Tranexamic acid for the prevention of postpartum hemorrhage: a cost-effectiveness analysis

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Short Title: Cost-effectiveness of prophylactic tranexamic acid

Abstract

Objectives: To estimate the cost-effectiveness of alternative risk-dictated strategies utilizing prophylactic tranexamic acid (TXA) for the prevention of postpartum hemorrhage.

Design: Cost-utility analysis using a Markov decision-analytic model.

Setting: All US labor and delivery units.

Population: A cohort of 3.8 million women delivering in the US.

Methods: We constructed a microsimulation-based Markov decision-analytic model estimating the lifetime costs and benefits of three alternative risk-dictated strategies for TXA prophylaxis versus the status quo (no TXA). Each strategy differentially modified risk-specific hemorrhage probabilities by preliminary estimates of TXA's prophylactic efficacy. Costs and benefits were considered from the healthcare system and societal perspectives.

Main outcome measures: Incremental costs, quality-adjusted life-years (QALYs), and adverse maternal outcomes averted.

Results: All TXA strategies were dominant versus the status quo, implying that they were more effective while also being cost-saving. Providing TXA to all delivering women irrespective of hemorrhage risk assignment produced the most favorable results overall, with estimated cost savings greater than $670 million and approximately 149,505 hemorrhage cases, 2,933 hysterectomies, and 70 maternal deaths averted, per annual cohort. Threshold analysis suggested that TXA is likely to be cost-saving for health systems at costs below $184 per gram.

Conclusions: Our findings suggest that routine prophylaxis with TXA would likely result in substantial cost-savings and reductions in adverse maternal outcomes in this context. The

integrity of this conclusion is maintained across all risk-dictated strategies, even when the cost of TXA is significantly higher than what is supported in the literature.

Keywords:

Cost-effectiveness, health economics, Markov decision-analytic modelling, postpartum hemorrhage, prophylaxis, tranexamic acid

Tweetable abstract

Routine prophylaxis with tranexamic acid may be a cost-effective intervention for preventing postpartum hemorrhage.

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Introduction

Each year, more than 300,000 women die globally from complications during pregnancy and childbirth.[1] While the global maternal mortality rate (MMR) has decreased over the past 20 years, the United States (US) remains the only developed country to have sustained an increase in MMR during that time.[2] As of 2018, the US MMR is 17.4 deaths per 100,000 births, more than twice that observed in 1987 and considerably higher than in similarly-developed nations.[2,3]

The American College of Obstetricians and Gynecologists (ACOG) defines postpartum hemorrhage (PPH) as cumulative blood loss ≥1000 mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours of giving birth, regardless of mode of delivery.[4] Current estimates suggest that PPH accounts for 5.6% of maternal deaths in the US and 27% globally.[5,6]

Tranexamic acid (TXA) is an antifibrinolytic agent that acts by blocking the interaction of plasminogen with fibrin, preventing the dissolution of clots and reducing blood loss.[7] The WOMAN trial found that a single dose (1g) of TXA reduced the risk of death from bleeding by 21% in women with established PPH.[8] Limited international evidence supports a role for prophylactic TXA in preventing PPH, with reduced postpartum blood loss observed in vaginal (VD) and cesarean deliveries (CD).[9,10] Despite its potential to prevent PPH, routine prophylaxis with TXA remains absent from national obstetric care guidelines.

Cost-effectiveness is an indicator of the comparative value of health interventions. TXA was previously demonstrated to be cost-effective for the *treatment* of PPH in low resource settings.[11] A recent analysis also supports these findings in the US.[12] To our knowledge, no previously published cost-effectiveness analyses have examined routine prophylaxis with TXA in the US. In this study, we endeavor to provide preliminary estimates of the cost-effectiveness

of policies governing routine prophylaxis with TXA in a US-based, risk-stratified population of delivering women.

Methods

Model overview

This study was funded by a National Heart, Lung, and Blood Institute grant (K23HL141640). The George Washington University Institutional Review Board reviewed the study and determined it did not constitute human subject research. We developed a microsimulation-based Markov decision-analytic model using TreeAge Pro Healthcare 2020 (Williamstown, MA) to evaluate the cost-effectiveness of four competing strategies. The strategies investigated include the status quo (no prophylactic TXA), and the provision of TXA to women at high risk for PPH, at high and medium risk for PPH, and to all delivering women irrespective of risk assignment. We employed Markov modeling because this allowed the evaluation of discrete events that can occur multiple times throughout the human lifespan, including pregnancy and childbirth.

The primary analysis employed a healthcare system perspective, which includes hospitals, providers, and payers. Outcomes of interest for the primary analysis included net costs and the number of PPH cases, procedures, and maternal deaths averted. A secondary analysis was conducted from the societal perspective, incorporating costs to society due to morbidity and premature mortality. In the secondary analysis, we considered incremental costs and quality-adjusted life-years (QALYs).

The model structure was adapted from decision algorithms published by the French College of Gynecologists and Obstetricians as guidelines for the management of PPH.[13] All patients enter the model as delivering mothers, are assigned to a risk stratum, and proceed through one of two mutually exclusive subtrees for VDs and CDs. VD PPH patients progress through a treatment subtree comprised of pharmacotherapy, balloon tamponade (BT), uterus-sparing surgeries (i.e., uterine artery embolization [UAE], uterine artery ligation [UAL], compression sutures [CSU]), and hysterectomy. CD PPH patients progress through a treatment subtree comprised of pharmacotherapy, uterus-sparing surgeries (UAL and CSU), and hysterectomy (Figure S1). Patients progressing through the VD and CD subtrees may experience all or some of the interventions within those trees.

Patients also experience risk of death due to PPH and all-cause mortality, which are smoothed throughout the model. Because Markov models assume state transitions are completed at the end of a cycle, they fail to capture events occurring between cycles. To account for the impact of this on transitions to the "dead" state, we employed a half-cycle correction under the assumption that, on average, transitions between health states occur approximately halfway through the cycle.[14] Surviving patients enter a healthy, postpartum state. If patients did not undergo hysterectomy, their fertility is preserved, and they may experience additional pregnancies.

We considered a base case of 3.8 million delivering mothers with an average age of 28 years, matching US deliveries in 2018.[15,16] We surveyed PubMed and Google Scholar to counter reporting bias while capturing literature estimates for model inputs. Whenever possible, we prioritized estimates specific to the US. When necessary, the literature review was expanded to include estimates from similarly high-income countries.[17-19] All state-transitions were assumed to

occur over one-years' time. All future costs and benefits were discounted at an annual rate of 3% and were considered over a lifetime time horizon to reflect the cost and quality of life implications of PPH and its associated fertility implications (Table 1).

Probabilities for risk assignment, mode of delivery, and PPH by risk assignment were derived from a recent analysis by Ahmadzia et al. adapting risk stratification algorithms developed by the Association of Women's Health, Obstetric and Neonatal Nurses (AWHONN).[16] The effect of prophylactic TXA on the risk of PPH was captured by pooled estimates of risk ratios derived from the literature.[9,20-25] To reflect variability in clinical settings and provider response to treatment-resistant PPH prior to hysterectomy, a frequency-weighted treatment success rate was generated synthesizing estimates for UAE, UAL, and CSU. Age-specific birth and death rates were derived from the Centers for Disease Control National Vital Statistics reports.[15,26]

Costs

Cost estimates were obtained through a literature review process prioritizing US estimates published within the past 20 years. We used price estimates from the Centers for Medicare and Medicaid Services to approximate healthcare costs when estimates could not be obtained from the literature.[27] A charge-to-cost ratio of 3.1 was utilized to approximate cost from published hospital charge data.[28] All costs were converted to their equivalents in 2018 US dollars using the US gross domestic product deflator.[29]

The costs assessed differed between the primary and secondary analyses (Table 2). The primary analysis considered costs associated with procuring healthcare, including malpractice costs for all hemorrhage-related death.[12] Due to variability in the duration of inpatient management, we assumed that PPH managed non-surgically entails two excess hospital bed days, whereas PPH managed surgically entails three excess bed days and one ICU day.[30] The cost of TXA wastage was modeled as the product of percent wastage for intravenous solutions and pharmaceuticals and the average cost of TXA per gram, assuming a 1g prophylactic dosage.[12,31-38] Delivery costs were assumed to be packaged estimates, incorporating provider time and pharmacological interventions. Separate costs for administering TXA were not considered because we assumed that intravenous access was obtained during delivery.

The secondary analysis included indirect economic costs in addition to the costs considered in the primary analysis. We estimated the economic cost of familial and societal disruption due to maternal morbidity and mortality as a function of productivity loss.[39] Traditional labor-based approaches risk undervaluing the productivity of women, considering the gender-wage gap and the unequal distribution of household labor in Western countries.[40] Accordingly, we also estimated the value of unpaid, economically productive household labor by women as the product of household labor time and the federal minimum wage (Appendix S1).[41,42]

Benefits

The secondary analysis incorporated QALYs, the product of years of life lived in a particular health state and the utility weight of that state, as a measure of effectiveness.[43] The

utility of total health was 1, whereas the utility of death was 0. The remaining utility weights were obtained through mixed methods. Whenever possible, utility weights came from the Cost-Effectiveness Registry operated by the Center for the Evaluation of Value and Risk in Health.[44] When estimates were not available, we approximated their value by surveying generalists and subspecialists within our institution. We employed a multiplicative approach for combining utility weights to account for combined physical and psychological impacts of PPH on patient quality of life (Appendix S2).[45]

Sensitivity analyses

Sensitivity analyses were performed to assess the robustness of the model under each perspective. One-way deterministic sensitivity analyses were conducted by varying each available parameter individually across its range (Figure S2). We performed probabilistic Monte Carlo simulations, randomly sampling each parameter's distribution over 10,000 trials, estimating the percent of scenarios in which TXA strategies were likely to be cost-effective. We assigned beta distributions to probabilities and utility weights, gamma distributions to the majority of costs, and triangular distributions to the remaining parameters, in keeping with recommendations from the literature.[46]

Results

Primary analysis

All TXA strategies were considered superior in cost-savings and outcomes averted relative to status quo in the base case analysis (Table 3). Providing TXA to high-risk patients resulted in estimated cost-savings of $316 million for US healthcare systems annually. This strategy additionally prevented 65,502 PPH cases, 8,238 balloon tamponades, 10,776 uterus-sparing surgeries, 1,322 hysterectomies, and 27 maternal deaths per annual cohort. Including medium risk patients more than doubled these benefits. Providing TXA to all patients irrespective of risk proved to be superior to all other strategies. This resulted in cost-savings of $670 million and prevented 149,505 PPH cases, 19,447 balloon tamponades, 24,079 uterus-sparing surgeries, 2,933 hysterectomies, and 70 maternal deaths per annual cohort.

One-way sensitivity analyses for the primary analysis identified 5 variables accounting for >95% of the total uncertainty of the model. From greatest to least uncertainty, these variables were: the risk ratio of PPH in VD with TXA (48%), cost per bed-day (27%), probability of PPH in high-risk patients (11%), probability of pharmacotherapy failure (6%), and maternal age (5%). The model was found to be insensitive to variation in the value of all assessed variables. To better approximate the limits of TXA's cost-saving potential, we conducted an additional threshold analysis of the cost per gram of TXA. This analysis suggested that TXA is likely to be cost-saving for health systems at costs below $184 per gram. Results of the probabilistic sensitivity analysis suggested that prophylactic TXA strategies are cost-saving versus the status quo in >99.9% of simulations.

Secondary analysis

All TXA strategies were dominant when compared to the status quo in the secondary analysis, meaning they were simultaneously more effective and cost-saving to society (Table 4). The ranking of strategies in the secondary analysis reflected that of the primary analysis, with the provision of TXA to all patients irrespective of risk generating the greatest net benefit.

One-way sensitivity analyses identified 5 variables accounting for >95% of the total uncertainty of the model. In order of greatest to least uncertainty, these variables were: the PPH utility weight (77%), cost per bed-day (10%), post-hysterectomy utility weight (4%), success rate of uterus-sparing surgery in CDs (2%), and probability of pharmacotherapy failure (2%). As in the primary analysis, the model was insensitive to variation in the value of all assessed variables. Results of the probabilistic sensitivity analysis showed TXA strategies are dominant versus the status quo in >99.9% of simulations.

Discussion

Main findings

This study sought to determine whether prophylactic TXA was likely to be cost-effective in a risk-stratified population of delivering mothers, given preliminary evidence supporting its clinical benefit in this capacity. Our analyses suggest that prophylactic TXA is likely to be cost-saving, both for health systems and for society as a whole, under the conditions explored in the model. This was confirmed in >99.9% of simulated scenarios. Moreover, our analyses suggested expanding coverage with TXA to lower risk patients results in greater maternal benefits and

more cost-savings than limiting its administration to only high-risk patients. These conclusions were robust to variation in the value of all assessed model parameters.

Interpretation

The results of our analyses suggest that maternal care guidelines should consider prophylactic TXA for the prevention of PPH, pending further investigation. While the utility of prophylactic TXA for high-risk patients is obvious, our analyses suggested substantial cost-savings when lower risk patients are also given prophylactic TXA. This is important clinically because many times, 'low risk' women have unpredictable PPH that can be severe. The benefits of prophylactic TXA, however, extend beyond its potential to drive cost-savings. By reducing the incidence of PPH, TXA decreases demand for additional uterotonic agents.[9,47] This results in lower costs to patients and fewer adverse drug reactions associated with uterotonics, including fevers, chills, bronchospasm, and painful uterine contractions.[48] This translates to reduced morbidity and improved quality of life.

As an antifibrinolytic agent, TXA has been demonstrated to reduce blood loss and improve serum hemoglobin and ferritin levels in trauma, orthopedic surgery, and obstetric patients.[8,9,47,49-52] By reducing blood loss and the burden of anemia following delivery, TXA can improve the functional health of mothers who get prophylaxis therapy. Moreover, by reducing blood loss, TXA decreases reliance on already limited transfusable blood products, reducing costly transfusion reactions and secondary implications on future pregnancies if antibodies are developed.[53]

Our analyses also suggested that prophylactic TXA results in reduced need for interventional radiology and surgical interventions like hysterectomy. In addition to obvious cost-savings, this has important implications for the preservation of future fertility.[54-57] Reduced reliance on these interventions may have a dramatic impact on quality of life for patients and families, with additional economic benefits to society.[58-60]

A final consideration for providers is the risk of adverse drug events such as venous thromboembolism and seizures.[12] While frequently cited as justification for not expanding TXA coverage, these concerns do not appear to be supported by recent research. Two landmark multinational trials failed to find an association between TXA and venous thromboembolism.[8,50] While the risk of seizures with TXA has been documented in cardiac surgery, this association was not found to be significant in the WOMAN trial, nor in patients at increased risk for seizures due to acute traumatic brain injuries.[8,61] This discrepancy may be explained by the comparatively older patient population and the higher doses of TXA used in cardiac surgery.[62] As such, it appears that TXA is likely well-tolerated at the doses used in obstetrics. Accordingly, we did not include TXA-associated adverse drug events in our model.

Strengths and limitations

The validity of economic models is dependent upon the extent to which their structure mirrors reality and their inputs approximate true value. Accordingly, the greatest strength of this study is to be found in the ways in which our model reflects the experiences of patients and the consequences of their interactions with the US healthcare system. This is most apparent when

considering the limitations of previous studies and the improvements that we make to better account for the unique impacts of PPH on patients, families, healthcare systems, and society.

Two previously published cost-effectiveness analyses have evaluated the use of TXA in treating PPH.[11,12] Only the study by Sudhof et al. was specific to the US, whereas the study by Li et al. evaluated TXA in developing countries with limited applicability to the US context. While our study and that by Sudhof et al. employed similar costing perspectives, there are meaningful differences between our two studies. Sudhof et al considered fewer granular outcomes in their analysis.[12] By structuring their model as a linear decision-analytic process, Sudhof et al were unable to model the effects of PPH interventions on future fertility outcomes. By contrast, our model allowed us to consider both future pregnancies and loss of fertility.

A further distinction between our two studies is in the magnitude of the cost-savings and maternal deaths averted: we estimate rewards that are a factor of 10 greater than those of Sudhof et al.[12] There are several potential explanations for these differences. We considered a more expansive subset of costs than did Sudhof et al., who limited their analysis to outcomes that were statistically significant in the WOMAN trial.[8,12] By including procedures such as UAE in our model, we likely offer a closer approximation of the economic benefits of TXA in countries with advanced healthcare systems like the US. Moreover, Sudhof et al. failed to estimate the societal costs of maternal death, something that we address in our secondary analysis.[12] Despite these differences, our cost-saving thresholds for TXA differed by only $10 per gram. The difference in magnitude of deaths averted between our two analyses may be explained by how we modeled TXA. Sudhof et al. modeled TXA's direct mortality benefit in established PPH, while we modeled its effect on the incidence of PPH, thereby reducing the size of the population at risk for hemorrhage-associated mortality.[12]

Despite these notable improvements, limitations still affect our model in meaningful ways. Given the structure of our model was adapted from decision algorithms published by a foreign medical society, its generalizability to the US-context may be limited. However, we conducted a review of published guidelines for the management of PPH in the US and found recommendations encompassing all treatment modalities within our model.[63-66]

We modeled the effect of TXA by only considering its impact on the risk of PPH as opposed to the mortality-reducing benefit found by the WOMAN trial.[8] We made this decision because the WOMAN trial was conducted in low-resource settings where the mortality-reduction from TXA is likely to be greater than in the US. We also chose not to include blood transfusion in our model given that previous studies, including the WOMAN trial and CRASH-2, did not demonstrate a statistically significant risk reduction for transfusion associated with the provision of TXA.[8,50] This conservative approach likely underestimates the potential costs saved with prophylactic TXA.

While our analyses suggested it may be economically advantageous, an additional limitation in our modeling of prophylactic TXA is the paucity of reliable sources evaluating its clinical benefit. Of the limited research on the efficacy of prophylactic TXA, most occurred in settings different from our own. To overcome this, we opted to include studies conducted in international settings most similar to the US. While including international estimates presents a limitation to our study, including estimates from upper middle-income countries allows us to approximate conditions in the US, which has comparatively poorer maternal outcomes than other high-income countries.[67] Despite these adjustments, more efficacy data is necessary before a definitive ascertainment of TXA's cost-effectiveness in this context can be made. This provides an opportunity for future study.

We also made assumptions within our model that likely overestimate the benefit of strategies incorporating prophylactic TXA for PPH. The status quo scenario assumes no current use of prophylactic TXA in labor and delivery, a condition that may be violated by specific provider preferences and individualized hospital protocols governing its use. This may impact the benefit estimated for patients at high risk for PPH as it is more likely that high-risk populations would already be receiving prophylaxis, were such practices in place. Our model also assumes complete compliance were universal prophylactic TXA strategies employed, something unlikely to occur in practice, given the prevalence of planned and unplanned home births and supply chain issues that may impact access to TXA. Taken together, these assumptions likely estimate a benefit greater than what would be observed.

A final limitation of our model relates to the utility weights included in our secondary analysis. Following the recommendations of the Second Panel on Cost-Effectiveness in Health and Medicine, we sought to prioritize estimates that were derived from patient-centered sources utilizing preference-based methodologies.[68] When we were unable to identify sufficient sources fulfilling this criterion, we surveyed eleven obstetricians and maternal-fetal medicine subspecialists to collect their estimates for these inputs. This presents a limitation to our methodology, as expert estimates may not accurately correspond to the experiences of patients and families. This limitation too provides an opportunity for future study.

Conclusion

Ultimately, the results of this preliminary analysis suggest that a policy of routine TXA prophylaxis for delivering women is likely to result in substantial cost-savings and reduction in

maternal morbidity and hemorrhage-related maternal mortality in the US. These health system and societal benefits were obvious for women at high risk for hemorrhage; however, the benefits more than doubled if considering all women at delivery. Together, results from the international context and the present study lend support for advancing current and future nationwide trials evaluating the effectiveness of TXA in preventing PPH. In addition to the ongoing NIH multisite CD trial (NCT03364491), further evidence among VD patients is needed before a formal recommendation can be made to adapt existing maternal care guidelines in the US to include prophylactic TXA for the prevention of PPH.

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Disclosure of Interests

The authors report no conflicts of interest.

Contribution to Authorship

WD and HA contributed to the study concept. Data acquisition was done by WD, ME, JK, and HA. Model construction and economic results analysis was done by WD. WD, ME, JK, and ME all contributed to manuscript preparation, including drafting and revision.

Details of Ethics Approval

The George Washington University Institutional Review Board reviewed the study and determined that it did not constitute human subject research.

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877 **Table 1:** Model inputs estimating probabilities, costs, utilities, and other features

878

	Parameter	Base Case Estimate	Range[a] (DSA)	Distribution (PSA)	Source
Probabilities and Risk Ratios	**Low-Risk Assignment**	0.26	-	-	16
	Medium-Risk Assignment	0.46	-	-	16
	High-Risk Assignment	0.28	-	-	16
	Vaginal Delivery, Low Risk	0.92	-	-	16
	Vaginal Delivery, Medium Risk	0.51	-	-	16
	Vaginal Delivery, High Risk	0.54	-	-	16
	Cesarean Delivery, Low Risk	0.08	-	-	16
	Cesarean Delivery, Medium Risk	0.49	-	-	16
	Cesarean Delivery, High Risk	0.46	-	-	16
	PPH, Low Risk	0.02	-	-	16
	PPH, Medium Risk	0.068	0.062 - 0.078	Beta	16
	PPH, High Risk	0.10	0.092 - 0.116	Beta	16
	Balloon Tamponade Success	0.83	0.77 - 0.89	Beta	69-74
	Conservative	0.89	0.84 - 0.93	Beta	69,75-110

	Surgical Success, Vaginal				
	Conservative Surgical Success, Cesarean	0.88	0.84 - 0.92	Beta	69,75-90, 100-110
	First-line Therapy Failure	0.27	0.16 - 0.37	Beta	76, 111-116
	PPH Mortality	0.00039	0.00029 - 0.00049	Beta	117-121
	Wastage	0.03	0.023- 0.037	Beta	34-38
	Relative Risk of PPH with Prophylactic TXA, Vaginal Delivery	0.55	0.27 - 0.83	Triangular	9,20-23
	Relative Risk of PPH with Prophylactic TXA, Cesarean Delivery	0.40	0.36 - 0.43	Triangular	23-25
	Other Cause Mortality	**			26
	Additional Pregnancies	**			15
	Labor Force Participation Rate, by Age and Sex	**			122
Costs (2018 USD)	**Vaginal Delivery**	6,997	5,503 - 8,491	Gamma	123-128
	Cesarean Delivery	10,669	7,928 - 13,410	Gamma	123-128
	Tranexamic Acid, gram	36	29 - 43	Gamma	12,31-33
	Balloon	305	202 - 408	Gamma	129-131

	Tamponade				
	Conservative Surgery, Vaginal Delivery	6,101	4,686 - 7,265	Gamma	12,27,69,75-110,128, 132-140
	Conservative Surgery, Cesarean Delivery	712	99 - 963	Gamma	12,27,69,75-90,100-110, 134-140
	Hysterectomy	10,056	5,241 - 14,871	Gamma	123,128, 141,142
	Hospital Bed (D)	1,949	1,441 - 2,457	Gamma	123, 143-146
	ICU Bed (D)	3,705	2,776 - 4,634	Gamma	147-151
	Paid Labor Value (Y)	41,028	[21,216 - 98,332]	Triangular	152
	Malpractice	1,072,095	[418,140 - 1,237,300]	Triangular	12
	Federal Minimum Wage (H)	7.25	-	-	42
Utility Weights	**Vaginal Delivery, Well**	0.94	0.91 - 0.98	Beta	142, 153-155
	Cesarean Delivery, Well	0.92	0.90 - 0.94	Beta	141,153,155,156
	Postpartum Hemorrhage	0.88	0.77 - 0.99	Beta	11,12,141, 157,158
	Balloon Tamponade	0.90	0.84 - 0.96	Beta	Expert
	Conservative Surgery, Vaginal Delivery	0.84	0.80 - 0.89	Beta	159-162 and Expert
	Conservative Surgery, Cesarean Delivery	0.92	0.89 - 0.94	Beta	Expert

	Hysterectomy	0.77	0.66 - 0.88	Beta	Expert
	Post-Hysterectomy	0.84	0.78 - 0.90	Beta	141,155, 158-166
	Not Pregnant, Well	0.96	0.94 - 0.97	Beta	Expert
	Death	0	-	-	Assumption
Other	**Starting Age (Y)**	28	[12 – 49]	Triangular	16
	U.S. Births, 2018	3,791,712	-	-	15
	Hours of Unpaid Labor (Y), by Age and Sex	**			167
	Monte Carlo Simulations	10,000	-	-	Assumption
	Cycle Length (Y)	1	-	-	Assumption
	Cycle Number	Until Death	-	-	Assumption
	Discount Rate	3%	-	-	Assumption

Abbreviations: *DSA, deterministic sensitivity analysis; PSA, probabilistic sensitivity analysis; USD, United States dollars; PPH, postpartum hemorrhage; ICU, intensive care unit; TXA, tranexamic acid; H, hour; D, day; Y, year*

Symbols: *a, the range reflects the 95% confidence interval unless otherwise noted; **, from source distribution; [], min-max range*

884 **Table 2:** Costs considered, by health state and costing perspective

Health State	Vaginal Delivery	Cesarean Delivery	Medical Malpractice	(+/-) TXA	Hospital Bed-day	Balloon Tamponade	Conservative Surgery	ICU day	Hyster-ectomy	Variable	Productivity Loss (D/Y)	Productivity loss (D)
Death Other Cause/ Collecting State										X	O	
Death PPH (VD)	X		X	X	X						O	
Death PPH (CD)		X	X	X	X						O	
Death PPH + Balloon Tamponade	X		X	X	X	X					O	
Death PPH + Conservative Surgery (VD)	X		X	X	X	X	X	X			O	
Death PPH + Conservative Surgery (CD)		X	X	X	X	X	X	X			O	
Death PPH + Hysterectomy (VD)	X		X	X	X	X	X	X	X		O	
Death PPH + Hysterectomy (CD)		X	X	X	X	X	X	X	X		O	
Alive Pregnancy (VD)	X			X								O
Alive Pregnancy (CD)		X		X								O
Alive PPH (VD)	X			X	X							O
Alive PPH (CD)		X		X	X							O
Alive + Balloon Tamponade	X			X	X	X						O
Alive + Conservative Surgery (VD)	X			X	X	X	X	X				O
Alive + Conservative Surgery (CD)		X		X	X	X	X	X				O
Alive + Hysterectomy (VD)	X			X	X	X	X	X	X			O
Alive + Hysterectomy (CD)		X		X	X	X	X	X	X			O
Alive Healthy												
Alive Healthy, post-Hysterectomy												

885 ***Abbreviations:*** *TXA, tranexamic acid; ICU, intensive care unit; D, day; Y, year; PPH,*
886 *postpartum hemorrhage; VD, vaginal delivery; CD, cesarean delivery*

887 ***Symbols:*** *X, health system and societal costing perspective; O, only societal costing perspective*

888 **Table 3:** Lifetime cost savings and outcomes averted per annual cohort, by strategy[a]

Strategy	Cost Savings (2018 USD)	PPH Cases Averted	Balloon Tamponades Averted	Conservative Surgeries Averted (UAL, UAE, CSU)	Hysterectomies Averted	Maternal Deaths Averted
Status Quo	0	0	0	0	0	0
High Risk Only	315,518,299	65,502	8,238	10,776	1,322	27
High and Medium Risk Only	655,682,752	138,846	16,852	23,385	2,860	64
All Risk Categories	670,354,193	149,505	19,447	24,079	2,933	70

889

890 ***Abbreviations:*** *USD, United States dollars; PPH, postpartum hemorrhage; UAL, uterine artery*
891 *ligation; UAE, uterine artery embolization; CSU, compression sutures*

892 ***Symbols:*** *a, assuming 3.8 million births*

893

894 **Table 4:** Lifetime cost-effectiveness of prophylactic tranexamic acid, by strategy

Strategy	Cost (2018 USD)	Incremental Cost	QALYs	Incremental QALYs	Cost per QALY
Status Quo	12,660	0	26.0256	0	486.43
High Risk Only	12,577	-82.89	26.0293	0.0037	483.18
High and Medium Risk Only	12,487	-172.57	26.0337	0.0081	479.65
All Risk Categories	12,484	-175.49	26.0341	0.0086	479.53

895

896 ***Abbreviations****: USD, United States dollars; QALY, quality-adjusted life-year*

897