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Impacts on practice

The effectiveness of new oral anticoagulants in atrial fibrillation is extensively being studied, but also innovative medical devices aimed at this disease condition need to be evaluated (e.g. Watchman).

Regardless of the type of treatment, the same end-points (stroke or systemic embolism, death from any cause) have been assessed in clinical trials so that meta-analysis techniques can be applied.

Our study employed network meta-analysis to synthetise the effectiveness data of warfarin, new oral anticoagulants, and Watchman and showed the potential advantages of the new treatments as well as the economic implications in terms of budget impact.
New and old anti-thrombotic treatments for patients with atrial fibrillation

Andrea Messioli · Dario Muratea · Valeria Fadda · Sabrina Tripoli

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Keywords Atrial fibrillation · Budget impact · Cost-effectiveness · Dabigatran · Left atrial appendage closure · Network meta-analysis · Watchman · Oral anticoagulants

Introduction

Patients with non-valvular atrial fibrillation are at risk for stroke and can therefore require chronic treatment. While warfarin has long been the standard of care, the new oral anticoagulants (namely, dabigatran, rivaroxaban, and apixaban) have recently been proposed as an alternative. One advantage of these new agents is that, contrary to warfarin, they do not require any dosage individualization based on laboratory parameters; other potential advantages include reduced stroke risk compared with warfarin and fewer drug-drug interactions leading to untoward effects [1–3].

In the past years, also the research on medical devices has focused on patients with non-valvular atrial fibrillation. An innovative device (Watchman) has been tested in this area, and a randomized trial [4–6] has shown that this device can be at least as effective as warfarin in reducing the risk of stroke. Watchman (WATCHMAN Left Atrial Appendage System, Atritech Inc., Plymouth, Minnesota) is a nitinol device implanted percutaneously that seals the left atrial appendage.

The main aim of the present analysis was to try an indirect treatment comparison involving pharmacological agents and devices. For this purpose, we omitted to compare individual pharmacological agents with one another and we placed our emphasis on contrasting the overall class of oral anticoagulants versus the implant of the medical device. Although this type of analysis was hampered by the limited information available on Watchman's effectiveness, our results generated a useful synthesis of current therapeutic evidence. A secondary aim of our work was to examine the main determinants of the economic profile of the treatments concerned; anyhow, our economic evaluation was kept at a basic level, and so a complete cost-effectiveness assessment of this therapeutic issue was not an objective of this commentary. In summary, we firstly performed a three-arm network meta-analysis to comparatively evaluate the effectiveness of new anticoagulants vs warfarin versus Watchman; then we carried out a budget impact analysis which was restricted to only the new drugs, due to the insufficient information on the expected degree of use of Watchman. Our methods for network meta-analysis have already been described [7–9] as well as those for budget impact analysis [10, 11].

Network meta-analysis

Our analysis examined two direct comparisons (new anticoagulants vs warfarin and Watchman vs warfarin), based on “real” randomised controlled studies, and one indirect comparison (new anticoagulants vs Watchman) for which no real controlled trial was available.

The results of the network meta-analysis, which separately evaluated two end-points (incidence of stroke and mortality), are presented in Fig. 1. For both end-points, the
direct comparison between Watchman and warfarin was
based on the only randomised trial currently available,
while the other direct comparison (new oral anticoagulants
vs. warfarin) was the meta-analytic result of three "real"
trials comparing a new oral anticoagulant (dabigatran or
rivaroxaban or apixaban, respectively) versus warfarin. The
indirect comparison (Watchman vs. new oral anticoagu-
lants) was the statistical result of the application of a
standard network meta-analysis software [9]. Table 1
summarises the information about the four randomised
trials from which the effectiveness data were drawn.

As regards stroke (Fig. 1, Panel A), the results of net-
work meta-analysis incorporated the non-inferiority finding
for the comparison of Watchman vs warfarin and con-
firmed the superiority of anticoagulants over warfarin
(RR = 0.91 with 95% CI of 0.85 to 0.97; risk difference = −0.7 %; number needed to treat = 143; 95% CI:
91 to 250). More interestingly, the indirect comparison of
this network meta-analysis found no statistical difference
for the comparison of Watchman vs new anticoagulants
(RR = 0.68; 95% CI: 0.36 to 1.32).

As regards cardiovascular mortality (Panel B), the
results of network meta-analysis incorporated, also in this
case, the non-inferiority of Watchman vs warfarin and the
superiority of anticoagulants over warfarin (RR = 0.79
with 95% CI of 0.68 to 0.92; risk difference = −0.8 %; number needed to treat = 125; 95% CI: 77 to 333). The
indirect comparison found no statistical difference for the
comparison of Watchman vs new anticoagulants (RR = 1.00;
95% CI: 0.48 to 2.07).

Budget impact analysis

Several reports have studied the cost-effectiveness of the
new oral anticoagulants (particularly dabigatran) with quite
favourable pharmacoeconomic results [12, 13]. In contrast,
no economic analysis has been carried out for the Watchman

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**Fig. 1** Results of our network meta-analysis. Each direct
comparison is represented by a solid line and each indirect
comparison by a dotted line. The end-point is stroke in Panel
A and death in Panel B. Plus sign (+) indicates which
treatment is favoured at levels of statistical significance.
minus sign (−) indicates which
treatment is favoured at levels of statistical significance.
Equal sign (=) denotes comparisons showing
no significant difference, and t
indicates which treatment is
favoured by a trend in cases of
no significant difference.
RR relative risk; CI confidence
interval

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**Table 1** Summary of the trials included in the network meta-analysis for stroke prevention.

<table>
<thead>
<tr>
<th>Trial</th>
<th>Comparator</th>
<th>Event</th>
<th>Number of Patients</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panel A</td>
<td>Watchman vs Warfarin</td>
<td>Stroke</td>
<td>143</td>
<td>0.91 (0.85 to 0.97)</td>
</tr>
<tr>
<td>Panel B</td>
<td>Watchman vs Warfarin</td>
<td>Cardiovascular Mortality</td>
<td>125</td>
<td>0.79 (0.68 to 0.92)</td>
</tr>
</tbody>
</table>

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**Panel A**

Watchman

New Oral Anticoagulants

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**Panel B**

Watchman

New Oral Anticoagulants

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**New Oral Anticoagulants**

Dabigatran

Rivaroxaban

Apixaban

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Table 1: Characteristics of the four randomised trials included in our network meta-analysis

<table>
<thead>
<tr>
<th>Trial's acronym</th>
<th>Innovative intervention</th>
<th>Median follow-up (years)</th>
<th>End-point</th>
<th>Event rate</th>
<th>Trial's results</th>
</tr>
</thead>
<tbody>
<tr>
<td>RE-LY [1]</td>
<td>Dabigatran 150 mg twice daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>2</td>
<td>Death from any cause</td>
<td>438/6076</td>
<td>RR = 0.88 (0.77–1.00)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke or systemic embolism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>134/6076</td>
<td>p = 0.051</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>487/6022</td>
<td></td>
</tr>
<tr>
<td>ROCKET AF [2]</td>
<td>Rivaroxaban 20 mg/day&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.94</td>
<td>Death from any cause</td>
<td>582/7081</td>
<td>RR = 0.89 (0.82–1.03)</td>
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<td></td>
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<td>Stroke or systemic embolism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>269/7081</td>
<td>p = 0.12</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>306/7090</td>
<td></td>
</tr>
<tr>
<td>ARISTOTLE [3]</td>
<td>Apixaban 5 mg twice daily&lt;sup&gt;a&lt;/sup&gt;</td>
<td>1.8</td>
<td>Death from any cause</td>
<td>603/9120</td>
<td>RR = 0.90 (0.89–0.99)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Stroke or systemic embolism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>212/9120</td>
<td>p = 0.047</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>263/9081</td>
<td></td>
</tr>
<tr>
<td>PROTECT AF [4]</td>
<td>Watchman</td>
<td>1.5</td>
<td>Death from any cause</td>
<td>21/463</td>
<td>RR = 0.62 (0.34–1.24)</td>
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<tr>
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<td>Stroke or systemic embolism&lt;sup&gt;b&lt;/sup&gt;</td>
<td>18/463</td>
<td>p = 0.01</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>Controls</td>
<td>12/244</td>
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Relative risk; HR hazard ratio

<sup>a</sup> Pooling the three anticoagulants into a single treatment option yielded a meta-analytic RR of 0.91 (95% CI: 0.85 to 0.97; I² = 26%) for cardiovascular mortality and 0.79 (95% CI: 0.68 to 0.92; I² = 51%) for stroke (data from the three trials, comparator = warfarin; meta-analysis model = random effect)

<sup>b</sup> Stroke included ischemic and hemorrhagic stroke

<sup>c</sup> All analyses were based on the intention-to-treat principle; 95% CI are indicated in parenthesis

<sup>d</sup> From page 888 of the original publication

...device, mainly because of scarce information on its effectiveness. In this framework, we restricted our economic analysis to a budget-impact prediction focused on the new oral agents to try to solve the uncertainty about the extent of their use and, more importantly, the extent of economic consequences.

Dabigatran has already been approved for atrial fibrillation by EMA and by several national regulatory agencies, and its price has already been determined in several countries. The drug price has generally undergone some rebates in comparison with the price level previously adopted for prevention of post-operative thromboembolic events. In Europe, 1 year of dabigatran treatment for atrial fibrillation costs around GBP 900 in the UK and less (or slightly less) than EUR 1,000 elsewhere [12]. The globalization of pharmaceutical markets has much increased the international homogeneity of drug prices; hence, transferring the cost of innovative drugs from one country to another within Europe tends to imply a reasonable approximation.

Predicting the economic impact of replacing warfarin with these new agents (at least in a certain proportion of patients previously given warfarin) is a crucial point in terms of pharmaceutical governance, especially in countries like Italy where the national health system provides full economic coverage of all essential treatments. This prediction is more important when the new drug has a favourable cost-effectiveness [13] and is therefore likely to be not only reimbursed by national health systems but also employed quite extensively.

In carrying out our budget-impact predictions, we firstly estimated the number of patients that could potentially receive the treatment concerned. For this purpose, we used two different approaches applied in two separate scenarios denoted as Scenario A and B. The first approach ("front-to-tail", i.e. characterized by an antero-gradual modality) relied on the prevalence values for this disease condition (with extrapolation to a population of 60 million) and then assumed that all patients affected by the disease are candidate to receive the treatment. The second ("tail to front", i.e. characterized by a retrograde modality) relied on retrieving the annual consumption of warfarin and then converted this consumption into an estimate of the number of patients assumed to be under chronic treatment with warfarin and therefore switchable to dabigatran. Of course, the first approach (Scenario A) tends to give higher values of consumption for the new drugs than the second (Scenario B). Irrespective of which approach is used, the estimated number of potential patients must be subjected in both cases to a downward adjustment to take into account that, in a real-world setting, only a fraction (F) of the potential...
patients actually receive the treatment. In our simulation, the option of using the new oral anticoagulant has been referred to dabigatran, the first of the three new oral anticoagulants that has received regulatory approval and for which preliminary information on its price level is already available. As shown by recent analyses [14, 15], the effectiveness of dabigatran seems to be similar to that of apixaban and rivaroxaban. Indeed, an indirect meta-analytical comparison favoring dabigatran over rivaroxaban has been published by Manhù and Hansell [14] and by Fadda et al [16], but its statistical significance was borderline in both studies. "Appendix" describes in detail the equations used in our simplified budget impact prediction.

The results of our analysis (Fig. 2) differed quite substantially between Scenario A and Scenario B. In Scenario A, the starting point was that the prevalence of non-valvular atrial fibrillation is around 1.75% in Italy [17]. Normalization to a population of 60 million yielded a nationwide estimate of about 1 million patients; if one third of these patients (fraction, F = 0.33) are assumed to receive dabigatran (N = 333,000), the budget impact at steady state is EUR 300 million per year.

In Scenario B, the starting point was the annual expenditure of warfarin in Italy (EUR 10.4 million in 2010). Assuming that each patient receives 600 tablets per year and considering a cost of EUR 3.33 for every 100 warfarin tablets (yearly cost per patient = EUR 20), this figure of national expenditure translated into an estimate of about 500,000 Italian patients receiving warfarin every year. If one third of these patients (F = 0.33) are assumed to receive dabigatran (N = 165,000), the budget impact at steady state is EUR 148 million per year. These two scenarios are intended to represent a rudimentary form of sensitivity analysis.

Conclusive remarks

The current status of the treatments discussed herein is quite different.

As regards the new oral anticoagulants, more than 50,000 patients have been accrued in the three pivotal trials, and many more are being treated as the three drugs become available worldwide for this new therapeutic indication. The cost per patient is quite similar across different countries, but the degree of reimbursement differs, even though decisions on this issue are still underway in several countries, including Italy. In summary, more time is needed to exactly define the place in therapy of these new oral anticoagulants.

As regards Watchman, the device was approved for marketing in Europe and other CE Mark countries in 2009. Its unit cost is around 5,000 euros (website AcrossItaly, Acrossitaly Project, Italy, URL: www.osservatorionovazione.net/acrossitaly.htm), to which one should however add the cost of the in-hospital implantation procedure. Watchman is still an investigational device in the US, limited by to investigational use and not available for sale. The FDA in fact requested more information than the PROTECT AF study produced, and this led to developing another randomized trial (PREVAIL), in which enrolment is expected to be completed in the second quarter of 2012 [18]. Overall, Watchman has accrued more than 2,000 patients enrolled in prospective studies and nearly 4,000 patient-years of follow up [19]. A report about its safety has been published in February 2011 [5]. At present, Watchman can at best be an option for patients unfit to receive both warfarin and the new anticoagulants [6]. As a result, the sustainability challenge for treating atrial fibrillation will be played essentially around the choice between warfarin and the newest agents.

The results of our network meta-analysis suggest no difference in effectiveness between the new anticoagulants and Watchman. However, this finding must be tempered by the very different regulatory status of these new options, the lack of mature safety data for Watchman and, above all, the very different setting needed for their administration or implant. Another point of uncertainty is whether or not the "real" patients in whom Watchman is implanted will be receiving also anticoagulant agents such as warfarin or the new oral anticoagulants.

In the absence of changes in the current "universalistic" reimbursement policy of countries like Italy, the sustainability challenge that national health systems will shortly face is likely to involve an extra budget of around EUR 200 million (in a 60 million inhabitant country) only for the new anti-coagulants in atrial fibrillation. Other drug classes...
however are critical as well in terms of sustainability. Maratea et al [10], estimated that triple therapy for hepatitis C could have a budget impact around EUR 120 million in Italy (years: 2013–2016); likewise, in another analysis focused in the Italian market as well, Messori et al. (unpublished observations) estimated an increase by at least EUR 100 million for innovative anti-cancer agents (reference years: 2013 to 2016). All of these analyses indicate that the challenge of sustainability will be particularly difficult in the near future and this holds true especially for countries where all essential pharmaceutical treatments have constantly been reimbursed with no exceptions.

In conclusion, the pre-requisite for a successful governance in this area is to explore in comparative terms the information available on effectiveness, safety, and cost for each of the new therapeutic options. Several regulatory agencies such as the National Institute for Clinical Excellence (NICE) and the Scottish Medical Consortium, often use the mixed treatment comparison method (also known as indirect treatment comparison) to gain more effectiveness data on new treatments: in fact, this method tends to be considered, not only by regulatory agencies but also by the scientific community, a useful tool for evidence synthesis, decision-making support and cost-effectiveness analysis, when possible. In the case of our study, although network meta-analysis proved to be helpful to explore this controversial issue, the well-known limitations of this technique should not however be overlooked [20,21]. The main advantage of our work is that data concerning drugs and devices have been collated into a single assessment; the need for a unified approach evaluating both drugs and medical devices is increasingly been recognised, also in the field of atrial fibrillation [22].

Funding None.

Conflicts of interest None.

Appendix

To improve our analysis we incorporated the parameters of both scenarios into a rudimental model that has previously been proposed for budget-impact predictions [10, 11]; its equations are as follows:

\[
PTS = \text{TARGET} \times \left(1 - e^{-0.603/\text{HLgrowth} \times \text{time}}\right) 
\]

(1)

where 
\(PTS\) = patients being treated at time \(t\); 
\(TARGET\) = yearly population receiving the treatment; 
\(HLgrowth\) = half-life of the process of drug uptake (or switched from warfarin) in the market

(nationwide yearly expenditure) = (yearly cost per patient) \times PTS_{time} 

(2)

By using this model, the time-course of the expected incremental expenditure from 2012 to 2016 had the pattern shown in Fig. 1 (Scenario A = solid line; Scenario B = dotted line). These predictions have considered dabigatran, but are intended to represent the entire class of new anticoagulants as other agents are approved. The yearly cost of dabigatran has been set at EUR 900.

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