Chapter XIX

APPLICABILITY OF RESULTS AND EXPLOITATION OF RESEARCH

Pierre Duhaut, Roland Chapurlat, Jean-Pierre Ducroix

The goal of clinical research is, ultimately, to improve the state of health of patients through prevention, better diagnosis, better therapy to slow down the evolution, preserve the existing, improve the present, even, sometimes, to cure the patient. This chapter reviews the conditions of applicability of clinical research to patients actually cared for in daily medical practice.

Clinical research also makes it possible to promote in the medical career young colleagues who commit to it, and to maintain among medical practitioners a requirement for progress, conditions sine qua non for maintaining good quality care. This chapter also reviews the methods of promoting research in the different types of medical practice.

The ultimate goal of clinical research is to improve the management of patients in the diagnostic or therapeutic field, to possibly prevent certain diseases through a better understanding of risk factors or the application of resulting measures, to better distribute health resources available for the benefit of the greatest number… so it is essentially applied research at one end of the research spectrum, whereas basic research, aimed at better understanding the surrounding world without immediate action on it, is at the other end.

Clinical research must be applicable, since this is its primary ambition… what about in reality, and what can be the conditions of its applicability?

A- APPLICABILITY AND APPLICATION:

A- Applicability, affected population and criteria for inclusion or exclusion of patients in the studies:

One of the first conditions would be that clinical research be carried out on patients similar to those in daily practice, since its results will apply, precisely, to these patients. This is also one of the major difficulties: the patients included must give their informed consent, many randomized trials in particular include an age limit for inclusion, comorbidities often represent as many exclusion criteria to achieve a homogeneous population… whereas the patients treated daily are more often elderly, polypathological, and when they are seriously affected, may not be able to give informed consent. On the other hand, when the results of a randomized trial are published, the message tends to focus on the efficacy of the therapy, and the inclusion or exclusion criteria tend to be forgotten.

Most randomized cancer trials are based on a patient life expectancy of more than 6 months. As a result, patients with brain metastases, impaired general condition, comorbidities,

history of other cancers, are most often excluded. However, they are numerous in certain common cancers such as lung cancer, for which they can represent up to 65% of patients seen in first intention[1].

Randomized trials of thrombolysis in acute cerebrovascular accident (CVA) have shown a benefit - modest moreover - provided that it is carried out within the first three hours following the onset of symptoms, and that the patient does not present no obvious hemorrhagic risk: this does not represent more than 10% of patients in current practice in many regions [2]. If we can hope for an improvement in prognosis in a minority of patients among these 10%, it will be difficult highlight the impact of stroke thrombolysis in terms of public health.

Statins represent the only drug family in France classified as Medical Benefit 1 (SMR 1), on a scale ranging from 1 to 5 (1: proven maximum benefit, 5: non-existent or unproven medical benefit). Anti-tuberculosis drugs, antibiotics, loop diuretics are classified in 2, anti-epileptics in 3… It is however disturbing to note that all the studies concerning statins have been carried out in countries with high mortality and morbidity for cardiovascular disease, essentially the countries of northern Europe, whereas no study has been carried out in countries with low cardiovascular mortality such as France, or generally the countries around the northern rim of the Mediterranean. If cardiovascular mortality can reach 60% in Finland or Scotland, it does not exceed 40% to 45% in France: given this differential, what is the real benefit of prescribing statins in France? Can we justify their budget post, very important to Social Security, without having studied their impact in the conditions of their use? What do we think of the generalization of their prescription in people over 80 who have lived in good harmony all their lives with a cholesterol level of 2.4 g/l, without any other obvious cardiovascular risk factor? (The study in the elderly was also only done in countries with high cardiovascular mortality)[3] .

One of the basic principles of clinical epidemiology is that the results of a study apply to the population from which the cases come: this is particularly true in the treatment of risk factors, as opposed to treatments aimed at etiology (antibiotics essentially), since risk factors vary greatly from one region of the world to another.

B- Applicability in clinical practice and study sample size:

1- In the field of therapy:

We often hear that a trial is all the more valid as its sample size is large: this is often an argument of representatives of the pharmaceutical industry. Sample size and validity of course have little relationship, and we too often forget that a large sample size is necessary to demonstrate *marginal effectiveness:*

The first randomized trial on acyclovir and herpes encephalitis was interrupted after 20 inclusions: 8 out of 10 patients in the arm treated with acyclovir evolved favorably, while 8 out of 10 in the placebo arm died: efficacy was such that *a posteriori*, randomization would not have been necessary. Randomization, *the ultimate* in clinical studies because it equalizes all conditions at the start between the groups being compared, is only useful when the effectiveness is not visible to the naked eye. Anti-tuberculosis drugs, antibiotics in meningococcal meningitis did not require randomization.

When the efficacy is not immediately visible, i.e. when the action of the drug tested is marginal immediately, or the amplitude of the effect moderate, even modest in the medium or long term, a large sample size makes it possible to make a statistically significant difference between two large groups of patients. From then on, the individual benefit becomes more random (and generally very difficult to define), and the question arises of the difference between the statistically significant and the clinically significant.

Examples: No one would dream of contesting the value of intensive care management of acute myocardial infarction, with coronary angiography and thrombolysis or placement of a stent. Mortality is improved by 20%, which is presented as spectacular… and is found consistently in all studies.

This is a reduction in the relative risk of mortality of 20%.

However, the spontaneous mortality of uncomplicated acute myocardial infarction is 12%. Intensive care reduces it (removing the decimals) to 9%, and 20% (or 25%) represents the differential (12 – 9)/12. In other words, the absolute, effective reduction in mortality risk is 3%… [4].

What are the consequences in practice when caring for a patient in the emergency room?

- 23 lives are saved by treating 1000 patients: the treatment must therefore be applied.
- 9 serious haemorrhagic vascular accidents are caused, for the price of the 23 lives saved.
- Probably 973 patients were treated without noticeable benefit to them.
- The problem is that we do not know at the time of the prescription, and we will never know afterwards, which patient, which individual, will have benefited from the treatment. On the other hand, we will quickly know for whom the treatment will have been deleterious, and it is not certain – it is even unlikely – that these are the patients who would have died anyway.

A practical way to determine the applicability of the results is to ask about the frequency of the event, which can be judged by the incidence observed in the placebo group. If this is significant (for example 30% of women presenting at least one new vertebral fracture in 3 years of follow-up), with a notable relative risk reduction, this means that the product is of interest in a high-risk population. These high-risk individuals can easily be identified in clinical practice by observing the characteristics of the individuals included in the trial (e.g. postmenopausal women over the age of 70 on average who already have at least one vertebral fracture.

Important point: *the generalized application in clinical practice of the results of randomized trials with a very large sample size undoubtedly makes it possible to save a few lives in the best of cases, but above all reflects our inability to define the patients who really benefit from the treatment and to refine the contraindications: to be more applicable, clinical research of tomorrow will have to focus on the predictive factors of response. This is an approach sometimes considered in current clinical trials, with the publication of analyzes making it possible to define the groups with the best response. Too often, however, these analyzes are carried out a posteriori, to serve commercial interests. But more and more, these analyzes are planned in the protocols a priori, and facilitate the orientation of the care. For example, the analysis of a number of categories of patients who benefit most from the treatment of osteoporosis with zoledronic acid was planned in the protocol, which made it possible to highlight the best targets.*

In addition, therapeutic trials controlled against placebo are less and less carried out because there are reference treatments in a number of pathologies. As a result, the expected difference between a reference treatment and a new product is generally less than between a placebo and a new drug, so that the sample sizes increase. To escape this problem, intermediate judgment criteria are often used, but their clinical relevance is often lower than that of so-called hard clinical criteria. Certain genetic polymorphisms could be associated with a better response to treatment, and detecting them could allow treatments to be better individualized in the future.

2- In the field of observational studies:

There is no direct and desired action on the patient as in a randomized trial. An exposure factor can be rare but very toxic, an event can be rare but serious, and the very rarity of the exposure or the event will require population studies with a large sample size to be demonstrated.

Most cancers are not frequent pathologies, but highlighting their environmental risk factors in such a way as to prevent their action can be useful:

Examples:

- Exposure to asbestos is rather rare compared to cardiovascular risk factors, and mesothelioma remains a rare tumor today. Recognition of the toxicity of asbestos has, however, made it possible to reduce exposure by modifying a certain number of manufacturing processes.
- Hepatocarcinoma is not the most common cancer, but large cohort studies have confirmed the etiological role of the hepatitis B virus: the vaccine should make it possible to reduce its incidence.
- Observation of tens of thousands of newborns has made it possible to objectify the role of prone position in sudden infant death syndrome, a fortunately 'rare' event if it is related to the entire cohort. The applicability is obvious.
- Cancer registries based on the population make it possible to objectify regional differences in incidence, and to formulate hypotheses as to the factors favoring a particular cancer: the national registries of Scandinavian countries, exhaustive on the entire population, illustrate all the interest.

Important point: *a large sample size may be necessary in an observational study to highlight the effect of a correctable or modifiable risk factor, with non-'marginal' consequences and of the results and consequences (elimination or modification of the risk factor) more often justified in terms of public and individual health.*

C- Applicability, comparability of the arms of a trial, and confounding elements:

Because of its frequency, cardiovascular pathology is rich in multiple randomized trials, and beta-blockers, calcium-blockers, anti-hypertensives, hypocholesterolemic agents, anti-aggregating agents have been tested tirelessly for more than 20 years. For some drugs, a long-term survival benefit has been shown. For many, efficiency has focused on data that is less 'hard' than survival. For all of them, the trials have always been large, because the effectiveness of these different therapeutic classes cannot be seen with the naked eye.

Randomization, when it worked, made it possible to equalize the initial pathological conditions and the risk factors between the groups compared. *Its purpose is to eliminate from the comparison the confounding factors, these being able to explain by themselves all or part of the prognosis independently of the therapy tested.*

However, long-term mortality or morbidity does not only depend on the initial conditions, but also on the persistence, or not, of the action of the risk factors during the follow-up. Smoking is one of the major cardiovascular risk factors, which is moreover correctable. It is very likely that its long-term continuation worsens the prognosis, and one would think that stopping it could improve it.

No randomized trial in the cardiovascular field takes into account this major confounding factor *during the follow-up, and not only as an initial condition*, in the analysis of the results. However, it is not impossible to measure it and take it into account in multivariate analysis, which would make it possible to measure more accurately the extent of the therapeutic action once the powerful 'tobacco' risk factor has been eliminated. It would be interesting to know what would then remain of the effectiveness of the multiple treatments offered (increased? or reduced because marginal compared to the cessation of intoxication?). Should we continue to prescribe expensive cholesterol-lowering drugs, ACE inhibitors or sartans, or embark on vigorous and sustained anti-smoking campaigns when hundreds of millions of Euros have been spent each year in the framework of the common agricultural policy to… support tobacco growing in Europe?

Important point: *of all clinical studies, therapeutic trials are undoubtedly those whose results – or conclusions – are the most applied. However, the confounding elements during the test, unlike the initial confounding elements, are rarely measured and analyzed.*

D- Applicability, strength of conclusions, and strength of evidence. Value of judgment criteria:

It is rare that the application of the results of a study is direct... The information, although directly accessible by reading reviews, generally passes through a whole series of relays before being delivered to the prescriber: the pharmaceutical laboratories make significant promotional efforts by delivering a simple message, consensus conferences, continuing medical education sessions 'digest' the information and present it in the form of action to be taken... However, the reality is not that simple, and it is probably wrong to consider that a 'High school + 10 years' doctor should not like any scientist go to the source of the data.

Anti-aromatases very quickly obtained first-line prescription authorization in breast cancer, to the detriment of the oldest tamoxifen (Nolvadex®). This authorization came after the randomized trial published in the New England Journal of Medicine, concluding with the notable improvement in the prognosis of patients treated with anti-aromatase compared to the 'tamoxifen' arm (4,500 patients included), an improvement hailed by a rave editorial headlining 'the new stars in the breast cancer sky' [5] Advertisements on the last page in French general medicine journals followed the original article shortly (15 days…).

However, the survival curves published in this article show no difference in mortality. There is simply a statistically significant difference in terms of relapse-free survival, delayed by a few weeks in the 'anti-aromatase' arm. At the same time, patients on aromatase inhibitors frequently present with arthralgia, and their risk of osteoporotic fracture is significantly

increased compared to those on tamoxifen, due to the blockage of residual estrogen secretion. The overall benefit, quantified in the form of improved quality of life, is therefore difficult to transpose into clinical practice. What is the true impact on the lives of patients? Does this justify a cost 10 times higher than tamoxifen, knowing that the sums invested in one direction will not be in another, perhaps more effective?

The same question may arise with the generalization of anti-Alzheimer's treatments: they are expensive, slow down (perhaps?) the deterioration of the Mini Mental Score (MMS), but do they really change the lives of patients and their families? ? Should we spend millions of Euros on a therapy that is currently very fragile, or would it be better to invest them in basic research that could one day bring real improvement? (*Note of the translator, 12 years after the original edition of this chapter: hundred of thousands or more have been spent... before the ineffective drug had its reimbursement suspended !)*

Important points :

- Justice has understood for centuries the importance of the separation of powers: the investigating judge, the lawyer, the prosecutor, the judge, are different people and supposed to be independent. All these functions are currently combined into one in the evaluation of therapeutics: pharmaceutical companies produce the molecule, construct the randomized trial, organize it, analyze it, publish it - quite often at present - and present the results, in particular at congresses which they very largely finance . They have the financial power necessary for the whole, but the ultimate payers are the health insurance systems. Wouldn't it be better to apply the old principle of justice, ***with*** *companies* – essential – carrying out pharmacological research, defending their molecule, ***whereas*** *learned societies* – after all, medical doctors and PhD… – evaluating the molecule in a clinically independent scientific way, ***and*** *national authorities* such as the AFSSAPS or the FDA examining the file, before passing on more objective information?

- The results on 'light' judgment criteria (MMS for Alzheimer's, blood pressure figures for hypertension, bone density for osteoporosis, etc.) must be considered with more hindsight than the heavy clinical criteria (survival, incidence of stroke or myocardial infarction). myocardium, fracture incidence, etc. before generalizing therapy.

E- Applicability of medico-economic studies:

Physicians tend not to be interested in medico-economic studies… and in fact leave the decisions to non-physician economists. It is important to know the types of economic studies, their basic philosophy (cost-utility, cost-effectiveness, cost-benefit, etc.), which itself can already be discussed. It is then important to know the methods of calculation and to remember that like any study, their results only apply to the populations on which they were made: the costs differ considerably from one country to another within the countries of Western Europe, the amount of the consultation of a general practitioner is 5 times higher in the United States or the United Kingdom than in France, the total cost of work varies in costs, which vary greatly from one country to another, and the cost of drugs is also decided at national and not international level. Finally, the 'ingredients' (costs) included in the calculations vary just as considerably depending on what one wants to show: should only direct costs be included (total cost of hospitalization for example), or part of the indirect costs (benefits, estimate of the cost of the disability, continuation of home care, loss of earnings, etc.)? To what extent

should indirect costs be included (themselves highly variable depending on social or family status, social coverage, and of course the country)?

In the same national and economic context, the costs can vary considerably according to the clinical characteristics of the patient: the treatment of osteoporosis in men over 60 can thus vary by a factor of ten if we take into account age and history [6] For example, it is cost-effective in most healthcare systems to treat individuals at high risk of short-term fracture, rather than to prescribe preventive treatments for loss bone to a large part of the population previously selected on the basis of a measurement of bone mineral density. Thus it is especially the elderly, whose risk of fracture is the greatest, that it is the most cost-effective to take care of. Some countries make radical choices, reimbursing only one line of treatment, in generic form. For example, in the UK, only generic alendronate is reimbursed as a first-line treatment for postmenopausal osteoporosis. Similarly, only the first line of chemotherapy is reimbursed in the treatment of metastatic breast cancer.

Important points :

• Economic sciences, while using mathematical tools and scientific language, are closer to social sciences in the bases of their reasoning: they therefore reflect more a mode of social functioning than a 'reality' in the scientific sense of the term, and the results of their studies must be interpreted with this relativity in mind.
• We never prove that such and such a measure is 'economically' effective or profitable: we just provide a few clues that can help in the decision, valid only in a narrow geographical and temporal context.
• Physicians must understand the methodology of these studies in order to be able to discuss, with solid supporting arguments, their application to the people who will make the decisions, most often non-physicians in the current context.
• There are hardly any French medico-economic studies in the national or international medical press. What is the validity of decisions made on unpublished studies, whose methodology is not known, and which perhaps have simply not been made?
• This remains a very broad area of study for clinicians.

F- Application of the results… and rooted traditions:

It also happens that study results oppose certain rules of prescription firmly anchored in teaching and habits: the “double antibiotic therapy adapted to the germ”, repeated by generations of students is certainly an exemplary illustration. ‘Dual antibiotic therapy’ usually involves the addition of an aminoglycoside.

Multiple randomized trials comparing mono-antibiotic therapy to the same antibiotic with the addition of an aminoglycoside have been carried out, in very different clinical situations. They rarely supported the use of the aminoglycoside, and the consistency of their results is remarkable in itself. Two meta-analyses of these trials, one in immunocompetent patients, the other in immunocompromised patients, confirm the individual results of the vast majority of these trials: aminoglycosides do not improve the prognosis in any way clinical and bacteriological (cure/mortality, eradication of the germ). On the other hand, their only statistically and clinically significant effect is represented by… their nephrotoxicity [7] [8]. The results of these multiple studies and their synthesis would be easily applicable. What resistance prevents them from being at least cited in consensus conferences?

Important points :

• Medical studies provide a large body of knowledge… but it must be considered as the basis on which to build the moving front of applicable knowledge.

• The conclusions of a consensus conference should never be taught without dissecting the foundations and the way to arrive at the minimum common denominator (among whom?) that establishes them.

II- PROMOTION OF CLINICAL RESEARCH:

The application to patients of the results when they are applicable constitutes undoubtedly the essential element of the valorization of clinical research: the sole aim of clinical research is the improvement, in one way or another, of the patient's condition.

Other elements, however, should not be overlooked:

I- Valuation and teaching of the second cycle:

The teaching of basic sciences in undergraduate medical school is often directly linked to the corresponding research, and years did not pass between the discovery of introns and their introduction into genetics or molecular biology courses. Communicating the results of ongoing clinical studies goes a little worse, because it is too often considered to be reserved for specialists. The resistance to the teaching of critical reading, and its successive postponements in official programs bear witness to this. Resistance to the teaching of biostatistics, an essential tool for a documented critical reading, is even greater on the part of both students and teachers. Everyone however agrees to say, even to think, that the clinical sciences are profoundly evolutionary…. So ? How to reconcile the evolutionary character of knowledge and a teaching of fixed pace?

Some medical schools have introduced medical reasoning lessons for more than a decade: others have yet to do so, and critical reading cannot be conceived without serious teaching of the tools on which it feeds. You cannot interpret a paper without understanding its epidemiological and statistical methods, and you cannot apply its conclusions without understanding its foundations. Clinical research must therefore be introduced into education at two levels:

1- The essential teaching of methods and techniques, their applications, but also their strengths and weaknesses and the variability of the resulting interpretations. This must be the subject of specific teaching before the critical reading modules;

2**- The integration of the reading of specific articles in the specialty modules**, aims to make students dismantle the birth, the evolution, and in some cases, the outcome of a medical concept: why do we favor, or do we denigrate, such a diagnostic technique or such a therapy at such a time?

Examples:

• Ten years elapsed between the abandonment of pulmonary arteriography, the 'gold standard' examination for pulmonary embolism, and the demonstration that the angio-scan which replaced it was falsely negative in… 50% cases. During these 10 years, nature has

replaced the medical therapeutic care for tens of thousands of patients… at the time of high-performance intensive care. The comparison of the two techniques simply had not been done before. How many students, and a fortiori how many practitioners, knew this ? The diagnostic value of CT, including the helical technique, remains debated and poorly evaluated five years later [9].

• Thirty years, multiple debates and congresses and tens of thousands of articles have passed between the widespread application of post-menopausal hormone therapy in the 1970s and the measurement of its positive and negative effects at the start of the 2000s: luckily, the negative effects (increase in the incidence of breast cancer and cardiovascular accidents) were more or less offset by the positive effects (reduction in the incidence of colon cancer and fractures osteoporosis). But was it necessary to leave such a role to chance, and could we not have prevented the negative effects by knowing them, that is to say by randomizing the treatment before its generalization to hundreds of thousands of NON-sick women? ? Again, how many students and practitioners knew the scientific basis on which prescription had become widespread?

B- Valuation and teaching of the third cycle:

The third cycle of medical studies includes of course the thesis and the specialty dissertation, but also multiple university degrees which are often obtained on the basis of an examination and a dissertation. Theses and dissertations can be bibliographical, and then rest unread in the libraries of the services, because of moderate interest, ... they can also - for an almost similar investment of time and work (provided they are well supervised) -, be the subject of original clinical research conducted by the candidate, validating his diploma and being the subject of a publication for the benefit of the patients, the candidate, the department and the director of the project…

C- Promotion of research and communication of results:

All results must be accessible, and therefore published. A negative result is sometimes as interesting as a positive result, even if it is more difficult to publish in practice.

1- Congresses and meetings:

The results can be communicated at national and international congresses, and thus allow the establishment of links and cooperation with other teams working on related themes. Communications and posters also make it possible to motivate and promote young colleagues in the discipline, and to increase the attractiveness of a service. In practice, there is no effective research without the contribution of the youngest, and this research in return is useful for their careers... and therefore for maintaining a good level of the quality of care offered by a service.

2- Written publications:

There is a publication strategy, and we should not be afraid – or let ourselves be discouraged – by the refusals of journals: a publication can be refused several times for more or less justified reasons. The justified reasons are used to improve the paper for a future submission. The less justified reasons only reflect the subjectivity inherent in all human activity… and should not prevent the continuation of the work.

Medical journals that have been in existence for a few years are provided with an impact factor, calculated on the basis of the number of readers, the number of citations of their articles in subsequent works and other indices of impact in the communication of knowledge. This impact factor is not necessarily a reflection of the quality of the work (a generalist journal with multiple readers, addressing frequent pathologies such as cardiovascular diseases will have a higher impact factor than a highly specialized neurosurgery journal or medical biostatistics), but is often considered in evaluating a candidate's resume. It is taken into account in the evaluation of the research activity of a service or unit. One can therefore, for a given work, attempt a journal likely to accept the article in the corresponding specialty with the highest impact factor, even if it means being refused, and then going down the scale of impact factors.

Publications on the Internet are proliferating today: not all of them have an impact factor at the moment, but the situation will undoubtedly change considerably in the next decade and publication strategies will have to be adapt.

D- Promotion of research and improvement of the training of health professionals:

There is no care without health actors (medical or paramedical), and there is no high-level care without high-level actors participating in their continuous improvement... a well-built career must therefore be - among other things - on well-conducted research, and this aspect of the medical career must be addressed very early with residents at the start of the course. Most research masters are validated after submission of an article in an international journal. Even if there is no written rule, most universities require, for a science thesis to be defended, that it has been the subject of 2 or 3 original first-author articles accepted in international journals with reading committee, with an impact factor greater than 2 or 3 most often (with the exception of very specialized specialties with a narrow readership). The number of original publications accepted as first author on the same theme often rises to 6 for the defense of an authorization to supervise research. This cannot be improvised and it is better to plan the implementation of the work, and therefore of the publications, several years in advance depending on the age of the candidate and the calendar of opportunities: a little realism does not interfere with the conduct of good quality research and the development of a service.

General medicine is no longer an exception to this rule: since the transformation of the former boarding school competition into a national classifying examination, it has become a specialty like the others. The creation of departments of general medicine in universities, and with them, positions of professors, lecturers, and more recently, heads of clinics in general medicine, formalize de facto careers in general medicine similar to careers carried out in the others. specialties. General medicine remains an immense field of clinical investigation that can be organized within networks of liberal doctors, and the methods of clinical epidemiology are particularly suited to this type of applied research.

E- Valorization of discoveries:

Consider patenting or licensing a technique as early as possible in the research process. Thinking about it when publishing the discovery is already too late because everyone will be able to appropriate the work done for free. Patent filing is very important in a research career, often more than the publications themselves. They are sources of income for the institution, for a research group, and contribute to the influence of a school. This is a field that is initially

very difficult, as it is mastered only by specialists in patent law. It is therefore advisable to seek advice from the development units of universities or research institutes (INSERM, CNRS). The benefits are also important for patients, because the filing of a patent, then its industrial transfer, are the key to the rapid development of a new technique.

References :

1. Vardy J, Dadasovich R, Beale P, Boyer M, Clarke SJ. Eligibility of patients with advanced non-smal cell lung cancer for phase III chemotherapy trials. BMC Cancer 2009;9:130-136.

2. Barroso B, Morisset C, Larrieu JM, Bertandeau E, Dakar A, Mangon H, Rouanet F. Stroke thrombolysis in the emergency department as an alternative service for community hospitals lacking a stroke unit. Eur J Emerg Med 2008;15:71-74.

3. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomized controlled trial Drugs 2004; 64 Suppl 2:43-60.

4. Gruppo Italiano per lo Studio della Streptochi-nasi nell'Infarto Miocardico (GISSI). Long-term effects of intravenous thrombolysis in acute myocardial infarction: final report of the GISSI study. Lancet 1987;2:871-874.

5. Coombes RC, Hall E., Gibson LJ, Robert Paridaens MP, Jassem J, Delozier T, et al., for the Intergroup Exemestane Study A Randomized Trial of Exemestane after Two to Three Years of Tamoxifen Therapy in Postmenopausal Women with Primary Breast Cancer. NEJM 2004;350:1081-1092.

6. Schousboe JT, Taylor BC, Fink HA, Kane RL, Cummings ST, Orwoll ES, Melton LJ, Bauer DC, Ensrud KE. Cost-effectively of bone densitometry followed by treatment of osteoporosis in older men. JAMA 2007; 298:629-637.

7. Paul M, Benuri-Silbiger I, Soares-Weiser K, Leibovici L. β lactam monotherapy versus β lactam-aminoglycoside combination therapy for sepsis in immunocompetent patients: systematic review and meta-analysis of randomized trials BMJ 2004;328:668- 682.

8. Paul M, Soares-Weiser K, Leibovici L. Beta lactam monotherapy versus beta lactam-aminoglycoside combination therapy for fever with neutropenia: systematic review and meta-analysis. BMJ 2003;326:1111-1120.

9. Rathbun SW, Raskob GE, Whitsett TL. Sensitivity and specificity of helical computed tomography in the diagnosis of pulmonary embolism : a systematic review. Ann Intern Med; 2000;132:277-232.