

Generic versus brand-name cardiovascular drugs: a remarkable update

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Despite a significantly lower cost than their brand-name counterparts, generic medicines market share does not exceed 50% of the market volume in many developed countries [1]. Indeed, every clinician is repeatedly exposed to anecdotal evidence from patients, colleagues, and of course company representatives, claiming that generic drugs are not as effective and/or safe as their branded counterparts [2].

In the cardiovascular context, such claims are supported by an alleged scarcity of randomized evidence, especially on antiplatelet agents, ACE inhibitors and statins. Last year, we were also exposed to such claims during a course in which general practitioners were warned against generics, and we immediately felt the need to check the literature. We made our best, but we were able to find only one meta-analysis of randomized trials (RCTs) that evaluated the clinical equivalence of more than one generic and branded cardiovascular drug [3]. Also, the meta-analysis was rigorously made but was published in 2008, combined

only efficacy outcomes, included only 50, 23 and 71 subjects in the evaluation of antiplatelet agents, ACE inhibitors and statins, respectively, and most of these patients had been followed for less than two days [3]. An easy victory for company representatives, on drugs that have combined sales which exceed \$100 billion yearly and dominate the cardiovascular pharmaceutical market [4, 5].

We thus felt the urgency of updating and expanding the randomized evidence on the topic and, in collaboration with other meta-analysts from several research centers, we carried out a meta-analysis of RCTs comparing the efficacy and adverse events, either serious or mild/moderate, of all generic versus brand-name cardiovascular drugs. This meta-analysis has just been published in the European Journal of Epidemiology [6]. Given the seriousness of the topic and the potential implications for the global pharmaceutical market, we feel that the findings are worthy of attention from the public health community.

The authors made a systematic, extensive search, including Clinicaltrials.gov in addition to the classic online databases (PubMed, Scopus, Embase, and the Cochrane Controlled Clinical Trial Register), up to December 2014, and made several attempts to contact the investigators of all potentially eligible trials, including the hundreds of trials reporting only bioequivalence (rather than clinical equivalence) outcomes. As regards efficacy outcomes, most of the included studies evaluated the typical outcomes used for the drug class under examination (e.g. LDL cholesterol for statins, systolic blood pressure for anti-hypertensive drugs, etc.), but different outcomes (for each drug class) were aggregated into the overall meta-analysis, which thus used a standardized effect size (Cohen's *d*) as the measure of association, pooled using a random-effect, generic inverse variance approach.

In contrast, in order to avoid the exclusion of the many trials with zero events in both groups, the data on serious adverse events were first reconstructed from single trials using published 2X2 tables, then combined using individual data random-effect logistic regression, with single study as the cluster unit. A number of stratified analyses and meta-regression were used to explore the potential influence of several a-priori selected variables.

The meta-analysis included 74 RCTs: 53 evaluated at least one efficacy outcome (overall sample 3051), 32 trials measured mild or moderate adverse events ($n=2407$), and 52 reported on serious adverse events ($n=2952$). For both soft and hard outcomes, all of the 53 RCTs showed non-significant differences between generic and brand-name drugs. The between-study heterogeneity was mild to moderate in all comparisons, with non-significant aggregate effect sizes for any drug class and in any stratified meta-analysis. A similar scenario was observed for both mild/moderate and serious adverse events. Overall, the results clearly indicate that using generic instead of brand-name cardiovascular drugs does not imply a loss in either efficacy or safety.

Although the authors acknowledged that the available evidence is still suboptimal, we believe that these findings provide a more solid confirmation to observational analyses and to the previous meta-analysis on randomized trials, with respect to which the updated meta-analysis included from 10 to 15 times more

subjects consuming statins, ACE inhibitors and antiplatelet agents, and included 24 vs 7 trials with a follow-up of 4 weeks or more [3]. This represents a remarkable update, as it helps reassuring physicians about prescribing generic cardiovascular drugs to patients, and health care organizations about endorsing their wider use.

As an important side findings, the authors noted that less than one-third of the included trials published after 2005 had their protocol registered online. Therefore, the authors suggested that more journals in the field should adhere to ICMJE recommendation, which requires trial protocol registration before publication, and that a check is made on the publication pattern of generic trials starting from clinical trial registries, as a relevant proportion of RCTs likely remain unpublished [7].

We wish to add that, if we consider the magnitude of the generic market, with approximately 2900 generics approved by FDA from 2001 to 2013 [8], the overall number of trials that is available on the topic seems very scarce, especially when compared to, e.g. the several hundreds of RCT protocols evaluating just statins that have been registered in ClinicalTrials.gov, or included in published meta-analyses [9]. On one side, such a scarce amount of research likely reflects the legitimate limited interest of the large pharmaceutical companies in funding this type of studies. On the other side, however, it reinforces the concerns on the possibility of obtaining high-quality clinical evidence when the funding available is mostly public or non-profit. As recently noted for another hot-topic in the public health agenda such as e-cigarettes [10], higher non-profit funding would thus be needed to increase the size of evidence and to secure publication and dissemination of results on generic medicine clinical outcomes.

Although some tools like network meta-analysis might be used to attempt overcoming the limitations of single studies and the scarcity of head-to-head comparisons [11], conclusive, reliable and independent evidence is particularly needed on the comparison between generics and branded medicines, given the enormous drug-budget savings that can be achieved with more extensive use of cheaper generic medicines.

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