and 40% of females have a glycated haemoglobin equal or below 7.5%.

One-year follow-up
Patients’ compliance during 1-year of follow-up. After 1-year of follow-up, 2.5% of the patients withdrawn from the trial and 5% of the patients discontinued treatment.

The reasons for drug discontinuation were 1.7% for side effects (mainly gastrointestinal) and 3.3% others (clinical or patient’s refusal).

CV events during 1-year of follow-up.

After 1-year of follow-up, 1.0% had CV death and 3.4% hospitalization for CV events (primary end point).

Conclusions
A large network of GP's randomized a wide range of subjects at high CV risk and the 1-year follow-up is adequate and almost complete.

Very few patients have been withdrawn from the trial and the experimental treatment is well tolerated.

The rate of events observed in the primary end point is very close to the rate estimate used to calculate the sample size (4.4% and 4.0%).

It appears feasible to conduct a pragmatic, large-scale, randomized, double-blind clinical trial in the setting of general practice.

Declaration
Funding: The Risk and Prevention Study was provided by the pharmaceutical companies producing the fish oil. The Collaborative Group of Risk and Prevention trial is the Sponsor of the study that means that is responsible of the development of the research and of the management and analysis of the resulting data.

Ethical approval: None.

Conflicts of interest: None.

References