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Cost-Effectiveness Analysis of Vaginal Misoprostol versus Dinoprostone Pessary: a large noninferiority RCT in France.

Authors

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Short title: The cost-effectiveness of Misoprostol versus PGE2 pessary

Synopsis: We have shown disparate cost-effectiveness results between 25-µg vaginal misoprostol versus dinoprostone pessary according to the clinical outcome and the payer perspective.

This article is considered to be a **Clinical Article**.

Key words: Dinoprostone, labor induction, misoprostol, cost-effectiveness analysis, PGE2 pessary, vaginal

Abstract word count: 215 words

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Abstract

Objective: To assess the cost-effectiveness of vaginal misoprostol (PGE1) (25µg) compared to a slow-release dinoprostone (PGE2) pessary (10µg) for labor induction due to an unfavorable cervix at term.

Methods: We used data from an open-label multicenter, randomized noninferiority trial which recruited women for whom labor was induced for medical reasons, a Bishop score ≤ 5 at ≥ 36 weeks, and a cephalic-presenting singleton pregnancy with no prior cesarean delivery. The Incremental Cost Effectiveness Ratio (ICER) was assessed from the payer's perspective, with the focus on inpatient care costs and using the Caesarean Deliveries Avoided (CDA) rate as primary analysis and the rate of Vaginal Delivery within 24h (VD24) as secondary analysis.

Results: Analyses were based on 790 women in each group. Differences between treatment arms were the mean cost per patient of €4,410 and €4,399, a CDA rate of 80.1% and 77.9% and a VD24 rate of 46.1% and 59.4% for dinoprostone and misoprostol respectively. Dinoprostone is not cost-effective according to the CDA and misoprostol was either a cost-effective or a dominant strategy according to the VD24.

Conclusion: Misoprostol and dinoprostone have equal cost management with mixed efficacy according to the clinical outcome used. Finally, misoprostol may be an attractive option for hospitals since the price is lower and it is easier to use.

Trial Registration. ClinicalTrials.gov: NCT01765881. URL:

<https://clinicaltrials.gov/ct2/show/NCT01765881>

ClinicalTrialRegistrer.eu: 2011-000933-35. URL:

<https://www.clinicaltrialsregister.eu/ctr-search/trial/2011-000933-35/FR>

Introduction

Induction of labor (IOL) is a common procedure, performed for approximately 40% of nulliparous and 30% of multiparous women [1]. It is recommended for women with a medical indication and may be justified after 39 weeks of gestation to improve the safety for mothers as well as infants [2, 3].

At present, the drug of reference for induction is slow-release dinoprostone (PGE₂) [4]. In comparison, misoprostol, a synthetic analog of prostaglandin E₁ (PGE₁) is a less expensive, thermostable and easier-to-use drug. Misoprostol has been in use for several years and the optimal dose and route of administration have been widely studied [5, 6]. Therefore, a low-dose by vaginal (25 µg) route is recommended as a first-line treatment for IOL by the American College of Obstetricians and Gynecologists (ACOG) [7], the International Federation of Gynecology and Obstetrics [8], and the World Health Organization [9].

Economic data comparing vaginal misoprostol and dinoprostone are sparse and are based on extremely small studies. A 2003 RCT compared the efficacy and cost of misoprostol (i.e., 50 µg renewed 6 hours later) to those of dinoprostone (either in a 0.5-mg gel renewed 6 hours later or a 10-mg slow-release pessary) and concluded that misoprostol was the most cost-effective strategy [10]. More recent studies from 2016 and 2017, in the US and Spain respectively, have shown cost saving results in favor of vaginal misoprostol in comparison to dinoprostone [11, 12]. Since 2018, misoprostol is no longer reimbursed in France and dinoprostone is the gold standard for IOL management.

The CYTOPRO (CYTOtec® vs PROpess®) trial was designed to test the hypothesis that 25-µg of vaginal misoprostol every four hours would not be inferior to a 10-mg

slow-release dinoprostone pessary in terms of Cesarean Delivery (CD) rates. We hypothesized that vaginal misoprostol is cost-effective compared to dinoprostone and since this concerns a large population, it could provide substantial public health savings. The primary objective of this work was to assess the cost-effectiveness of misoprostol compared to dinoprostone using CD rates. In addition, we aim to use Vaginal Delivery rate within 24 hours (VD24) in a secondary analysis.

Methods

Study design and patients

The CYTOPRO trial was an open-label, multicenter, randomized, noninferiority trial conducted from September 2012 to June 2015 in four French centers and aimed to compare the efficacy and safety of intravaginal misoprostol (25 µg) every four hours to a 10-mg slow-release dinoprostone pessary (PGE₂) [13]. Participating centers were public centers with two in the Paris area (Bicêtre and Poissy), one in Strasbourg and one in Toulouse, which all belong to the French Obstetrics and Gynecology Research Group. This study was supported by the French Ministry of health and was sponsored by the Toulouse University Hospital Center. Clinical data were prospectively collected while economic data were retrospectively collected using a claims database.

The study population was women aged of 18 years or older with a viable singleton fetus in cephalic presentation, a gestational age of 36 weeks or more, an unfavorable cervix (Bishop score ≤ 5), and ≤ 3 uterine contractions per 10 minutes, as recorded by electronic fetal monitoring (EFM) for 30 minutes on admission for a medically indicated IOL. Non-inclusion criteria included a previous CD, a history of myomectomy, suspected fetal distress on EFM on admission, unexplained bleeding, suspected chorioamnionitis, fetopelvic disproportion, estimated fetal weight > 4500 g,

placenta previa, active herpes infection (primary infection or recurrence within 7 days), any known allergy or intolerance to prostaglandin agents, and any contraindication to vaginal delivery. Patients were randomly assigned in a 1:1 ratio using the permuted block method with 20 women per block with sealed envelopes for allocation. Randomization was stratified by center and parity (nulliparous/parous) [13]. After providing the patient with information about the trial when there was a medical indication for IOL, informed consent was requested and provided immediately before IOL.

In the misoprostol arm, the clinical care provider placed a 25- μ g capsule in the woman's posterior vaginal fornix, every 4 hours with a maximum of 4 capsules per day. Before each administration, if the fetal heart rate (FHR) was non-reassuring, or if the woman had at least two painful contractions in 10 minutes, the capsule was not placed. In the other arm, the pessary was placed by the healthcare provider in the posterior vaginal fornix until labor started or for a maximum of 24 hours. In cases of non-reassuring FHR or uterine tachysystole, the pessary was removed and replaced after normalization of electronic fetal monitoring if removed within the first 12 hours. Women in both groups were monitored identically, with a one-hour FHR analysis every 4 hours [13].

Setting and perspective

The economic analysis was performed from the French National Health Insurance (FNHI) perspective and focused on costs associated with inpatient stays. The time horizon of the study was limited to the inpatient stay associated with the delivery. No discount rate was applied.

In France, public and private hospital fees are based on Diagnoses Related Group (DRG) rates to which can be added extra charges if applicable (i.e., expensive drugs such as medicines with special constraints which are hospital-reserved drugs and day prices for reanimation or intensive care unit stays) [14]. DRGs include medical and paramedical staff fees, institutional costs, and common drugs but access to details is not allowed. Through DRGs, the French health insurance totally reimburses inpatient delivery stays. According to the delivery management parameters (parity, IOL, caesarian, duration) and the occurrence of complications, several DRGs are possible with different rates for both mothers and infants. All the mother- and infant-related DRGs associated with delivery were extracted from the inpatient database and were all considered in the analyses. DRG rates also include the price of medications compared (i.e., misoprostol versus dinoprostone) because they do not belong to additional expensive medication. In the context of the FNHI perspective, the costs of the two drugs studied were not considered. Nevertheless, in France, one slow-release dinoprostone pessary costs €83 (\$99) per patient while a misoprostol capsule costs €0.44 (\$0.5), at up to four capsules per patient.

Clinical and economic outcomes

Our goal was to estimate the Incremental Cost Effectiveness Ratio (ICER) defined as the mean incremental cost between the misoprostol group and the dinoprostone group divided by the mean incremental effectiveness between the groups. This ratio represents the estimated monetary value required for one unit of effectiveness [15].

The main aim of any obstetrician is a vaginal delivery, with a healthy mother and child. Therefore, comparably, the CD rate is a more relevant outcome than the timing of the delivery which is subsequent [16]. Moreover, the rate of Vaginal Delivery within 24h (VD24) is a useful clinical outcome which also has significant implications with

regards to hospital costs and patient satisfaction [17]. In addition, it provides a basis of comparison with the published body of literature. Considering these obvious facts, we used the rate of Caesarean Deliveries Avoided (CDA) for the primary analysis followed by the VD24 rate for a secondary analysis. The VD24 rate was calculated including women with CD in the denominator, meaning the entire population.

We used DRG rates ranging from 2012 to 2015 according to the date of delivery and expressed them in euros (2020) using French annual consumer price indices and costs, and converted them into US dollar (2020) using the average exchange rate in 2020 both available on the OECD website.

Statistical analyses

Following the analyses in the associated clinical paper, we focused on the per-protocol (PP) population. Economic data for mother or infant were not available for five patients and were imputed by a single imputation method. Descriptive analyses of costs were performed on the incomplete dataset according to the treatment used with mean and bias-corrected and accelerated 95% bootstrapped confidence intervals [18]. A non-parametric Mann-Whitney Wilcoxon test was used to assess cost differences between groups for each variable. Finally, differential costs, effectiveness, and ICERs between misoprostol and dinoprostone were estimated on complete datasets. Bootstrap replications of mean cost and mean effectiveness were used to graphically determine the 95% credible interval of the ICER, with a confidence ellipse [19]. In particular, it allows the variations in outcomes in the ICER calculation to be considered as a probabilistic sensitivity analysis [20].

The ICER, bootstrap replications and associated confidence ellipses are drawn in the Cost-Effectiveness Plane (CEP). The CEP is divided into four quadrants. ICERs with

a negative value are respectively in the southeast or northwest quadrant and do not require interpretation because the new strategy is less costly and more effective (i.e., a dominant strategy) or costlier and less effective (i.e., dominated strategy) than the reference strategy. ICERs with positive values are in the southwest and northeast quadrant and those in the northeast quadrant are generally compared to the collective Willingness To Pay (WTP) threshold which represents the maximum monetary value that a decision-maker might be willing to pay for a particular unit change in the outcome.

Ethical approval

The French national agency for medicine and health product safety (ANSM) (2011-71 000933-35, A110414-12) and the committee for the protection of people participating in biomedical research (CPP, 1.11.08) approved the trial which is registered at clinicaltrials.gov (NCT 01765881).

Results

Characteristics of the 1,580 women (figure 1), 790 in each arm, included in the PP population are described in table 1. No significant difference was observed between the PP and the intention-to-treat population described in the associated clinical paper and between arms. The most common indications for IOL were post-term pregnancy, premature rupture of membranes, diabetes, and hypertensive disorders.

Economic analyses

The cost comparisons between groups are summarized in table 2. The total mean cost was estimated at €4,400 for the misoprostol group and €4,414 for the dinoprostone group. Mean costs did not significantly differ between groups. We

noticed a slight difference between groups related to the use of Oxytocin with a higher cost in the dinoprostone arm (€4,407 vs €4,473, $p=0.09$). In addition, women in the misoprostol group without a VD24 had a costlier inpatient management (€4,883 vs €4,499, $p<0.001$).

Cost-effectiveness analysis

Table 3 summarizes both primary and secondary cost-effectiveness analyses. First, the misoprostol group underwent 2.3% more CD and a cost saving equal to €11 (\$12) per patient. Therefore, in a cohort of 100 patients, misoprostol allows cost saving of €5 (\$5) per patient despite one additional CD. Second, the misoprostol group had 13.5% more VD24 with a cost saving of €18 (\$20) per woman. According to the secondary analysis, misoprostol is considered as a dominant strategy because it is less expensive and more effective.

Figures 2 and 3 graphically summarize both cost-effectiveness analyses with a 95% credible interval as the basis for the probabilistic sensitivity analysis. According to the primary analysis, we observed a confidence ellipse in the four quadrants which does not lead to a significant conclusion. Nevertheless, the main part of ICER bootstrap replications is located in the northwest and southwest quadrants (i.e., misoprostol a less effective and equally less costly or costlier strategy than dinoprostone), which highlights the trend of dinoprostone being cost-effective compared to misoprostol according to the CD rate. According to the secondary analysis, the 95% confidence ellipse is located in the northeast and southeast (i.e., misoprostol a more effective and equally less costly or costlier strategy than dinoprostone), which emphasizes the cost-effectiveness of misoprostol versus dinoprostone. The misoprostol strategy is considered either a cost-effective or a dominant strategy according to the VD24 rate.

Discussion

In both primary and secondary analyses, we could not arrive at a conclusion on the cost-effectiveness of misoprostol compared to dinoprostone. On the one hand, according to the CDA rate, dinoprostone is not cost-effective. Besides, related clinical differences were not significantly assessed. On the other hand, according to the VD24, misoprostol is either a cost-effective or a dominant strategy. The FNHI perspective used in this study does not clearly identify a cost-effective or dominant strategy for one or the other notably because both treatments are supported in the DRG rates. An analysis from the hospital point of view could provide clearer conclusions and highlight the benefit of misoprostol.

Economic data related to vaginal misoprostol versus dinoprostone are sparse but seem to converge to a cost-saving use of misoprostol. In 2003, Ramsey et al found cost saving of approximately \$500 with significantly less time to delivery or vaginal delivery, and no differences according to the CD rate. The sample size remained limited with 35 – 38 women per arm. Two more recent works, respectively in 2016 and 2017 in the USA and Spain, focused on the clinical outcome and/or cost of vaginal misoprostol versus dinoprostone. The first one used single-dose misoprostol 50mcg and showed less time to active labor and delivery and no difference according to CD associated with a \$440 hospital cost saving per patient. Nevertheless, only 50 women were included in the misoprostol arm in this retrospective study. The second, with 24 women in the misoprostol and the dinoprostone arms, targeted intrauterine growth restriction fetuses and showed a \$315 cost saving per patient for the misoprostol group. Healthcare systems are different around the world, especially because of health care organizations, reimbursement conditions and different unit prices for healthcare resources, which makes the comparison between studies more

difficult. However, considering French incremental prices between misoprostol and dinoprostone, our results are consistent with those in the literature.

Approximately 25% of women have induced labor in high-resource countries [8, 9]. Therefore, improvement in IOL management is of major interest, particularly in economic terms given that the effectiveness between current strategies is quite similar [21, 22]. However, as a result, the Society for Maternal-Fetal Medicine recently issued a statement that IOL is a reasonable option for low-risk nulliparous women at or after 39 weeks [3]. The likely increase in the IOL rate makes our trial especially interesting as it provides additional health-economic information. Our primary analysis with the CD rate was based on a non-significant clinical difference between treatment arms. Associated clinical work demonstrated no noninferiority of misoprostol but according to a limited difference in CD rate, both drugs remain considered ref. We believe that this similar efficacy in terms of CD rate underlines the need for additional economic data. Moreover, a significant difference in VD24 rate was estimated between treatment arms and minor differences between the groups for neonatal and maternal morbidity [13].

The DRG and associated rates for each group were quite similar and were mainly affected by additional costs for CD and intensive care which were also similar. This is observable on the confidence ellipses incremental cost variation which was between -€500 and €500. Given that treatment prices are already included in DRG rates, they do not affect the costs analyzed here. Nonetheless, from the hospital perspective, the cost of common drugs is important. FNHI funds hospitals through the DRG rate for stays and the great interest for hospitals is to reduce hospitalization expenses. Firstly, one slow-release dinoprostone pessary costs €83 per patient while a misoprostol capsule costs €0.44, at up to four capsules per patient. Therefore, roughly €82

difference per patient can be applied to the IOLs performed for 22% of the more than 750,000 births per year in France with possible hospital savings of up to €13.5 million annually [23, 24]. Secondly, the higher proportion of VD24 in the misoprostol arm (59.4% vs 46.1%) could have a substantial economic impact for hospitals as this clinical outcome is directly related to inpatient cost. In other countries where the incremental price of misoprostol compared to dinoprostone is higher and where the national population is larger, cost saving could be significant. This is particularly true for the US where one slow-release dinoprostone pessary costs \$463.88 and one misoprostol capsules costs \$0.72 to \$5.38, or for low- and middle-income countries with large populations. Nevertheless, a micro-costing methodology is required to consider all cost components in a hospital setting and to confirm these conclusions [25].

This work is based on the largest RCT that compares low-dose vaginal misoprostol to the slow-release dinoprostone pessary but has some limitations. The main limit is that we were unable to implement a micro-costing methodology in the RCT because the trial was not designed for this purpose. A hospital perspective would have been a more suitable perspective in this context. Nevertheless, we retrospectively accessed a large part of the mother and infant DRG which allowed us to use an FNHI perspective. Economic data were also missing for 5 women or infants. Imputation was implemented in compensation. Finally, we analyzed the PP population for two reasons. First, there was no difference between intention-to-treat and PP population outcomes in the associated clinical paper. Therefore, we adhered to their primary analysis ref 13, for which the per-protocol analysis was first considered in accordance with a noninferiority trial design (ref 13). Second, the major protocol deviations for

excluded women led to additional missing economic data directly associated with these deviations.

From the FNHI perspective, cost management for women who received misoprostol or dinoprostone for IOL is equal. This study contributes additional economic information to associated clinical work to help decision-makers to determine the benefit of one treatment over the other. On the one hand, using CDA rate, we cannot affirm that misoprostol is more cost-effective than dinoprostone. However, using VD24 rate, misoprostol is a dominant strategy. Finally, misoprostol may result in significant cost saving from the hospital perspective, and becomes more attractive than dinoprostone given that the effectiveness is similar and it is easier to use.

Author contributions

Mounie Michael participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

Costa Nadège participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

Gaudineau Adrien participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

Molinier Laurent participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

Vayssière Christophe participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

Derumeaux Hélène participated in designing, planning and conducting the study, analyzing the data and writing the manuscript.

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Conflicts of interest: The authors report no conflict of interest.

Statement of informed consent:

The French national agency for medicine and health products safety (ANSM) (2011-000933-35, A110414-12) and the committee for the protection of people participating in biomedical research (CPP, 1.11.08) approved the trial. We obtained a signed consent and the form is filed with our records.

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Figure 1. Eligibility Process and Randomization

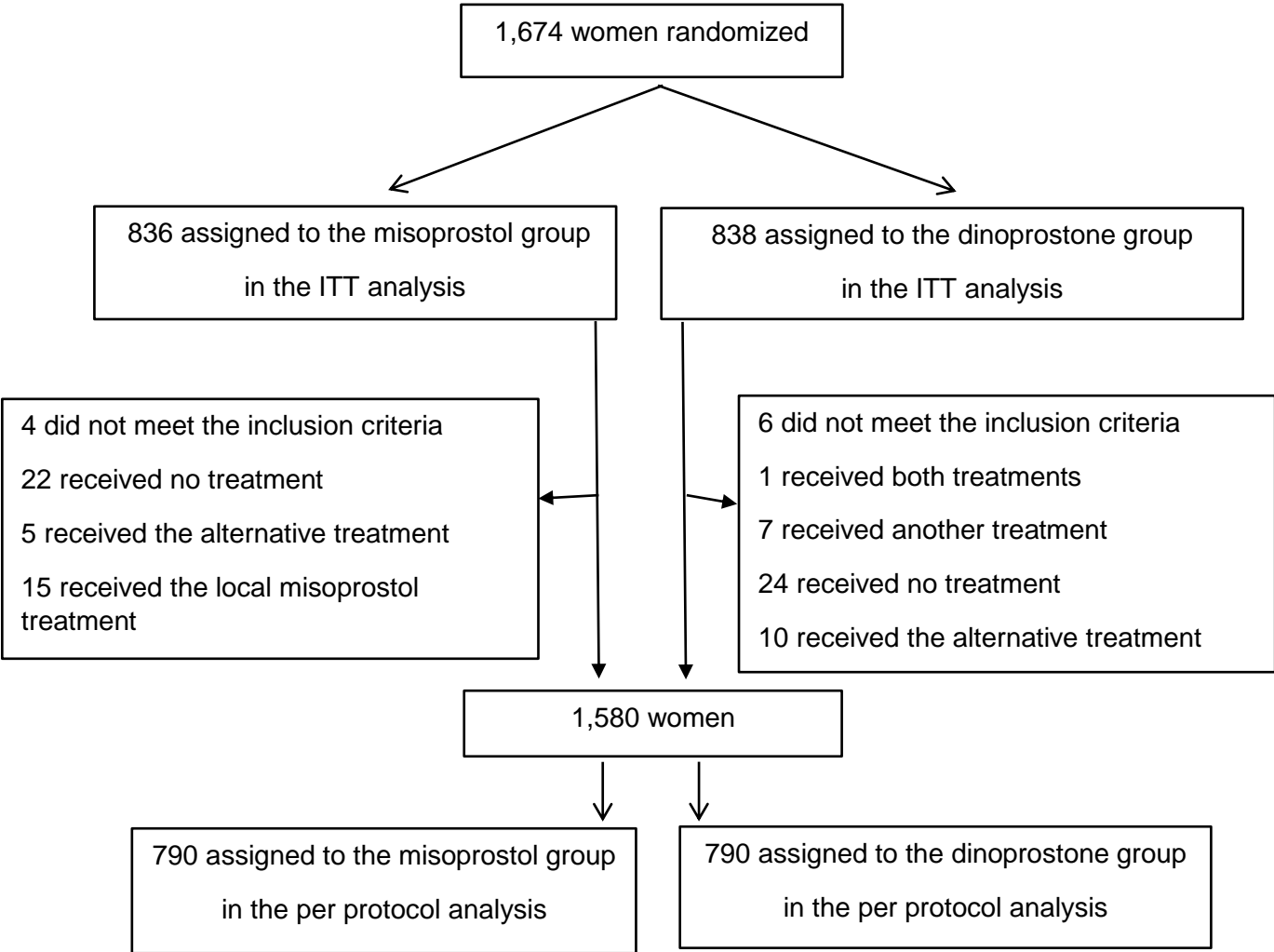


Figure 2. Incremental cost effectiveness ratio and 95% confidence ellipse according to the CDA rate (primary analysis)

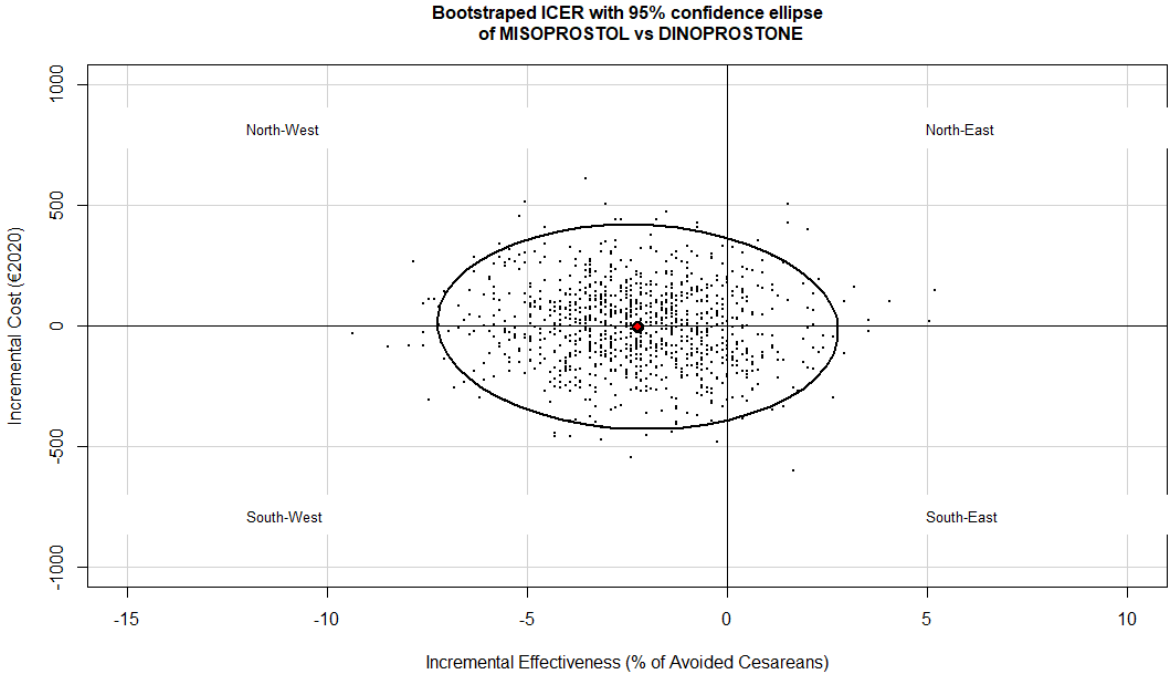


Figure 3. Incremental cost effectiveness ratio and 95% confidence ellipse according to the VD24 rate (secondary analysis)

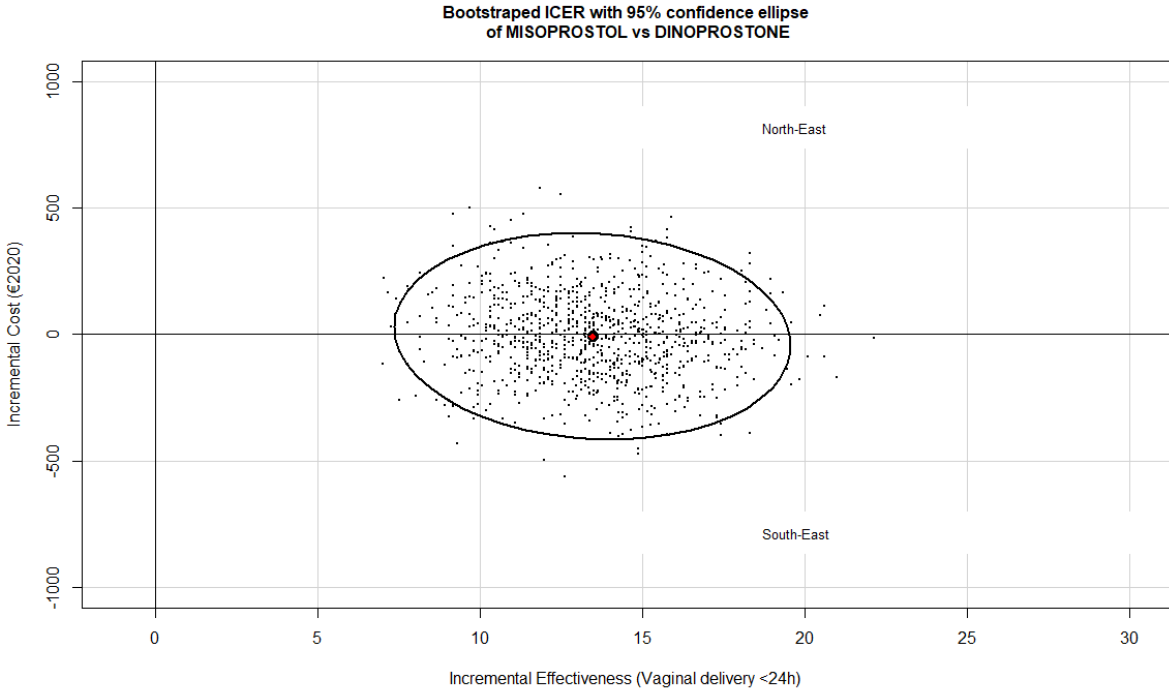


Table 1. Baseline characteristics of the population

	Misoprostol n=790	Dinoprostone n= 790
Maternal age (years; median, Q1-Q3)	30.8 (27.2 - 34.7)	30.6 (26.9 - 34.3)
Nulliparous (n, %)	467 (59.1)	478 (60.5)
BMI (kg/m ² ; median, Q1-Q3)	26.9 (22.7-31.2)	26.4 (22.8-30.5)
Gestational age* (weeks; median, Q1-Q3)	39 (36.7.-41.0)	39 (36.7-41.0)
Bishop score [†] (median, Q1-Q3)	3 (2-4)	3 (2-4)
Epidural (n, %)	719 (91.0)	714 (90)
Indication for induction (n, %):		
Prolonged and post-term pregnancy [‡]	214 (27.1)	234 (29.6)
Premature rupture of membranes	186 (23.5)	178 (22.5)
Diabetes	137 (17.3)	134 (17.0)
Hypertensive disorders	111 (14.1)	97 (12.3)
Fetal growth restriction	46 (5.8)	43 (5.4)
No reassuring fetal heart rate	34 (4.3)	32 (4.1)
Other	133 (19.0%)	150 (16.8%)

Q1-Q3: First and third quartile; *available for 1,216 women; [†]available for 1,576 women; [‡]Prolonged pregnancy, taken in isolation, was not a systematic indication for IOL

Table 2. Cost comparison in euros/US dollars (2020) according to adjustment variables, primary and secondary clinical outcomes

		Misoprostol		Dinoprostone		P
		N (%)	Mean [95% CI]	N (%)	Mean [95% CI]	
Global		789 (100)	4,400 [4,210-4,736] (5,023 [4,806-5,406])	786 (100)	4,414 [4,227-4,812] (5,039 [4,825-5,493])	.230
Nulliparous		478 (60.6)	4,473 [4,315-4,821] (5,106 [4,926-5,503])	464 (59)	4,556 [4,339-5,107] (5,201 [4,953-5,830])	.266
Multiparous		311 (39.4)	4,287 [3,733-4,823] (4,894 [4,261-5,506])	322 (41)	4,211 [3,721-4,572] (4,807 [4,248-5,219])	.604
Days in NICU	0	657 (83.3)	3,748 [3,694-3,817] (4,279 [4,217-4,357])	647 (82.3)	3,670 [3,621-3,723] (4,189 [4,134-4,250])	.113
	[1-5]	85 (10.8)	5,175 [4,957-5,492] (5,908 [5,659-6,269])	90 (11.5)	5,486 [4,947-7,281] (6,263 [5,647-8,312])	.454
	[6-15]	40 (5.1)	8,678 [7,960-9,568] (9,906 [9,087-10,922])	40 (5.1)	9,806 [8,892-11,362] (11,194 [10,151-12,970])	.225
	[16- +]	7 (0.9)	31,715 [20,283-44,572] (36,204 [23,154-50,881])	9 (1.1)	23,274 [15,500-38,146] (26,568 [17,694-43,546])	.210
Oxytocin use	No	329 (41.7)	4,389 [4,074-4,942] (5,010 [4,651-5,642])	254 (32.3)	4,312 [4,004-5,076] (4,922 [4,571-5,795])	.546
	Yes	460 (58.3)	4,407 [4,225-4,847] (5,031 [4,823-5,533])	529 (67.3)	4,473 [4,242-4,882] (5,106 [4,842-1,007])	.089
Vaginal delivery within 24 h	No	320 (40.6)	4,883 [4,632-5,522] (5,574 [5,288-6,304])	421 (53.9)	4,499 [4,333-4,746] (5,136 [4,946-5,418])	<0.001
	Yes	469 (59.4)	4,070 [3,860-4,529] (4,646 [4,406-5,170])	362 (46.1)	4,329 [3,969-5,027] (4,942 [4,531-5,739])	.329
Cesarean delivery	No	614 (77.8)	4,204 [3,988-4,588] (4,799 [4,553-5,237])	630 (80.2)	4,218 [3,999-4,598] (4,815 [4,565-5,249])	.556
	Yes	175 (22.2)	5,087 [4,871-5,437] (5,807 [5,561-6,207])	156 (19.8)	5,209 [4,940-5,717] (5,946 [5,639-6,526])	.880

P-value from the Mann Whitney Wilcoxon test; CI: Confidence Interval (bias-corrected and accelerated); NICU: neonatal intensive care unit

Table 3. Summary of clinical and economic outcomes used in ICER Calculation

Primary outcome: Caesarean Deliveries Avoided (n = 1,580; 790 vs 790)					
	Cost € (\$) Mean [95% CI]	Effectiveness Mean [95% CI]	ΔCost	ΔEffectiveness	ICER
Dinoprostone	4,410 [4,214-4,744] (5,034 [4,811-5,416])	80.1 [77.1-82.9]	-11 (-12)	-2.28	4.82 (5.26)
Misoprostol	4,399 [4,206-4,710] (5,022 [4,801-5,377])	77.9 [75.1-81.0]			
Secondary outcome: Rate of Vaginal Delivery within 24 h (n = 1,577; 787 vs 790)					
	Cost € (\$) Mean [95% CI]	Effectiveness Mean [95% CI]	ΔCost	ΔEffectiveness	ICER
Dinoprostone	4,417 [4,222-4,739] (5,042 [4,820-5,410])	46.1 [42.3-49.3]	-18 (-20)	13.49	-1.33 (-1.48)
Misoprostol	4,399 [4,206-4,710] (5,022 [4,801-5,377])	59.4 [56.1-62.9]			

CI: Confidence Interval; ΔOutcomes: Misoprostol – Dinoprostone; ICER: Incremental Cost Effectiveness Ratio