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Original article

The cost implications of the use of telmisartan or ramipril in patients at high risk for vascular events: the ONTARGET study

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Abstract

Background:
The recently published ONTARGET trial found that telmisartan was non-inferior to ramipril in reducing CV death, MI, stroke, or heart failure in patients with vascular disease or high-risk diabetes. The cost implications of ramipril and telmisartan monotherapy use based on the ONTARGET study are reported here.

Methods and results:
Only healthcare system costs were considered. Healthcare resource utilization was collected for each patient during the trial. The authors obtained country-specific unit costs to the different healthcare care resources consumed (i.e., hospitalizations events, procedures, non-study, and study drugs) for all enrolled patients. Purchasing power parities were used to convert country-specific costs into US dollars (US$ 2008). The total undiscounted costs of the study for the telmisartan group was $12,762 per patient and is higher than the ramipril group at $12,007 per patient, an un-discounted difference of $755 (95% confidence interval [CI], $218–$1292); The discounted costs for the telmisartan group was $11,722 compared with $11,019 for the ramipril group; a difference of $703 (95% CI, $209–$1197). The difference in costs is exclusively related to the acquisition cost of telmisartan over generic ramipril.

Limitations:
This analysis only considered direct healthcare system costs. Costs accrued outside the hospital were not collected. Combination therapy was excluded since it would likely be more expensive than ramipril alone, with no additional benefit and a risk of some harm.

Conclusions:
Based on these results, it is suggested that for the ONTARGET patients, the use of telmisartan instead of ramipril increases costs by 6.3%. These findings suggest that the choice to put patients on telmisartan should be justified based on the patient's susceptibility to specific adverse events to minimize the cost implications.

Introduction

The role of angiotensin-converting-enzyme (ACE) inhibitors in high risk patients without left ventricular dysfunction or heart failure was evaluated in the Heart Outcomes Prevention Evaluation (HOPE) study[1]. The HOPE study looked at a primary outcome of a composite of myocardial infarction, stroke, or death from cardiovascular causes in 9541 patients with a history of cardiovascular disease. The results of this study demonstrated that rampiril is beneficial (i.e., prevents cardiovascular death, myocardial infarction, and stroke) for a broad range of patients without evidence of left ventricular dysfunction or

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heart failure who are at a high risk of cardiovascular events. The economic analysis of the HOPE study supported the use of ramipril in that population of patients by demonstrating that, in North American patients, ramipril was cost-neutral or cost-saving over 90% of the time[2].

The role of angiotensin-receptor blockers (ARBs) was unknown in this population of patients. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) is a large randomized trial that compared the ACE inhibitor ramipril, the ARB telmisartan, and the combination of the two drugs in patients with vascular disease or high-risk diabetes. It was found that telmisartan was non-inferior to ramipril, but the combination of drugs was associated with more adverse events without an increase in benefits.

The results of the ONTARGET trial have the potential to have a substantial impact on the clinical practice[3] of cardiologists and other physicians involved in the treatment of cardiovascular diseases and diabetes. Therefore, it is important to assess the cost implications of widespread use of telmisartan in this patient population. In this paper the estimated cost of management strategies using telmisartan or rampiril monotherapy based on the outcomes of the ONTARGET study are reported and the implications of these findings discussed.

Methods

Clinical trial

The ONTARGET[4] study was a large multi-center randomized controlled trial, recruiting 25,260 patients from 733 centers in 40 countries. Eligible patients were those with coronary artery, peripheral vascular, or cerebrovascular disease or high risk diabetes mellitus with end-organ damage. The main study outcomes were: death according to any cause, myocardial infarction, stroke, and hospitalization for heart failure. Secondary outcomes for the ONTARGET study were: revascularization, hospitalization for angina, worsening or new angina, new diagnosis of diabetes, any heart failure, new atrial fibrillation, renal impairment, and renal failure requiring dialysis. The primary objective of the trial was to determine whether the ARB telmisartan was not inferior to the ACE inhibitor ramipril and whether a combination of the two drugs was superior to ramipril alone.

A total of 8542 patients were randomized to receive telmisartan (80 mg daily); 8576 patients were randomized to receive ramipril (10 mg daily); and 8502 patients were assigned to receive a combination of the two drugs (combination group, telmisartan 80 mg daily plus ramipril 10 mg daily) for a mean follow-up of 56 months. It is important to note that all patients received conventional treatments for their condition, regardless of their randomized treatment assignments. These treatments include aspirin, diuretics, anti-anginal therapy, anti-hypertensive medication, and cholesterol-reducing agents according to their respective physicians. Therefore, all comparisons are based upon telmisartan vs ramipril in addition to the above therapies. Results of the clinical trial are shown in Table 1.

Cost analysis

The initial hypothesis was that for the patients participating in the trial, the management strategy of the use of telmisartan will be either cost-neutral or cost-saving compared to the management strategy of the use of ramipril. Thus, the cost analysis was performed in a way consistent with the underlying assumptions

Table 1. Summary of the ONTARGET results.

	Telmisartan group ($n = 8542$), *n* (%)	Ramipril group ($n = 8576$), *n* (%)
Primary outcome (CV death, MI, stroke, or hospitalization for heart failure)	1423 (16.7)	1412 (16.5)
Death from CV causes, MI, or stroke	1190 (13.9)	1210 (14.1)
Cardiovascular death	598 (7.0)	603 (7.0)
Myocardial infarction	440 (5.2)	413 (4.8)
Stroke	369 (4.3)	405 (4.7)
Hospitalization for heart failure	394 (4.6)	354 (4.1)
Death from any cause	989 (11.6)	1014 (11.8)

of the trial. Since the ONTARGET clinical trial demonstrated that a combination of ramipril and telmisartan were not superior to each of the drugs individually and in fact were slightly worse due to increased adverse events, this arm was not included in this analysis as it is a foregone conclusion that the cost of two drugs with no clinical benefit (and some harm) would not be a dominant strategy from an economic standpoint. Therefore, this analysis only compared the economic implications of telmisartan vs ramipril. Although a perspective that encompasses both the impact to society as well as the medical costs should be used, the authors were unable to include societal costs as they were not collected as part of the trial and it was felt that developing these on an international level would be highly contentious at best.

Healthcare utilization for each patient was extracted from the study CRFs. The authors obtained and assigned country-specific unit costs to healthcare care resources consumed for each hospitalization event, procedure, and study and non-study drug for all patients from all countries. Unit costs were applied to utilization data of individual patient services to arrive at a cost per patient, and then averaged within each treatment group (telmisartan or ramipril). Purchasing power parities (PPP) were used to convert country-specific costs into US dollars (US$ 2008). A discounting rate of 3% was applied to the cost of resources used throughout the duration of the ONTARGET study in order to adjust all future costs to their present value.

Healthcare utilization

Healthcare utilization involves documenting the resources that were consumed by patients receiving telmisartan or ramipril. Hospitalizations for each outcome event and procedures were extracted from the specific Case Report Forms (CRFs). Collection of resource utilization data through CRFs ensured consistency in its measurement for this analysis. Procedures (i.e., CABG, PCI, etc.) were also extracted from the specific CRFs. The authors accounted for all separate events for a specific patient rather than the first event or the most serious events (in contrast to the composite primary outcome) to better reflect the consumption of care by patients. Table 2 lists the total events per randomization group. Information about the non-study medications taken at home was collected in the trial. Community care and investigations performed out of hospital as an outpatient were not recorded. Given that a substantial proportion of expensive procedures or investigations were performed while patients were hospitalized, it was likely that most of the major components of healthcare resource utilization had been collected during the trial. A possible exception would be same day investigations not requiring hospitalization such as nuclear testing or echocardiograms, although coronary angiography (same-day procedure) was recorded. Information was also collected regarding when prescription of ARBs or ACE inhibitors became clinically indicated, patient cross-over to another group, and compliance for telmisartan or ramipril groups. The compliance of patients for study drugs was observed at each visit by the study nurses by counting the study pills. However, non-study drugs were only recorded as prescribed. Information on all hospitalizations was collected, but hospitalizations not related to a cardiovascular, diabetic diagnosis, or renal failure were subsequently removed from the analysis as they were responsible for a small amount of healthcare expenditure and were equally distributed among the groups.

Table 2. Frequency of all hospitalizations and procedures.

	Telmisartan group	Ramipril group
Myocardial infarction	514	526
Stroke	410	431
TIA	127	162
CHF	706	692
Angina (new or worsening)	1306	1315
Atria fibrillation	405	421
Cardiac arrest	27	33
Pulmonary embolism	46	25
Limb infections	208	204
Hypoglycemic event	62	68
Hyperglycemic event	171	175
Ketoacidosis	6	9
Renal failure – no dialysis	83	83
Renal failure – dialysis	52	48
PCI with stent	733	743
PTCA (no stent)	152	145
Peripheral angioplasty/surgery	400	397
CABG	245	256
Cardiac catheterizations only	906	900
Carotid endarterectomy	100	72
Limb amputation	59	51

TIA, Transient Ischemic Attack; CHF, Congestive Heart Failure; PCI, Percutaneous Coronary Intervention; PTCA, Percutaneous Transluminal Coronary Angioplasty; CABG, Coronary Artery Bypass Graft.

Unit costs

Although the use of healthcare resources was recorded prospectively, the associated unit costs were developed at the end of the trial. The authors endeavored to obtain specific unit costs for all events, procedures, study, and non-study drugs from all countries. The sources for unit costs were much more heterogeneous in nature. Different countries have different methods of determining event costs. Some countries in the ONTARGET study provided costs based on a DRG system, while other may have used their hospital accounting system.

All unit costs were converted into a single currency (US$ 2008) using the purchasing power parities (PPP)[5]. The use of PPP to convert all costs to a single currency reflects the purchasing power differences between countries and, thus, is preferred to the use of exchange rates. It allows us to aggregate the costs figures from different countries to arrive at an average cost per patient for the duration of the study in each strategy management.

Publicly available unit costs for healthcare services were not always easily accessible by foreigners (such as ourselves) because of language barriers and difference in the organization and disbursement of healthcare resources. In those cases where costs were unobtainable to us, national investigators or local experts provided unit costs for all events, procedures, and medications recorded in ONTARGET via a standardized questionnaire.

A complete dataset of unit costs was not available in all countries, but most expensive events or procedures were obtained. To impute missing data in this analysis, the authors divided the ONTARGET countries into six areas based on their geographical location, healthcare system, and overall economic status from the OECD[6]. The 40 ONTARGET countries were regrouped into: North America (2), South America (4), Western Europe (16), Eastern Europe (7), Asia Pacific high income (7), and Asia Pacific low income (4). The consumer price index was used to adjust unit costs to 2008 US$[7].

There were two notable exceptions to this process. Events and procedures related to hospitalizations in this study such as myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) are time-limited, and the consumption of care is mostly limited to that period of time. Stroke and renal failure are exceptions to this rule as the delivery of care to patients who suffered a stroke or have dialysis continues for months and years after the initial hospitalization. Hence, it is important to collect these costs over a long period of time. A period of 12 months was used for stroke and up to the end of the study for permanent dialysis. Few reliable sources of costing are available for the two events and it was necessary to generate unit costs for most countries based on their respective PPP ratio. For that reason, a sensitivity analysis was performed to assess various estimates of some unit costs such as stroke, transient ischemic attack (TIA), and renal failure with or without dialysis

Statistical analysis and sensitivity analysis

Unit costs were applied to utilization data of individual patient services to arrive at a cost per patient and then averaged within each treatment group (telmisartan or ramipril). Given that cost data are unlikely to be normally distributed, the bootstrap method was used to calculate standard errors and 95% confidence intervals[8] for the incremental average cost, and *t*-tests (significance level 0.05) were used to compare the difference. The bias corrected and accelerated (BCa) method was used for confidence intervals[9] for average costs. All analyses were completed using SAS 8.2.

A sensitivity analysis was performed to assess the effect of various estimates of some unit costs such as new diagnosis of TIA, renal failure with or without dialysis, and stroke on the result of the analysis. Variations of these unit costs were potentially more significant as they were extracted from various publications whose sample size was not very large and they are known to be expensive events. The sensitivity analysis was performed using a lower or higher estimate (±25%).

Results

Hospitalization, procedure costs, and non-study drugs

The costs for hospitalizations and procedures related to the development of various conditions were similar (NS) in both groups (Table 3). These costs were $4356 per patient for the telmisartan group and $4500 per patient in the ramipril group. The costs for procedures such as coronary artery revascularization procedures (PCI or CABG), carotid endarterectomy, and peripheral revascularization were also similar (NS) in the two groups, at $2417 per patient for the telmisartan group and $2379 per patient in the ramipril group. In each group the costs of non-study medications were substantial, but were nearly identical (NS), with $3470 per patient for the telmisartan group and $3449 per patient in the ramipril group. The sub-total costs for hospitalizations, procedures, and non-study drugs were similar (NS), at $10,243 per patient for the telmisartan group and $10,329 per patient in the ramipril group.

Study drug costs

Ramipril is available as a generic drug in many countries (but not all) and telmisartan is available only as a brand name (and not in all countries). The acquisition cost of

Table 3. Average costs per patient (with 95% CI) for all ONTARGET patients.

Category of cost	Telmisartan cost (95% CI)	Ramipril cost (95% CI)	Difference Tel. vs Ram. cost (95% CI)	*p*-value
Hospitalizations	$4356 (4048, 4667)	$4500 (4202, 4835)	−$144 (−580, 292)	0.520,51
Procedures	$2417 (2272, 2569)	$2379 (2228, 2527)	$38 (−173, 249)	0.724,20
Medications (nn-study)	$3470 (3402, 3538)	$3449 (3386, 3517)	$21 (−74, 116)	0.663,74
Study drug	$2519 (2487, 2552)	$1678 (1647, 1709)	$841* (795, 887)	<0.001
Total cost measured	$12,762 (12,391, 13,161)	$12,007 (11,636, 12,406)	$755* (218, 1292)	0.005,90
Total cost measured (discounted)	$11,722 (11,385, 12,088)	$11,019 (10,680, 11,387)	$703* (209, 1197)	0.005,29

*$p < 0.05$.

telmisartan is generally comparable to ramipril (brand name), but more expensive than ramipril as a generic. The approach chosen for this analysis was to use the cheapest cost when generic and brand names are both available to reflect the practice in the general population. The costs of study drug for the telmisartan group ($2519 per patient) were significantly higher than in the ramipril group ($1678 per patient), a difference of $841, (95% confidence interval [CI], $795–$887).

Overall costs

The total costs measured (non-discounted) for hospitalizations, procedures, non-study drugs, and study drugs for the telmisartan group were $12,762 per patient and were significantly higher than the ramipril group at $12,007 per patient, a difference of $755 (95% confidence interval [CI], $218–$1292).

Using a discounting rate of 3%, the total discounted costs for the telmisartan group were $11,722 per patient and were higher than the ramipril group at $11,019 per patient, a difference of $703 (95% confidence interval [CI], $209–$1197).

Sensitivity analyses

Unit costs for new diagnosis of TIA, stroke, and renal failure with or without dialysis were selected for the sensitivity analysis as variations were potentially more significant than other variables. Varying these unit costs by ±25% had limited impact on total costs measured per patient either individually or grouped. The total costs measured per patient did not change significantly and the differences between groups remained as described above.

Discussion

In this analysis, it was demonstrated that the use of telmisartan instead of ramipril increased the total costs measured per patient by 6.3% in the ONTARGET study. Note, however, that the sub-total costs for hospitalizations, procedures, and non-study drugs were slightly reduced in the telmisartan group ($10,544 per patient) compared to ramipril group ($10,645 per patient), but the difference in total costs measured was largely related to the acquisition costs of telmisartan (brand name) in comparison to ramipril (generic in most countries). The approach the authors decided to use in this analysis was to use the cheapest form (generic or brand name) normally available to the patient in a specific country.

Only direct healthcare system costs were used for this analysis. Although it is suggested that a societal perspective be considered, it is recognized that the use of other perspectives is acceptable and might be more appropriate in some cases[10,11]. Cost items which were missing include out-of-hospital patient costs as well as non-medical costs such as loss of productivity and the time provided by family and friends caring for patients. There is no good reason to believe that these costs are likely to be higher in either of the two groups. Hence, it seems that this analysis can be seen as a reasonable proxy for a societal perspective as well.

Based on the results, it is suggested that the use of telmisartan instead of ramipril in the ONTARGET trial increases costs and this was entirely related to the cost of telmisartan in comparison to cheaper form of generic ramipril. When generic telimisartan becomes available it would expected that this would alter the authors' findings. Until pricing is determined, the authors cannot speculate the full implications of generic telmisartan, but if it is assumed that it will be priced similarly to generic ramipril then the total treatment cost with telmisartan should be similar to ramipril. In addition, in view of evidence of high PPAR-gamma activity relative to other ARBs, there may be other benefits not captured in the ONTARGET trial[12,13].

Although rampiril costs less than telmisartan, these findings should not preclude us from following the clinical recommendation[4] that the choice between telmisartan and ramipril should be based on the patient's susceptibility to the adverse event profile of each drug. The findings, however, suggest that transferring patients from ramipril to telmistaran should be justified to minimize the cost implications.

Transparency

Declaration of funding
This work was supported by an unrestricted grant from Boehringer Ingelheim as part of the ONTARGET study. Boehringer Ingelheim was not involved in the design, conduct, interpretation, and analysis presented in this manuscript.

Declaration of financial/other relationships
A. Lamy, X. Wang, P. Gao, W. Tong, A. Gafni and R. Ferreira have no conflicts of interest to declare. A. Dans, J. Young, and K. Teo declare consulting and lecture fees and grant support from Boehringer Ingelheim. A. Avezum declares consulting and lecture fees from Boehringer Ingelheim and GlaxoSmithKline. Salim Yusuf declares consulting and lecture fees and research grants from Boehringer Ingelheim, AstraZeneca, Sanofi-Aventis, Servier, Bristol-Myers Squibb, and GlaxoSmithKline.

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