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Economic Evaluation

Cost-Utility of Prasugrel in Postangioplasty Diabetic Patients

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ABSTRACT

Objectives: To prevent thrombotic events after angioplasty, current guidelines recommend dual antiplatelet therapy with aspirin and thienopyridine. Clopidogrel is the only thienopyridine currently available in the Brazilian National Health System. The purpose of this study was to determine the cost-effectiveness of prasugrel, an alternative thienopyridine, compared with clopidogrel in patients with acute coronary syndrome and diabetes mellitus who underwent angioplasty.

Methods: A state-transition Markov model was created to simulate the progression of diabetic patients after angioplasty. The model had a lifetime horizon and discounted outcomes at a 5% annual rate. The risks of myocardial infarction and death were calculated using data from the diabetes subgroup, and the risks of bleeding were calculated using data from the overall group from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction 38 trial. Direct costs were estimated using official Brazilian open data. Quality of life values were obtained through literature search. Univariate and multivariate sensitivity analyses were performed.

Results: Prasugrel was associated with more quality-adjusted life-years (QALYs) (5.03 vs 4.94) and higher costs (US$975.11 vs US$575.97), resulting in an incremental cost-utility ratio (ICUR) of US$4303.86/QALY. In one-way sensitivity analysis, the costs of prasugrel had the greatest impact on ICUR, followed by the initial age entering the cohort. In the probabilistic sensitivity analysis, all ICUR values simulations were less than one Brazilian gross domestic product per capita/QALY (US $5802.86).

Conclusions: Given the appealing economic profile, the clinical debate between reducing the risk of myocardial infarction and increasing the risk of bleeding may overcome economic concerns in the Brazilian National Health System.

Keywords: acute coronary syndrome, cost-benefit analysis, economic, models, platelet aggregation inhibitors.

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Introduction

According to the World Health Organization, cardiovascular disease (CVD) is the leading cause of death and disability worldwide, accounting for 17.3 million deaths per year, a number that is expected to grow to >23.6 million by 2030.[1] In Brazil, the death rate for CVD in the population from 35 to 74 years old was 552.8 per 100 000 in 2010.[2] CVD encompasses many different health conditions, including myocardial infarction (MI) and unstable angina, which compose the acute coronary syndrome (ACS).[3] Among several available treatments, angioplasty is an important option in the management of ACS.[4] Current guidelines recommend dual antiplatelet therapy to prevent thrombotic events after angioplasty, including aspirin and a thienopyridine.[5,6] Clopidogrel is the thienopyridine most commonly used and the only one available in the Brazilian National Health System (Sistema Único de Saúde).[7]

Prasugrel is a potential new option because it is a thienopyridine agent with a faster onset of action and increased potency, which is more effective in reducing the combined incidence of cardiovascular death, nonfatal MI, and nonfatal stroke than clopidogrel (hazard ratio [HR] for prasugrel vs clopidogrel 0.81; 95% confidence interval [CI] 0.73-0.90; P <.001). Nevertheless, this enhanced effect of prasugrel did result in an increased risk of major bleeding (HR 1.32; 95% CI 1.03-1.68; P =.03), including fatal bleeding (0.4% vs 0.1%; HR 4.19; 95% CI 1.58-11.11). There was no significant difference regarding stroke, with 1% of incidence in both groups (HR 1.02; 95% CI 0.71-1.45).[8]

Due to the trade-off between reducing cardiovascular events and increasing the risk of bleeding, decision makers may choose to restrict prasugrel use to a subgroup of patients at higher cardiovascular risk, such as patients with diabetes mellitus (DM), and to avoid it in those at higher risk of bleeding, such as the elderly and those with low body weight.[9]

A subgroup analysis from the Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction (TRITON-TIMI) 38 (13 608 individuals) identified 3146 subjects with DM, including 776 receiving insulin. The primary endpoint (cardiovascular death, nonfatal MI, or nonfatal stroke) was significantly reduced with

prasugrel among subjects without DM (9.2% vs 10.6%; HR 0.86; P =.02) and with DM (12.2% vs 17.0%; HR 0.70; P <.001). Despite the fact that it seems plausible that patients with higher risks would benefit the most, the investigators were unable to find a significant interaction between DM and primary outcomes (P interaction =.09).[9]

The reduction in MI must be highlighted in this subgroup of patients with DM. Prasugrel reduced MI by 18% among subjects without DM (7.2% vs 8.7%; HR 0.82; P =.006) and by 40% in those with DM (8.2% vs 13.2%; HR 0.60; P <.001). There was a significant interaction when only MI was included (P interaction =.02).[9]

Although TIMI major hemorrhage was higher in prasugrel-treated participants without DM (1.6% vs 2.4%; HR 1.43; P =.02), rates were similar in clopidogrel- and prasugrel-treated participants with diabetes (2.6% vs 2.5%; HR 1.06; P =.81, P interaction =.29).[9]

Before incorporating prasugrel, decision makers must calculate the potential net clinical benefit compared with clopidogrel. In Brazil, health technologies are assessed by the National Committee for Health Technology Incorporation (Comissão Nacional de Incorporação de Tecnologias no Sistema Único de Saúde), which is responsible for analyzing the aspects of efficacy, safety, cost-effectiveness, and budget impact to recommend and help the Ministry of Health in the incorporation or disinvestment of new technologies for the National Health System.[10]

Hence, the purpose of this study was to evaluate the cost-utility of prasugrel compared with clopidogrel in diabetic patients undergoing angioplasty to provide useful economic evidence from the perspective of the Brazilian National Health System.

Methods

Model Description

A Markov model was constructed to simulate a cohort of 1000 postangioplasty diabetic patients over a lifetime horizon using Excel® software.[11] The model compared the costs and benefits of 12 months of prasugrel in combination with low-dose aspirin with 12 months of clopidogrel in combination with low-dose aspirin. Costs and benefits were discounted at 5% annually, giving the recommendations of the methodological guidelines for economic evaluation studies of health technologies in Brazil.[12]

A total of three mutually exclusive health states were created based on the risk of MI: stable, MI, and death. MI was selected because it was the only outcome with a significant interaction for DM. Each state was associated with specific costs and benefits. All patients began in the stable state and could transit to MI or death. Patients in MI state could transit to the stable state or death. The analyses included three different phases: from angioplasty to day 3 (first cycle), from day 3 to the end of the first year (second cycle), and annual cycles thereafter.

These phases were based on the findings of TRITON-TIMI 38, the only head-to-head controlled trial that evaluated clopidogrel versus prasugrel.[8] In this trial, 13 608 patients with moderate- to high-risk ACS who were scheduled for angioplasty were randomized to clopidogrel plus aspirin or prasugrel plus aspirin. The subgroup of diabetic patients (3146 patients) was prespecified.

Sources of Cost Data

The model used open data from the Brazilian Ministry of Health to consider costs of bleeding and MI (US$736.63) and costs of clopidogrel (US$0.046/tablet—loading dose of six tablets followed by one tablet a day for one year) and costs of death (US$462.55), with this one based on the costs of MI hospitalizations that resulted in patient death.[13,14] The costs of bleeding were calculated using the percent of patients who required blood transfusion in the pivotal trial (3% for clopidogrel and 4% for prasugrel within 15 months) based on the costs of hospitalizations for bleeding, totaling US$13.89 for clopidogrel and US$18.63 for prasugrel per year.[13–15]

The pricing of prasugrel (US$0.61/10 mg tablet), which starts with a single 60-mg loading dose and then continues at 10 mg once a day, was based on a price submitted to the Brazilian government by Daiichi Sankyo Company Ltd in 2020.[7,16] The costs of stroke were not included in the economic model because the pivotal trial found no difference in the risk of stroke (1% each) between the prasugrel and clopidogrel arms.[8]

The amounts in Brazilian Reais were converted to US dollars with September 15, 2020, as the reference date, using the official exchange rate of the Brazilian Central Bank (US$1 equal to R$5.24).

Efficacy

The efficacy (risk reduction for death and MI) was based on the TRITON-TIMI 38 study.[8] All model parameters are listed in Table 1. With clopidogrel, the risk of MI was 4.20% for the first cycle (three days after angioplasty) and 6.17% for the second cycle compared with 2.45% and 5.23% with prasugrel in its first and second's cycle, respectively. Because active therapy with clopidogrel or prasugrel had been discontinued by the third cycle, it was expected that incident rates in both treatment arms would be equal.

The risk of a new MI was divided among patients who had had an MI and patients who had not. These risks were estimated based on the subgroup of diabetic patients in the prospective Organization to Assess Strategies for Ischemic Syndromes registry, which provided long-term information on patients with and without DM with unstable coronary artery disease from six different countries.[17] The 2-year event rate was calculated for a 1-year probability of reinfarction (6.78%) or to have a new MI (5.5%).

The death probability was estimated using TRITON-TIMI 38 mortality rates,[8] which took into account the presence (5.8% annually) or absence of MI (2.8% annually), and the Brazilian population's predicted survival by age. The cohort started at 63 years old (55-71 years old) for both interventions, which was the mean age in the diabetic subgroup from the TRITON-TIMI 38.

Utilities

The utility for the event-free patients (0.874) was based on the data from the National Institute for Health and Care Excellence in their economic model comparing prasugrel with clopidogrel, where they looked at the utility values of an American cohort of patients who had undergone angioplasty using the EQ-5D instrument.[18] The disutility of 0.037 for nonfatal infarction and 0.0033 for bleeding requiring transfusion was subtracted from the patient`s total quality-adjusted life expectancy for each episode.[19]

Sensitivity Analysis

According to the Brazilian Society of Cardiology's angioplasty guidelines, the incidence of MI related to angioplasty in Brazil is approximately 3% to 5%, a range that has been progressively decreasing over the years, reaching 1.5% in the new millennium.[20] We adopted in the sensitivity analysis 1.5% as the lower and 5% as the upper limits of MI risk for clopidogrel and 0.9% and 2.9% for prasugrel, considering its relative risk reduction.

The probability of yearly infarction from other trials, such as the Bypass Angioplasty Revascularization Investigation (BARI) randomized trial; the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial; and the

Table 1. Parameters used in the Markov model to estimate the impact of prasugrel versus clopidogrel in diabetic patients after percutaneous coronary intervention.

Parameter	SV	LL	UL
Risk of MI in the first cycle with clopidogrel, %	4.20	1.50	5.00
Risk of MI in the first cycle with prasugrel, %	2.45	0.87	2.91
Risk of MI in the second cycle with clopidogrel, %	6.17	2.23	6.17
Risk of MI in the second cycle with prasugrel, %	5.23	1.89	5.23
Risk of MI in the third cycle, %	5.80	4.64	6.96
Death probability in the first cycle with clopidogrel, %	1.72	1.71	1.74
Death probability in the first cycle with prasugrel, %	1.00	0.99	1.02
Death probability in the second cycle with clopidogrel, %	2.53	2.51	2.55
Death probability in the second cycle with prasugrel, %	2.15	2.13	2.16
Death probability in the third cycle MI group, %	4.84	3.87	5.81
Death probability in the third cycle stable group, %	2.77	2.22	3.32
Age	63	55	71
Initial utility	0.874	0.869	0.888
MI disutility	0.037	0.037	0.037
Bleeding disutility	0.033	0.033	0.033
MI costs, $	736.63	589.30	883.96
Death costs, $	462.55	370.04	555.06
Prasugrel costs, $	0.61	0.49	0.73
Clopidogrel costs, $	0.05	0.05	0.05
Cost of bleeding, $	640.08	640.08	640.08

LL indicates lower limit; MI, myocardial infarction; SV, standard value; UL, upper limit.

Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial, was taken into account in the second cycle to specify the range of the probability of MI. The probabilities were 2.2% for BARI, 2.8% for COURAGE and 3.4% for FREEDOM.[21-23] The BARI trial's infarction risk was used as the lower limit because it was the lowest risk found in a group of diabetic individuals having angioplasty.[21] For the upper limit, the mean value of MI observed in TRITON-TIMI 38 (6.17%) was kept, because it was much higher than the risks observed in the other studies. For the prasugrel group, the risks were reduced by the relative risk reduction (0.848) estimated in TRITON-TIMI 38.[8]

Univariate and multivariate sensitivity analyses were conducted for the estimated incremental cost-utility ratios (ICURs) and derived cost-effectiveness acceptability curves. In the probabilistic analysis, simultaneous variations in all key parameters were performed using a Monte Carlo simulation of 1000 interactions. Gamma distributions were used for cost parameters and beta distributions for utilities. The parameters used in the model and their respective limits used in the sensitivity analysis are presented in Table 1.

Results

Compared with clopidogrel, prasugrel was associated with greater quality of life (0.09 incremental quality-adjusted life-years [QALYs]) and higher incremental costs (US$398.31), yielding an ICUR of US$4303.86/QALY (Table 2).

All of the results from the univariate sensitivity analysis were less than one Brazilian gross domestic product (GDP) per capita/QALY (US$5802.86). A tornado diagram with the parameters displayed in descending order of influence is depicted in Figure 1.[24] The cost of prasugrel, which was varied by 20% in the sensitivity analysis, was the parameter that had the greatest impact on the ICUR result, with values ranging from US$3871.77 to US$4735.94.

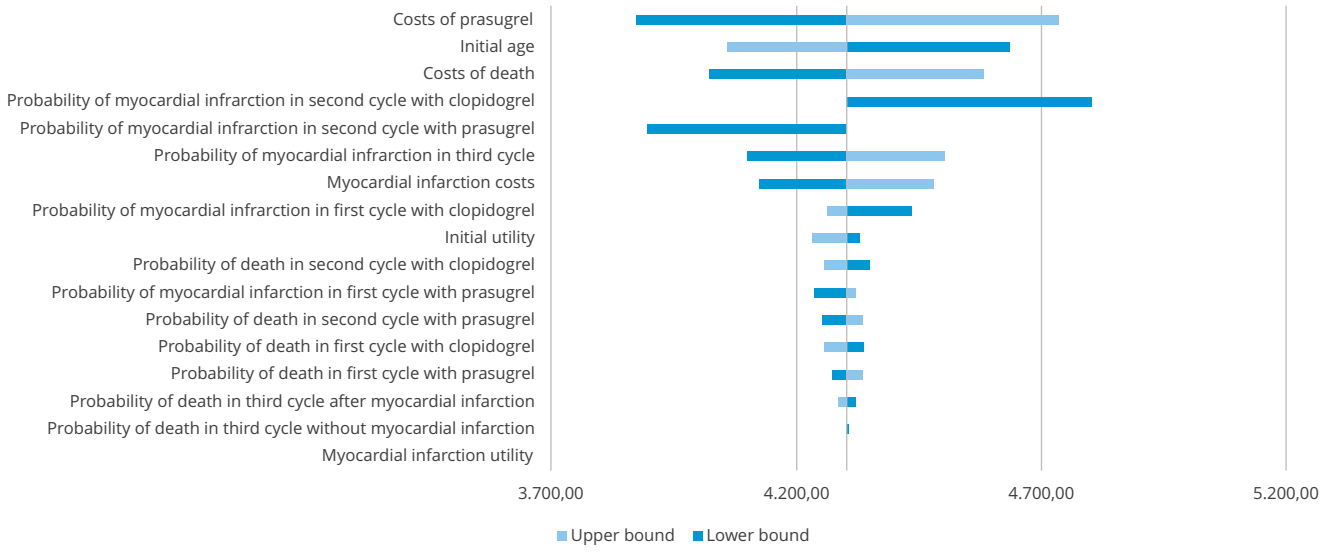
Prasugrel was cost-effective in all simulations in the probabilistic sensitivity analysis based on a willingness to pay of one Brazilian GDP per capita/QALY[24] (Fig. 2). In Brazil, there is no mandatory threshold, but it is well known that values less than one and especially less than three GDP per capita/QALY are less likely to be recommended. The cost-effectiveness acceptability curve depicts the likelihood of prasugrel being cost-effective across a range of cost-effectiveness thresholds (Fig. 3).

Table 2. Cost-utility results from prasugrel versus clopidogrel in patients with diabetes undergoing angioplasty.

Technology	Costs (US$)	QALYs	Incremental costs (US$)	Incremental QALYs	ICUR (US$)
Clopidogrel	575.97	4.94	399.14	0.093	4303.86
Prasugrel	975.11	5.03			

ICUR indicates incremental cost-utility ratio; QALY, quality-adjusted life-year.

Figure 1. Tornado diagram of univariate sensitivity analysis of prasugrel versus clopidogrel in the postangioplasty diabetic population.



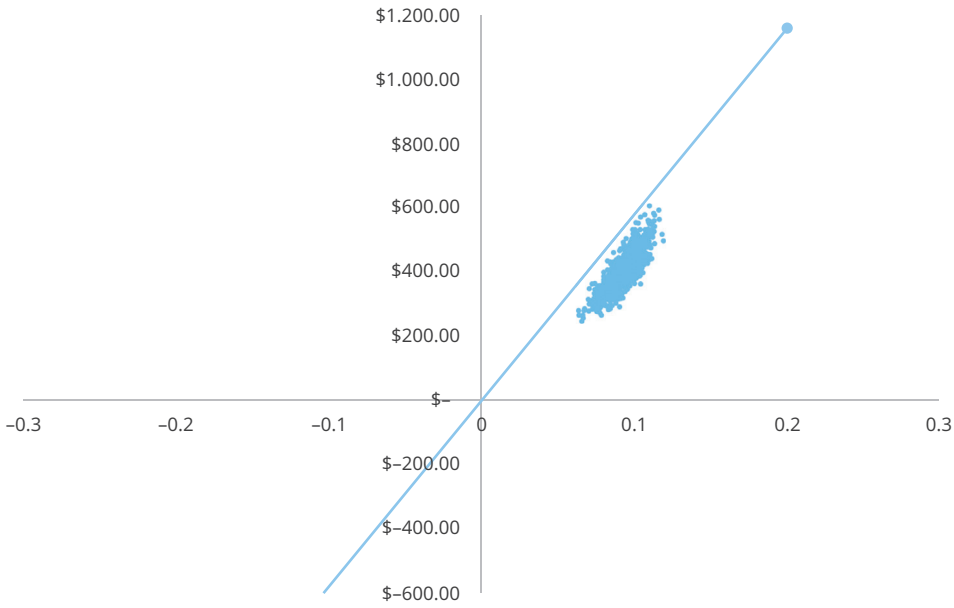
Discussion

In this model, developed in the context of the Brazilian National Health System, prasugrel was found to be cost-effective for one Brazilian GDP per capita/QALY. This finding is consistent with the Daiichi Sankyo model, which concluded that prasugrel was very cost-effective, with an ICUR value of US$2634/QALY.[25]

Even though it is not possible to directly compare the ICUR results with cost-effectiveness studies developed in other countries (given the use of local costs in the economic models), the gain in effectiveness is an interesting measurement of the model's credibility, given that the benefits gain is usually based on the same pivotal trial. The 0.093 incremental QALY identified in this model is very similar to the incremental QALYs gained in other studies comparing prasugrel and clopidogrel also based on the TRITON-TIMI 38 trial (not limited to diabetic patients), such as Mahoney et al[15] (0.095 QALY) and Davies et al[26] (0.137 QALYs).

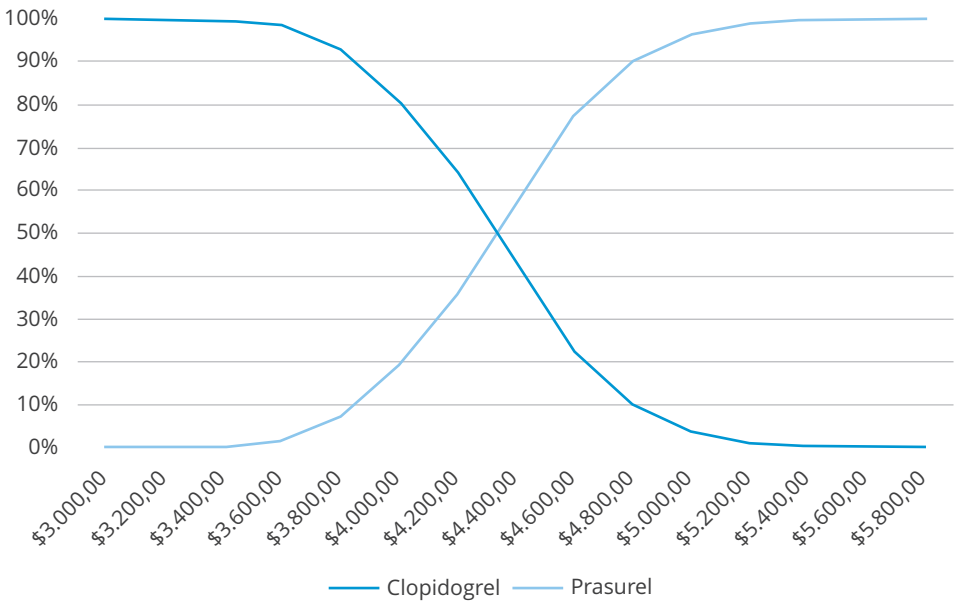
This study has some limitations. The model is specific for diabetic patients who undergo angioplasty, so the conclusions cannot be extrapolated for those receiving medical treatment or without diabetes. There is no utility estimation of MI and bleeding in the Brazilian population, so we used the utilities estimated in a different population. Even the TRITON-TIMI 38 substudy, which included health-related quality of life, could not be considered, because it presented a small number of events that limited the

Figure 2. Scatterplot—prasugrel versus clopidogrel for a willingness to pay of 1 Brazilian GDP per capita/QALY in the postangioplasty diabetic population.



GDP indicates gross domestic product; QALY, quality-adjusted life-year.

Figure 3. Acceptability curve—prasugrel versus clopidogrel. Cost-effectiveness acceptability curve obtained from probabilistic sensitivity analysis in the TRITON-TIMI 38 diabetic subgroup. The curve shows for prasugrel and clopidogrel, the proportion of 1000 simulated samples for which the strategy was cost-effective at varying levels of WTP per additional QALY.



QALY indicates quality-adjusted life-year; TRITON-TIMI, Trial to Assess Improvement in Therapeutic Outcomes by Optimizing Platelet Inhibition With Prasugrel Thrombolysis in Myocardial Infarction; WTP, willingness to pay.

estimates.[8] The pivotal study yielded the probabilities of dying or having a recurrent MI, which did not necessarily reflect real-life probabilities in Brazil. Finally, the economic evaluation during the drug incorporation decision takes into account not only cost-effectiveness but also the budgetary impact, which was not estimated and is critical for the long-term viability of the health system.

It should be highlighted that, although the model identified an economic profile that could be considered appealing for prasugrel incorporation, its safety may be considered a barrier. Bleeding is an important issue in this scenario. Although prasugrel is associated with a significant reduction in MI (9.7% in the clopidogrel group vs 7.4% in the prasugrel group; HR 0.76; 95% CI 0.67-0.85), the risk of bleeding is higher with prasugrel: spontaneous 1.6% versus 1.1%; requiring transfusion 4.0% versus 3.0%; life threatening 1.4% versus 0.9%; and fatal 0.4% versus 0.1%.[8] The key safety endpoint in TRITON-TIMI 38 was noncoronary artery bypass graft surgery–related thrombolysis in MI major bleeding which was again more frequent among patients receiving prasugrel than among those receiving clopidogrel (HR 1.32; 95% CI 1.03-1.68).[8] Hence, regardless of the financial costs, it is debatable whether a 24% reduction in the risk of a nonfatal infarction outweighs a 32% increase in the risk of bleeding.

The Brazilian Society of Cardiology (Sociedade Brasileira de Cardiologia), a nongovernmental organization, recently recommended prasugrel for dual antiplatelet therapy.[27] The final decision regarding its incorporation is reserved to the Brazilian Ministry of Health; therefore, this work intends to support that decision with independent data.

Conclusions

A range of sensitivity analyses indicates that, for diabetic patients undergoing angioplasty, dual antiplatelet therapy with prasugrel in comparison with clopidogrel presents a favorable economic profile. Beyond economic considerations, the trade-off between clinical benefits and bleeding risks must be considered. More research is needed to determine which patient subgroups will benefit the most from the incorporation of prasugrel into the Brazilian National Health System.

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