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REVIEW

From evidence-based medicine to personalized medicine, with particular emphasis on drug-safety monitoring

Évoluer d'une médecine fondée uniquement sur les essais randomisés vers une médecine personnalisée avec une pharmacovigilance accrue

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Summary Nowadays, guidelines are derived from the findings of randomized controlled therapeutic trials. However, an overall significant *P* value does not exclude that some patients may be harmed by or will not respond to the therapeutic agent being studied. Trials in patients with a low risk of events and/or a limited chance of providing significant differences in therapeutic

Abbreviations: ACE, angiotensin-converting enzyme; AR, absolute risk; ARR, absolute risk reduction; CI, confidence interval; HF, heart failure; ICD, implantable cardioverter-defibrillator; LV, left ventricular; NNT, number needed to treat; NNTH, number to treat to elicit a harmful outcome; NOAC, non-vitamin K antagonist oral anticoagulant; RCT, randomized controlled trial; RRR, relative risk reduction; SOLVD-P, SOLVD-Prevention; SOLVD-T, SOLVD-Treatment.

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effects require a large patient population to demonstrate a beneficial effect. Composite efficacy endpoints are often employed to obviate the need for a large patient population when low rates of events or limited therapeutic efficacy are anticipated. Results of randomized controlled therapeutic trials are commonly expressed in terms of relative risk reduction, whereas absolute risk reduction allows the calculation of the ''number needed to treat'' to prevent an adverse outcome. The number needed to treat is a far more clinically relevant variable than relative risk reduction. The clinician's mission is to match treatment to patient with the goal of achieving optimal therapeutic response. Drug-safety monitoring is also of major importance to avoid exposing patients to irreversible adverse effects. Unfortunately, drug-safety monitoring is often overlooked in routine clinical practice. Finally, the lack of long-term therapeutic data (> 5—10 years) is an unsolved dilemma, as most trials are limited to a duration of a few months or years.

MOTS CLÉS
Nombre de patients à traiter pour éviter un événement ;
Médecine dite fondée sur les preuves ;
Médecine personnalisée ou dite de précision ;
Pharmacovigilance

Résumé Les essais contrôlés randomisés ont permis au cours du temps d'améliorer les prises en charge thérapeutiques. Cependant la significativité des valeurs de *p* ne doit pas faire oublier que l'effet est lissé sur toute la population composée en réalité de patients répondeurs et non répondeurs à la thérapeutique testée. Les essais enrôlant des patients à faible risque d'évènements et/ou testant des thérapeutiques avec une efficacité limitée nécessite des populations de plus en plus importantes pour démontrer un bénéfice. Le développement de critères de jugement combinant de multiples critères traduit en réalité l'anticipation d'un faible risque d'évènements ou d'une faible efficacité thérapeutique. Le résultat des essais thérapeutiques est souvent exprimé sous la forme de réduction du risque relatif alors qu'il est plus pertinent d'être informé sur la réduction en risque absolu qui en outre permet d'estimer le nombre de patients nécessaires à traiter pour éviter un évènement. Le rôle des cliniciens-chercheurs est d'affiner la réponse thérapeutique et la sélection des patients afin d'améliorer le taux de patients répondeurs. L'autre mission importante du thérapeute est la pharmacovigilance qui permet de détecter des effets secondaires majeurs parfois irréversibles devant conduire au retrait du médicament ; dans les faits cette dernière est souvent négligée. D'autre part, une grande problématique non résolue est le manque de données à long terme (> 5—10 ans) car la plupart des essais se limite souvent à quelques mois ou années d'observation.

Interpretation of randomized controlled trials

The implementation of randomized controlled trials (RCTs) in recent decades has allowed a shift away from the historical practice of ''empirical'' therapy to that of ''evidence-based medicine''. Double-blind trials with random allocation to intervention groups allow an objective comparison of a group receiving a potentially active or innovative agent with a control group (placebo or reference agent). The British Medical Research Council is credited with the first randomized controlled trial, published in 1948; streptomycin was shown to drastically reduce mortality from pulmonary tuberculosis, compared with bed rest alone (55 streptomycin-treated patients versus 52 controls; mortality rates of 7% versus 27% at 6 months) [1].

The findings of RCTs have since allowed a dramatic improvement in therapeutic management, and are currently the backbone of therapeutic guidelines. However, an overall beneficial response, as evidenced by a significant *P* value, does not indicate that all patients benefit from the active intervention. Some patients do not benefit from the intervention, and some may even be harmed by the intervention. When the therapeutic efficacy of the agent is limited and/or patients are at low risk of events, RCTs require very large populations to detect an event relative reduction of only 20—30% with a statistical power of 90—95%. On the other hand, when the agent has shown a substantial clinical benefit compared with placebo or the reference drug, RCTs may be terminated early by the data safety board before full enrolment. In brief, calculation of sample size depends highly on the expected effect of the active intervention. Overall, when analysing the findings of RCTs, statistical significance does not necessarily mean clinical relevance. For instance, in 1958, Barritt & Jordan carried out an RCT comparing heparin with placebo in the treatment of pulmonary embolism [2]. The trial was interrupted after enrolment of the 35th patient because of five deaths and five recurrences in the 19 control patients, and no death or recurrence in the 16 patients who were randomized to heparin [2]. Similarly, a trial conducted in 1995 investigating fibrinolysis in the treatment of massive pulmonary embolism was interrupted after

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