A POPULATION BASED COHORT STUDY: THE EPIDEMIOLOGY OF PEDIATRIC VENOUS THROMBOEMBOLISM IN QUEBEC, CANADA

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Table of Contents

ABSTRACT

Background: Pediatric venous thromboembolism (VTE), although rare, is associated with significant morbidity and mortality. Published incidence and recurrence rates in children vary widely with incidence rates ranging from 0.07 to 0.49 VTE per 10 000 children/year[1,2] and recurrence risks ranging from 5.5% to 18.5%.[1,3] There is currently a paucity of studies evaluating temporal incidence trends, as well as risk factors for recurrence.

Objectives: To describe the age-adjusted incidence rate of pediatric VTE and its trend over time, to determine VTE recurrence rate and overall all-cause mortality following VTE, and to determine predictors of VTE recurrence and all-cause mortality.

Methods: A retrospective population-based cohort of all children (ages 1-17 inclusive) with a first time diagnosis of VTE in the province of Quebec between January 1st, 1994 and December 31st, 2004 was obtained from a comprehensive administrative hospital database (Med-Echo). Provincial census estimates were used to calculate age-standardized incidence rates (IR) of pediatric VTE. The incidence rate trend was then analyzed over the eleven-year study period using Poisson linear regression with time as both a continuous (yearly) and categorical (time periods) variable. Rate of VTE recurrence and all-cause mortality were determined. Univariate Cox-proportional hazards models and log rank testing were used to assess which risk factors would be incorporated into the final multivariate Cox-proportional hazards model evaluating risk of VTE recurrence and all-cause mortality.

Results: In total, 487 incident cases of VTE in children 1-17 years of age were documented. Based on the estimated provincial census person-years during the study period, the age-standardized IR was 0.29 VTE per 10 000 person-years (95% confidence interval (CI) 0.26-0.31). Females had a statistically significant higher VTE incidence rate (per 10 000 person-years) than males, 0.37 and 0.21 per 10 000 person-years, respectively with an incidence rate ratio comparing females to males, adjusted for age group of 1.75 (95% CI 1.46-2.10). Trend analysis showed no statistically significant change in the age-standardized IRs over the 11-year period. The VTE recurrence rate was 2.77 (95% CI 2.2-3.4) per 1000 person-months (overall risk of 16%). Recurrence was associated with the presence of a chronic disease, defined as a diagnosis of inflammatory bowel disease, cystic fibrosis, lupus, sickle cell disease or nephrotic syndrome, (hazard ratio (HR) 2.3; 95% CI 1.2-4.3), presence of a central vascular line at time of initial VTE (HR 1.9; 95% CI 1.0-3.3) and portal vein thrombosis as the initial VTE presentation (HR 4.1; 95% CI 1.5-11.0). Overall all-cause mortality was 6.4%, hazard modeling of known risk factors for VTE was inconclusive for mortality.

Conclusions: Pediatric VTE is more frequent than previously described, however its incidence appears to be stable over time. Females are more prone to VTE than males in this age group. Risk of recurrence in our cohort is at the higher end of previously reported values, and is higher in those with a pre-existing chronic illness, central vascular line or with an initial diagnosis of portal vein thrombosis. All-cause mortality was lower in our cohort than previous large studies of VTE in this age group.[1,4] Our findings highlight the need for future studies to address sex differences in the incidence of pediatric VTE to help determine effective primary thromboprophylaxis strategies in children at high risk

for VTE, as well as determine effective secondary prophylaxis strategies in children at high risk for VTE recurrence.

RÉSUMÉ

Introduction: La thromboembolie veineuse (TEV) pédiatrique est un phénomène rare mais dont les séquelles peuvent être dramatiques. Selon la littérature, l'incidence est estimée entre 0.07 et 0.49 TEV par 10 000 enfants/année et la risque de récidive se situe entre 5.5 et 18.5%, toutefois, la qualité et le nombre d'études concernant le sujet demeure un facteur limitatif pour une meilleure compréhension de cette complication.

Objectifs: Décrire le taux d'incidence de la TEV pédiatrique selon l'age ainsi que la tendance dans le facteur temps; de déterminer le taux de récidive ainsi que décrire les facteurs de risque de récidive et de mortalité.

Méthodologie: En utilisant la base de données Med-Écho, une cohorte rétrospective des enfants âgés entre 1-17 ans (inclusif) avec un diagnostic d'un première TEV dans la province de Québec entre le 1 janvier 1994 et la 31 décembre 2004 a été établi. Une estime basée sur le résultat des recensements provinciaux a été utilisée pour standardiser et calculer les taux d'incidence. Le taux décrit annuellement et en trois catégories de temps, a été évalué en utilisant la méthode de Régression Linéaire Poisson pour établir si une tendance existe. Le taux de récidive et de mortalité ont été détermines et une analyse univariable du modèle de Cox et le « Log Rank » ont été utilises pour établir quels facteurs de risque seront incorporés dans le modèle finale de multivariable de Cox.

Résultats: Au total, nous avons observé 487 épisodes de TE chez des enfants âgés entre 1 et 17 ans. Le taux d'incidence de TEV pédiatrique ajusté pour la distribution d'age de la population, calculé en utilisant des estimations basées sur les recensements provinciaux, est de 0.29 TEV par 10 000 personnes-années (intervalle de confiance à 95% (IC) 0.26-0.31). Le taux d'incidence ajusté pour variation en catégories d'age des

femmes comparativement aux hommes est 1.75 fois plus élevé (IC à 95% 1.46-2.10) et est statistiquement significatif, avec des taux respectifs de 0.37 et 0.21 par 10 000 personnes-années. L'analyse de l'incidence de TEV pédiatrique entre 1994-2004 ne démontre aucune différence significative pendant cette période. Le taux de récidive est de 2.77 (IC à 95% 2.2-3.4) par 1000 personnes-mois (risque de 16%). La récidive est associée avec le diagnostic d'une maladie chronique, incluant la maladie inflammatoire intestinale, la fibrose kystique, l'anémie falciforme, le lupus, et le syndrome néphrotique (le *hazard ratio* (HR) 2.3; IC à 95% 1.2-4.3), la présence d'une ligne centrale (HR 1.9; IC à 95% 1.0-3.3) ainsi qu'une une thrombose du système portal comme premier épisode de TEV (HR 4.1; IC à 95% 1.5-11.0). La mortalité à tout cause est 6.4%, estimation de HR pour plusieurs facteurs de risque par modèle de Cox hazard était indécisif.

Conclusion: Le TEV pédiatrique est plus fréquente que la littérature ne le suggère, et sa tendance ne semble pas avoir change entre 1994 et 2004. Les femmes semblent avoir une incidence accrue par rapport aux hommes dans ce groupe. Le taux de récidive dans notre cohorte se situe à la limite supérieure des résultats des études précédentes. Le taux de récidive est plus élevé chez les enfants atteints d'une maladie chronique, avec une ligne centrale ou un diagnostic initial de TEV du système portal. La mortalité de notre cohorte est inferieure à ce que la littérature suggère. Nos résultats soulignent la nécessite d'entreprendre de nouvelles études afin de déterminer l'usage de prophylaxie chez les enfants a haut risque de TEV et/ou de récidive.

List of Tables and Figures

TABLES:

FIGURES:

Statement of originality

I performed all aspects of this study, which included: 1) choice of study question, 2) design of study protocol, 3) data extraction, statistical analysis, and interpretation. Dr. Vicky Tagalakis obtained the MedEcho raw data used in this thesis. This thesis reports on this retrospective cohort study. I wrote all chapters of this master's thesis.

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Abbreviations

CAI: Commission d'accès à l'information

CHD: Congenital Heart Disease

CSVT: Cerebral Sinus Venous Thrombosis

CT: Computed Tomography

DVT: Deep Vein Thrombosis

IR: Incidence Rate

ISQ: Institut de la Statistique du Québec

Med-Echo: Maintenance et Exploitation des Données pour l'Etude de la Clientèle Hospitalière

MRI: Magnetic Resonance Imaging

PE: Pulmonary Embolus

PICC: Peripherally Inserted Central Catheter

PVT: Portal Vein Thrombosis

RAMQ: Régie de L'Assurance Médicale Québec

RVT: Renal Vein Thrombosis

SCD: Sickle Cell Disease

SLE: Systemic Lupus Erythematosus

U/S: Ultrasound

VTE: Venous Thromboembolism

Chapter 1: Introduction

Pediatric venous thromboembolism (VTE) is defined as deep vein thrombosis (DVT) of the upper extremity, lower extremity or central vasculature, pulmonary embolism (PE), cerebral sinus venous thrombosis (CSVT) and renal vein thrombosis (RVT) from the time of birth until 18 years of age. It is associated with significant morbidity and mortality, including recurrence, post-thrombotic syndrome, and even death from fatal PE.[5] DVT may embolize to the lungs causing PE via either the complete thrombus or part of it dislodging from the original vessel and then travelling through the venous system to end up in the pulmonary vasculature.[6] The incidence of pediatric VTE is largely unknown, but is thought to range from 0.07-0.49 cases/10 000 children.[1,2] Most studies to date have used registries or administrative databases, to estimate incidence of VTE, and differences in inclusion criteria and estimation procedures largely account for the variability in incidence estimates.[1-4,7-14] Moreover, there is both a lack of data and inconsistency in data reporting on temporal trends of the incidence of pediatric VTE. Information on temporal trends of VTE occurrence is essential in order to follow changes in burden of disease and help focus areas that require further research. Some authors have shown an increasing incidence of VTE in children over the past 20 years, however these findings are not always consistent.[2,15-18] Although pediatric VTE may be relatively rare, its burden of disease is high given the potential for long term morbidity and mortality in children.[2,16,17] A rise in incidence would lend support to the need for pediatric specific research in this field. Most current treatment and preventative strategies in children are based on the much more extensive adult literature in the field.[5] A more thorough

understanding of the epidemiology of pediatric VTE (i.e. incidence, recurrence risk, risk factors, and outcomes) is needed to advance the field.

Comprehensive, population-based hospital administrative databases allow for a straightforward and relatively low cost means to measure disease incidence and other epidemiologic characteristics of pediatric VTE, while maintaining a more thorough assessment of incidence than registries or sample based administrative database can. In this thesis, we studied the population incidence of pediatric VTE, evaluated temporal trends in its incidence, and evaluated the risk of adverse outcomes (recurrence and mortality) using a population based retrospective cohort of children with a first time diagnosis of VTE identified using the linked records from the RAMQ (Régie de l'Assurance Maladie Québec) provincial healthcare services database and the Med-Echo (maintenance et exploitation des données pour l'étude de la clientèle hospitalière) database. By providing a more contemporary estimate of pediatric VTE incidence, as well as defining which risk factors are most strongly associated with death and VTE recurrence, we hope to improve knowledge of this important problem and help focus future research on improving treatment and prevention strategies in pediatric populations.

Chapter 2: Literature Review

2.1 VENOUS THROMBOEMBOLISM

2.1.1 Overview of Coagulation

Coagulation is defined as a "process that leads to fibrin formation".[19] The coagulation cascade is an intricate stepwise set of events that lead to hemostasis.[20] This cascade is offset by a system of anticoagulant factors that ensure that hemostasis remains regulated.[20] The coagulation cascade, as depicted in **Figure 2.1**, includes numerous factors that contribute to this balance. The term venous thromboembolism is derived from the Greek words "thrombos" meaning clot and "embolos" meaning thrown or plug.[21] It can be defined as the presence of a blood clot in a vein and occurs when either inherited or acquired imbalances of this system lead to its unregulated activation.[20]

2.1.2 Historical Perspective

Thorough reviews of ancient medical literature and illustrations searching for early descriptions of VTE have been unsuccessful and no documented cases of venous thromboembolism can be found until the 13th century.[22] The first possible case description was in found in a French illustrated manuscript describing the case of young man with unilateral leg swelling. Although the case goes on to describe further complications of a septic ulcerated leg that was cured by a miraculous intervention of Saint Louis, this case

nevertheless appears to be the first possible documented case of venous thrombosis.[21,22] Post-partum VTE was not documented until the late 1600's by a British surgeon, who quite astutely noted that the progressive unilateral swelling of the woman's leg post-partum was likely due to a systemic change in the circulation of blood.[22] Though the aforementioned first documented case was described in a healthy 20 year-old young man, historically VTE was most commonly cited in association with pregnancy, surgery or cancer. Pediatric VTE, although cited as far back as the late 1800's[23,24], was so infrequently discussed in the literature that an extensive review of the literature in the early 1990's, found that from 1975 to 1991 only 308 cases of VTE in children between the ages of 2 months and 18 years of age were cited in the literature.[25]

2.2 OVERVIEW OF CURRENT KNOWLEDGE OF THE EPIDEMIOLOGY OF PEDIATRIC VENOUS THROMBOEMBOLISM

2.2.1 Incidence Rates

The most frequently cited current estimate of the incidence of pediatric VTE is between 0.07-0.14 events per 10 000 children and is essentially centred on two large registry-based studies that nonetheless have important limitations.[5,26] The Canadian Childhood Thrombophilia Registry was a prospective registry of consecutively diagnosed cases of pediatric VTE (1 month through 18 years of age) at 15 Canadian pediatric tertiary care centres over a two-year period (1990-1992). Designated individuals at each study centre registered all cases of upper and lower extremity DVT and PE at their centres (renal

vein, portal vein, central venous and central nervous system thrombosis were excluded). In its initial analysis, 137 cases of pediatric VTE were identified and the authors reported an incidence of 0.07 cases per 10 000 children in Canada.[1] Whether this estimate reflects the true incidence of pediatric VTE is subject to question. Their definition of VTE was limited to only certain types of VTE and did not include some of the more common forms found in children, such as renal vein thrombosis. The results of their study may be affected by selection bias, as only cases from the 15 study centres were included. Cases from other smaller pediatric centres which may be inherently different than cases at tertiary care centres are likely to have been missed, although this number is probably small given that the 15 participating tertiary care centres were the principal pediatric centres in Canada. Selection bias may have also occurred as cases cared for at non-pediatric centres would not have been included, which may be especially problematic for documenting cases in adolescents and/or in smaller regions. Information bias may have occurred as it is unclear if the population estimate used in the incidence calculations was that of all children in Canada or if the authors excluded provinces and territories that did not have participating centres (New Brunswick, Prince Edward Island, Northwest Territories and Yukon Territories). This may have led to either an overestimation of incidence, if some areas were excluded from the denominator but referred cases that may have been included if they were transferred to one of the larger pediatric tertiary care centres in the study, or an underestimation if the whole population of children in Canada was used as the denominator but only the cases at those 15 centres were included.

The other principal study was from the Netherlands, where all cases nationwide (<18 years of age) of VTE (n=99) were prospectively collected over a two-year period

(1997-1999) by a national survey system. All pediatricians at primary and secondary care centres and pre-established contact persons at tertiary care centres were sent monthly response cards to document new cases. An incidence of 0.14 cases per 10 000 children was found. Their incidence estimate was likely higher than the Canadian study as they included all types of VTE including central nervous system (CNS) venous thrombosis. Despite a relatively high response rate (91%)[4], there remains the possibility that not all cases were ascertained if health care professionals from other specialties cared for patients with VTE or if physicians failed to record all cases. Both of these studies used response-based registry systems, which for many of the reason stated above, including the fact that they may have missed many adolescent cases of VTE, may lead to an underestimation of the actual incidence rate of pediatric VTE.

Although the above incidence rates are frequently cited,[5,27-29] a wider range of incidence rates in children have been reported in the literature. Most recently, Tuckuviene and colleagues assessed the population-based incidence of pediatric VTE in Denmark using their country's comprehensive national administrative database. The Danish National Patient Registry is a comprehensive administrative database containing information on all hospital discharges in Denmark. They retrieved all cases of non-cerebral arterial and venous thromboembolism in children 0-18 years of age and confirmed all diagnosis by verification of hospital records. Between January 1, 1995 and December 31, 2006 they confirmed a total of 372 cases of venous and arterial thromboembolism over a 12 year period, they found an incidence rate of 0.21 venous thrombotic events per 10 000 person-years in children 0-18 years of age, although cerebral (CNS) VTE were excluded.[18]

Previously, Stein and colleagues also used an administrative database, the National Hospital Discharge Survey (NHDS), to assess incidence rates of pediatric VTE in the United States of America (US). The NHDS accounts for 8% of all hospitals and 1% of all hospital discharges in the US. Incidence was calculated using a multi-stage estimation procedure and annual US census data. The authors estimated that 75 000 discharge diagnoses of DVT and PE over the time period of 1979 to 2001 occurred, resulting in a rate of 0.49 VTE per 10 000 children/year.[2] A major limitation of this study was that it used a sampled database rather than a comprehensive one, so although this would appear to be the largest number of events of pediatric VTE studied to date, it is an estimate and not a true population parameter. Data from a sampled group of hospitals was used to extrapolate and estimate the national incidence rates. The use of discharge diagnoses per admission to count case number without an ability to differentiate multiple admissions for the same individual may lead to misclassification of cases, skewing the number of overall cases above what should be expected. The types of hospitals included in the sample may lead to selection bias as pediatric VTE is mostly cared for in tertiary care centres and it is not clear how many of the centres within this database fit this profile, which may lead to either over or underestimates of the true incidence.[2,4]

Other studies to date have estimated population-based incidence of pediatric VTE using registries or administrative healthcare databases in specific cities (Hong Kong, Worcester, and Malmo) or country-wide (Germany, United Kingdom) with estimates ranging from 0 to 0.5 events per 10 000 children or births, depending on the study.[3,7-9,11,13,14] A summary of population-based incidence studies is shown in **Table 2.1**.[2,3,7-11,13,14] The large variability across studies may be explained by inconsistent VTE definitions, with

some studies only assessing DVT and/or PE and others including CSVT, RVT and PVT; differing extraction methods with case identification based on discharge diagnosis, radiological records, registry responses and surveys in various studies; and different age groups in the various studies (0-18, <15, etc.). The highest quoted incidence rates are in the German Neonatal Registry, with 0.51 VTE per 10 000 neonates which is likely due to the fact that they studied only neonates who are known to have the highest incidence of VTE in pediatric aged patients. The NHS database also described a high incidence of 0.49 VTE per 10 000 children which used a sampled discharge database to estimate the number of VTE in children. Since events were defined as the presence of a discharge diagnosis consistent with VTE in the database, it is possible that children with multiple admissions for recurrent thrombi were counted more than once, leading to misclassification bias that may overestimate the true incidence. The lower estimate in the Canadian Thrombophilia Registry of 0.07 per 10 000 children may be biased by incomplete response in registries and limited definition of VTE excluding CSVT, RVT and portal vein thrombosis. The British Registry also had a low incidence but they only included patients from 1 month to 16 years of age and it is well established that the highest incidence is in older adolescents and neonates and their exclusion of these two groups may explain the lower incidence. Smaller studies such as the two in Hong Kong, the one in Malmo and the other in Worcester were limited to only certain hospitals in their respective regions and were not clear on their age distribution, with some having wide age categories since their studies included adults, or limited age categories not including all children under 18 years of age (ex. <15 years). The number of cases found in these small studies likely reflects how actively the few hospitals studied tested for VTE. It is unclear whether VTE was more

likely to be seen in private hospitals not included in the studies, and the exclusion of older adolescents may explain their lower rates.

To date, the population incidence rate of pediatric VTE in North American studies has been limited to the Canadian registry based study which may have underestimated the incidence as previously addressed and only evaluated extremity DVT and PE; the NHDS which was an estimated population incidence based on a sample of the total population and evaluated DVT, pregnancy and abortion related VTE; and a small area specific (Worcester, Massachusetts) study that only evaluated DVT and PE and included adults and children. The incidence rates ranged from 0 to 0.49 VTE per 10 000 children within these three North American Studies.[1,2,7] Given this large variation in incidence rates in North America as well as around the world, as well as the limited number of studies evaluating the burden of pediatric VTE in North America, a current population-based estimate of pediatric VTE incidence in North American areas is needed.

2.2.2 Trends In Incidence Of Pediatric Venous Thromboembolism

To date few studies assessed whether the incidence of pediatric VTE is rising. Many reviews in the field suggest that the incidence is increasing and authors attribute this increase to improvements in the care of critically ill children, longer lifespan of chronically ill children, increased use of indwelling central venous catheters and increased awareness of VTE amongst pediatric care providers.[5,30,31] However the results of the few studies completed thus far do not consistently show this trend.

The largest study to date to address incidence trends in pediatric VTE is the previously mentioned United States National Hospital Discharge Survey (NHDS). Stein *et al.* compared VTE occurrence rates from 1979-1982 to 1999-2001 and found no significant difference between the two time periods. Misclassification and selection bias in the NHDS, as previously discussed above, should not lead to differential misclassification within the two time frames studied, and therefore the lack of a change in incidence seems credible.

Raffini *et al.* retrospectively reviewed a cohort using another US hospital discharge database and compared the annual incidence of VTE in hospitalized children between 2001-2007 and found that the yearly incidence had increased by 70% over this time period (from 34 to 58 cases per 10 000 hospital admissions). Cases were identified from the PHIS (Pediatric Health Information System), an administrative database comprised of information from approximately 41 non-profit tertiary care children's hospitals across the US. In total, over the six-year period, there were 13 449 admissions with a discharge diagnosis of VTE, attributable to 11 337 individual patients (1401 had one or more recurrence). The results of this study are difficult to generalize to the general pediatric population as the denominator used in this study to calculate incidence was the number of hospital admissions and therefore may be more indicative of the frequency of VTE among hospitalized children.[15] Regardless, the large change in incidence rates throughout the study may be explained partly by information and selection bias. The initial (2001) incidence rates in this study did not include all 41 hospitals and over time the demographics of the types of patients admitted to tertiary care centres may have changed, especially given advancements in care of acutely ill children. Therefore, if over time only the sickest of children were being admitted to tertiary care centres and less medically complicated

children were cared for in community facilities, the incidence of VTE which is associated with many acute illnesses will be higher in tertiary care centre admissions but perhaps not in all children overall.

Most recently, a Danish cohort of all children (0-18 years of age) with noncerebral VTE between 1994 and 2006 was assessed for incidence rate trends. Denmark has a nationwide administrative database that contains comprehensive discharge information from all Danish hospitals. Information from the database on VTE diagnoses and population at risk from their national statistics were used to calculate yearly incidence of VTE in children and assess if incidence was changing over the study period when analyzed yearly and with time divided into two time periods and then assessed yearly. Neither analysis showed a statistically significant time trend, however there was a trend toward annual increase in the second half of the study that was not found to be statistically significant.[18] Although the incidence rates quoted in this study may be a slight underestimation since CSVT were excluded, the overall lack of trend of increasing incidence seems conceivable.

In contrast, other smaller studies have shown similar trends to the results from the PHIS study. In 2008, Vu and colleagues performed a cross sectional analysis of a national discharge database and showed that when comparing the years 1997, 2000, and 2003, of the 1.6 million discharges, the prevalence ratio of DVT was significantly higher for the years 2000 and 2003 than 1997.[17] Results of this study must be taken with caution as it is cross sectional and the number of hospitals included in the analysis increased over time. Moreover, the denominator used in their calculations was hospital discharges. It is possible that the hospitals added to the database in 2000 and 2003 included hospitals with more complex care and the increased incidence is simply due to selection bias. That same year,

Sandoval and colleagues published their centre's 14 year experience, showing an incidence of 9.7 DVT per 10 000 admissions (99 cases over the 14 year period) and when analyzing the incidence over the 14 year period they showed that the yearly incidence rose from 0.3 per 10 000 admissions in the 1992-1995 period to 28.8 per 10 000 admissions in the 2005 period.[16] Evidence of such a large change in incidence can be very convincing, however the results from a single centre study must be extrapolated with caution, as the demographics of patients admitted to their hospital may be quite different from the general population. Regardless, it is evident from the above literature that there is uncertainty as to whether or not the incidence of pediatric VTE is truly increasing.

2.2.3 Risk Factors for Pediatric Venous Thromboembolism

Large registry studies, such as the Canadian Childhood Thrombophilia Registry, have helped to identify risk factors for the development of VTE in pediatric patients. As noted above, the Canadian Childhood Thrombophilia Registry was a prospective cohort study at 15 pediatric tertiary care centres across Canada. All newly diagnosed cases of DVT including upper and lower extremity DVT and PE were included over a six-year period. Among 405 cases, only 3% of cases were spontaneous (i.e. unprovoked). Most patients therefore had risk factors, with most having two or more risk factors (>75%).[1,12] Similarly, Van Ommen *et al.* studied one hundred consecutively diagnosed pediatric patients with VTE in the Netherlands and assessed for the presence of a clinical risk factor. They found that 96% of patients had at least one risk factor present.[32] Unprovoked VTE in children is therefore a rare occurrence. Many risk factors for pediatric VTE have been

postulated based on their increased presence in children with VTE. Inherited thrombophilias, age, congenital heart disease, chronic medical illnesses, infections, cancer, central venous lines, trauma, surgeries have been frequently noted. Other factors such as obesity (2-4%), pregnancy (0.7%) and immobility (15%-17%), amongst others, have also been reported to occur amongst VTE pediatric patients, but not as consistently as the aforementioned risk factors.[4,12,15,18,33,34]

2.2.3.1 Pathogenesis of Venous Thromboembolism

The pathogenesis of VTE can be described according to Virchow's triad of hypercoagulability, venous stasis, and vessel wall injury. Risk factors for VTE can be characterized according to one or more of these components as shown in **Figure 2.2** and **Table 2.2**.

2.2.3.2 Inherited Thrombophilia

The hypercoagulable state, one component of Virchow's triad, arises through either acquired or inherited thrombophilias (IT). Inherited or congenital thrombophilias occur either through deficiency of one of the natural anticoagulants (e.g. protein S, protein C, antithrombin III) or through modulation of the coagulation cascade (e.g. Factor V Leiden, Prothrombin gene mutation). Acquired thrombophilias include development of anticardiolipin antibodies, lupus anticoagulant, anti β2 glycoprotein I antibodies, increased lipoprotein (a), increased homocysteine levels, increased coagulation factor levels such Factor VIII, although some of these may be associated with heritable conditions.[35,36] These abnormalities or deficiencies in normal coagulation proteins lead to

an imbalance in this system that favours thrombus generation. Factor V Leiden (FVL) and Prothrombin gene mutation are the most frequently encountered inherited thrombophilias in the general Caucasian population, with a prevalence of the heterozygous state in 5% and 2% respectively. These both arise from mutations in different coagulation proteins; with FVL causing resistance to activated protein C that normally participates in the inhibition of thrombus formation and prothrombin 20210A gene mutation that leads to an increased amount of thrombin generation. Deficiencies in protein C, protein S, and antithrombin III also lead to increased thrombus formation, as all three play an important role in the body's normal ability to regulate thrombus formation. Other inherited factors such as mutations within the MTHFR (methylene tetrahydrofolate reductase) gene may lead to hyperhomocysteinemia, which has been shown to be associated with increased odds of having had a VTE.[37] Other acquired factors such as lupus anticoagulant and other antiphospholipid antibodies, and increased levels of lipoprotein (a) and others also may play contributory roles in thrombus formation.[5,38]

The data on IT prevalence in children is scarce and the studies are limited by incomplete testing. In the previously mentioned Dutch study by Van Ommen *et al.*, of the 100 subjects with a VTE studied, 88 had at least a partial thrombophilia work up done, with the prevalence of various thrombophilic defects ranging from 1-13%.[32] Similarly, when a consecutive group of unselected children from the Hospital for Sick Children were analyzed for an underlying thrombophilia, of the 171 patients (all of whom were tested for protein C, protein S, antithrombin, factor V Leiden and prothrombin variant and 65% tested for lipoprotein (a) levels), 13% had a congenital thrombophilia.[36] Yet, the Canadian Thrombophilia Registry found that only 2% of their subjects had a congenital

thrombophilia, but it is not clear how many patients actually had a full thrombophilia work-up within their VTE cohort.[12] Moreover, the extent of tests undertaken as part of a thrombophilia work-up often differs depending on the centre or physician, making it difficult to assess the true contribution of various thrombophilic conditions to incidence of VTE. **Table 2.3** summarizes the main English language published pediatric studies on prevalence of inherited thrombophilic conditions in pediatric VTE. Of the studies with greater than 80% of subjects tested, the range of inherited thrombophilia is quite large between 13% and 74%.[36,39-43] Hagstrom *et al.*, Lawson *et al.*, Enhrenforth *et al.* and Heller *et al.* all evaluated selected individuals with VTE who had been tested for thrombophilic conditions.[40-43] Since it did not appear that their testing was of all patients with VTE it is likely that those being tested were those with a high clinical index of suspicion for inherited thrombophilia (ex. positive family history) thus explaining the higher prevalence in their studies. The two studies that evaluated consecutive cohorts of VTE cases showed prevalence rates between 13-19%, which may be a better depiction of the true prevalence amongst pediatric VTE cases.[36,39] Given the variability in testing, very few measures of effect are known with respect to individual inherited thrombophilias. Bonduel *et al.* in their case control study comparing 130 consecutive pediatric VTE patients (of whom 110 had thrombophilia testing) with 212 unrelated healthy adult controls showed an odds ratio of VTE in patients with FVL of 3.64 (95% CI: 1.14-11.6) and an odds ratio for VTE in patients with prothrombin 20210A variant of 1.06 (95% CI: 0.24-4.73).[39]

Despite these variable estimates of inherited thrombophilia prevalence in children with VTE, when 143 children between the ages of 1 and 15 years of age with a positive family history of thrombosis were followed for mean of five years, of which 56.6% were

carriers of a known inherited defect, none developed a VTE.[44] This finding has been confirmed in a second study.[45] Therefore although the presence of inherited thrombophilias seems to be frequent in children who develop VTE, the risk of VTE in children with inherited thrombophilias overall is quite low. This differs from adults, where the risk of thrombosis in those with an inherited thrombophilia increases with age and overall the prevalence of inherited thrombophilia (FVL, prothrombin 202010A, Protein C, S and antithrombin deficiency) in adults with VTE is approximately 30%.[46,47]

2.2.3.3 Age

Among children, age has been found to be associated with risk of incident VTE. The risk is highest during the neonatal (< 28 days) and teenage (>13 years of age) periods.[1,2,4,48] Compared to the total overall rate of VTE in children, neonates have an almost 100-fold increased risk of VTE and adolescents have a threefold increased risk.[1,2,5,12,14,15,49] The increased rate in the neonatal period occurs mostly in sick neonates and is often in association with prematurity, infections, dehydration and central venous catheters.[4,14,50] Certain types of thrombosis are also more common in the neonatal period, such as renal vein thrombosis, although the reason for this is unclear.[50] In teens, maturation of the hemostatic system transitioning to the adult state as well as the introduction of some acquired risk factors such as smoking and oral contraceptives likely contribute to the increased risk in this age group.[18,51] This bimodal distribution of VTE in children differs from the adult pattern where risk of VTE increases steadily with age and after the age of 45-60 it increases exponentially with advancing age.[52] The rate of VTE in those 85 years

and older has been found to be as high as approximately 90-100 cases per 10 000 persons annually.[53]

2.2.3.4 Central Venous Catheters

Central venous catheters both at the time of placement and as a foreign object that remains in the blood vessel contribute to endothelial wall injury and obstruction of flow through vessels. Multiple studies have confirmed that the most common risk factor associated with pediatric VTE is the presence of an indwelling central venous line (CVL), with prevalence among VTE cases ranging from 8%-77%.[4,12,18,34,36] The Netherlands registry published by Van Ommen *et al.* and the Canadian Thrombophilia Registry follow up study published by Monagle *et al*, both showed prevalence of CVL in approximately 60-64% of VTE cases.[4,12] The prospectively collected information on 171 consecutive children with VTE by Revel-Vilk *et al.* at the Hospital for Sick Children also showed a similar presence of CVL in 77% of their patients.[36] The other two studies that showed lower prevalence of CVLs ranging from 8-32% of VTE cases, both used retrospective medical record review to obtain data on associated risk factors.[18,34] Since CVL placement may not always be clearly recorded in medical records it is possible that in the registry studies, where often treating teams were completing the questionnaires, and in prospective studies, more complete data on risk factors might be obtained thus explaining this wide variation.

A few prospective studies have been done to assess the risk of developing a thrombosis in children with a CVL in place. These studies included any thrombus associated with a central line, whether it was only at the tip of the catheter or more

extensive. Dubois and colleagues performed a one-year prospective surveillance study of patients with a new peripherally inserted central catheter (PICC) line placed. Two hundred and fourteen of 728 eligible patients were included in the study and serial ultrasonography and angiography at PICC insertion and removal were completed. They showed that 9.3% (20 of 214) patients with a PICC line developed a thrombus with only 1 symptomatic case, and an overall incidence rate of 3.85 VTE per 1000 catheter-days.[54] In contrast, in a more acute setting, Beck and colleagues (at the same institution as Dubois' study) evaluated the incidence of thrombosis in patients with a CVL in an intensive care unit (ICU) setting, where 93 CVLs in 76 patients were evaluated (39 internal jugular, 23 femoral, 9 subclavian, 5 external jugular). Serial ultrasounds were performed to evaluate for thrombus and 18.3% (17 of 93) of patients developed a thrombus, 7 (7.5%) of which were symptomatic.[55] Talbott *et al.* enrolled 25 patients with a femoral venous line placed also in the pediatric ICU setting (of which 20 were evaluable) and serial ultrasound imaging demonstrated that 7 developed thrombi (35%), although 6/7 were initially asymptomatic.[56] The long-term consequences of CVLs were evaluated in one study of children with a history of a long-term (> 6 months) central venous catheter that had been removed at a median of 37 months prior to study evaluation. Despite all the 71 children being asymptomatic and never having been diagnosed with a prior VTE, 6% of children had evidence of post thrombotic syndrome on physical examination and 24% had some residual venous abnormality at the site of the prior CVL (7% had remaining obstructive thrombus) on ultrasound evaluation.[57] Post thrombotic syndrome refers to a constellation of physical signs and symptoms likely related to chronic venous hypertension after venous thrombosis.[58] A systematic review by Goldenberg *et al.* reported a frequency of PTS

ranging from 0-70% in children with a previous episode of VTE; however, after weighting for quality of study (many were retrospective and did not use a standardized PTS outcome assessment tool), the weighted mean frequency was 26% (95% CI 23-28%).[59] Overall, it appears that the risk of thrombus, as well as sequelae of thrombosis such as PTS, even in children without symptomatic VTE, is significant with central venous catheters.

2.2.3.5 Congenital Heart Disease

Both the presence of congenital heart disease (CHD) as well as its surgical repair has been associated with increased risk of VTE in children. It is estimated that anywhere between 4%-29% of pediatric VTE are associated with either CHD or its surgical correction.[1,4,12,15,18,33,34] Certain surgical repair procedures including bicavopulmonary shunts (BCPS) and the Fontan procedure for single ventricular physiology congenital heart disease and other palliative procedures for congenital heart lesions, are strongly associated with an elevated risk of thrombosis.[60] As a result, the American College of Chest Physicians (ACCP) in their "Antithrombotic therapy in neonates and children" guidelines recommend anticoagulation primary prophylaxis for these surgical procedures either in the immediate post-operative period or in some cases indefinitely.[61] More specifically they recommend: "For children who have a BCPS, we suggest postoperative UFH (unfractionated heparin)" and "For children after Fontan surgery, we recommend aspirin or therapeutic UFH followed by VKAs (vitamin K antagonists) over no therapy".[61] Congenital heart disease and its surgical repair likely contribute to thrombus formation through both increased venous stasis and endothelial wall injury.

2.2.3.6 Oral Contraceptive Pill

The oral contraceptive pill (OCP) was first linked to an increased risk of thromboembolism shortly after it was introduced onto the market in 1957.[62] The OCP contributes to Virchow's triad by causing a hypercoagulable state that arises from a decrease in natural anticoagulants and an increase in other coagulation factors that lead to the prothrombotic state.[63] One of the earliest reports in the early 1960's was that of a woman on the combined contraceptive pill for endometriosis who developed severe nausea on starting the pill and shortly thereafter developed a PE. The author of this case report proposed that the severe nausea may have led to dehydration that then caused the PE.[64] An editorial a few years later, in 1963, began to shed light on this possible association.[65] Since these first reports more than 50 years ago, the hormone dosage within the OCP has decreased and the types of hormones within the oral contraceptive pill have changed in attempts to decrease the risk of side effects and complications, including VTE, from its use. Given these many changes it is often difficult to extrapolate data from previous studies regarding oral contraceptives and risk of VTE as the types of OCP are constantly changing.[66]

A recent study using a Dutch cohort of women on varying doses and types of oral contraceptives compared the risk of type of progestin (first, second and third generation) and dose of estrogen, as well as the use of oral contraception versus no use in terms of risk of thromboembolism. The relative risk of thromboembolism in women aged 15-49 on a low dose estrogen pill (30-40 μg of ethinylestradiol) and various forms of progestin was between 2.9 and 6.4, with those on third generation progestins having the highest risk.[67] Increasing risk with higher doses of estrogen, as was used in earlier formulations of the oral

contraceptive pill, were the first evidence that perhaps the risk of VTE was not secondary to dehydration alone as was initially postulated.[66] Prevalence of OCP use in pediatric VTE cohorts has been shown to be approximately 4%.[4,12] Although in the recent Danish nationwide pediatric VTE cohort study, when females over 13 years of age were assessed alone, the use of OCP was prevalent in 79% of VTE cases.[18] Therefore its contributory role in VTE is clearly much higher in teenage females than in other pediatric groups.

2.2.3.7 Surgery

Surgery has been found to be a risk factor associated with VTE in children, with estimates of approximately 6-15% of VTE cases occurring in association with a recent surgical procedure.[3,4,12,18] The post-operative period is often a period of decreased mobility which can increase venous stasis and contribute to thrombosis risk, in addition there may also be some element of a pro-inflammatory state associated with the peri-operative period that may contribute to endothelial dysfunction.[5,68,69] In adults, anywhere from a quarter to half of acute pulmonary emboli are said to occur within three months of a surgery.[52] Tshifularo and colleagues evaluated 18 post surgical pediatric patients with VTE and found that 17 of the 18 (95%) had additional contributing risk factors, including infections, trauma, inflammation, and presence of a recent central venous line.[70]. As a result, it is unclear if surgery is an independent predictor of VTE risk in children

2.2.3.8 Chronic Diseases

Many chronic diseases have been found to be associated with venous thrombosis. Whether from the disease itself (through a hypercoagulable state or injury to vessel wall

from inflammation) or through complications from disease-related procedures, infections, central venous access devices, or medications, occurrence of VTE is more common in children with comorbid medical conditions. Raffini *et al.* showed that when comparing all admissions in the PHIS database, overall 64% of children did not have a complex chronic condition as opposed to admissions with VTE where only 37% did not have a complex chronic condition.[15] Inflammatory bowel disease (IBD), cystic fibrosis, systemic lupus erythematosus, nephrotic syndrome, and sickle cell disease are a few of the chronic conditions that have been found to be present in children with VTE.[1,12,15,48,71] In adult studies, the risk of VTE has been found to be associated with many similar chronic conditions.[52,72]

A Danish cohort study by Kappelman and colleagues showed an incidence rate of VTE of 8.9 events per 10 000 person-years in IBD patients under the age of 20. Hazard rate in this age group for unprovoked DVT and PE was 6.0 (95% CI 2.5-14.7) and 6.4 (95% CI 2-20.3) respectively, compared to age and gender matched controls where unprovoked was defined as in the absence of recent fracture, surgery, pregnancy or history of malignancy.[71]

Other chronic illnesses such as cystic fibrosis, auto-immune disorders, sickle cell disease, and nephrotic syndrome have also been documented within pediatric VTE cohorts.[1,12,48] Cystic fibrosis, has been found amongst one of the published pediatric VTE cohorts and in addition has been linked to higher recurrence risk as will be discussed in the following section.[34,48] Systemic lupus erythematosus and other autoimmune conditions have been shown to be prevalent in about 1.5%-6% of children who present with thrombosis, whereas sickle cell disease has been found to be associated with up to 2% of pediatric VTE in the Dutch cohort and in a single centre study in Alabama.[4,12,34]

Nephrotic syndrome has been linked to an increased risk of thrombosis through various mechanisms, one being the loss of natural anticoagulant proteins such as antithrombin through proteinuria.[73] Nephrotic syndrome and other renal diseases have been shown to associated with 3%-11% of VTE cases in children.[1,3,34,74] Independent predictors of developing a VTE in children with primary or secondary nephrotic syndrome are age greater than 12, history of VTE prior to nephrotic syndrome diagnosis and significant proteinuria.[74]

The presence of many chronic diseases has been noted to be associated with cases of VTE in children. Other than for IBD, little data is available to specify a specific risk estimate that can be attributed to these diseases alone. For many of these chronic illnesses, their association with prolonged hospital stays, periods of immobility, higher likelihood of requiring central venous access, and medications may confound their risk of VTE.

2.2.3.9 Cancer and Bone Marrow Transplantation

Cancer diagnosis and bone marrow transplantation, whether for a malignancy or other illness, have been shown to be associated with an increased risk of developing VTE in children. The Canadian Childhood Thrombophilia Registry found that as many as 25% of VTE cases were associated with cancer diagnosis and bone marrow transplantation.[12] Other studies have shown between 2-18% of VTE cases being associated with this risk factor.[15,18,33,34] Different malignancy types also likely confer differing risks. One study examining the impact of brain tumours on risk of VTE in children found only 3 events out of 462 children studied (0.64%), which was much lower than the 20% risk in adults with brain tumours without thromboprophylaxis, this is likely due to the differences in types of

brain tumours seen in children versus adults.[75] Two separate retrospective series assessing risk of VTE in pediatric and young adult sarcoma patients showed between a 14-16% risk of VTE, with one study showing a non-statistically significant odds ratio of 2.59 (95% CI 0.9-701) for those who had metastases versus those with localized disease.[76,77] In children, given that leukemia is the most common malignancy, it is not surprising that it is the most studied type of malignancy in terms of its association with VTE. Its association with increased risk of VTE is thought to occur through various mechanisms including increased thrombin generation related to leukemia, necessity of central venous catheter access for therapy, certain types of chemotherapy used such as asparaginase and steroids, the risk of infections, and possible concurrent inherited thrombophilias.[78] In 1995, Mitchell and colleagues reviewed the current English and German language literature and found an incidence of thromboembolism between 1-15% in acute lymphoblastic leukemia (ALL) patients. A total of 40 studies were found, of which 36 were case reports or series.[79] Since then, other studies have attempted to assess the risk with various protocols in ALL and have found incidences between 1.7% and 9%.[80-82] Although the risk may differ between types of cancers, the high prevalence of cancer patients in pediatric VTE cohorts points to a likely association, whether directly from the cancer itself or through associated treatments or risk factors.

2.2.3.10 Infectious Disease

Infectious diseases often coexist with other VTE risk factors such as surgery, cancer or chronic medical conditions. Several studies of children with VTE have shown that approximately 12% to as high as 60% of children with VTE have a concurrent

infection.[4,12,18,34] In one administrative database study of children without chronic medical conditions who had a discharge diagnosis of VTE, 9.5% of VTE cases were associated with an acute infection.[33] It seems plausible that infections may predispose to VTE through inflammation leading to endothelial dysfunction, increased central venous access requirements amongst other features.

2.2.3.11 Trauma

Trauma via various mechanisms, including decreased mobility, increased number of procedures and possibly abnormal coagulation factors may increase the risk of thrombosis. Various studies in pediatric VTE cohorts have found a prevalence of this risk factor in 6-10% of patients, which is similar to adult data.[4,12,18,33,52,83] There have been no studies however that have reported on estimates of effect, although overall risk of VTE among pediatric trauma patients has been noted to be higher in older children and in those with a higher injury severity score.[84,85]

2.2.4 Recurrent Venous Thromboembolism in Children

2.2.4.1 Recurrence Risk and Risk Factors

A well-known complication of VTE is recurrence. An individual's risk of recurrence plays a key role in guiding the appropriate duration of therapy for an initial episode of VTE. Pediatric studies have reported variable estimates of this risk with many studies hampered by relatively short follow up periods, varying duration of anticoagulant therapy, and varying VTE risk factor profiles. Adult studies have shown that the risk of

recurrence is highest in the first 6 months after incident VTE (8% at 180 days post VTE) and this risk never returns to baseline; similar long-term studies in children unfortunately are not available.[86-88] In adults, the presence of active cancer almost doubles that risk to 16% at 6 months and only active cancer has been found to be an independent predictor of increased risk of recurrence.[86,87] The initial Canadian Childhood Thrombophilia Registry documented an 18.5% recurrence rate over a median follow up of 18 months (range, 6 months to 3 years), however a longer term follow up study of this cohort showed only an 8% recurrence risk over a median follow up of 2.86 years (range, 2 weeks to 6 years).[1,12] The initial increased rate in the Canadian registry may have been due to chance since in the similar Netherlands registry a similar risk of 7% was found over a follow up period of 1 month to 1 year.[4] Another multicentre cohort study of 416 patients with a median follow up time of approximately 58 months, showed a recurrence risk of 7.6% for children with a VTE without a documented thrombophilia, 7.9% for children with a VTE and Factor V Leiden and 18% those with a VTE and prothrombin 20210A gene mutation.[89] Other studies have reported variable risks; the British Paediatric Surveillance Unit (BPSU) quoted a similar risk of recurrence of 5.5% over a median of 6 months of follow up,[8] whereas another study quoted a much higher recurrence risk of 21.3% in children with a first time spontaneous episode of VTE over a 7 year follow up period.[90] The higher risk of recurrence in the latter study may be explained by the fact that only those with unprovoked VTE were studied, and since their initial event was not attributable to a transient risk factor such as surgery or a central line, they may have had more permanent risk factors and therefore were more likely to recur. Studies assessing recurrence risk in children are summarized in **Table 2.4**. The risk of recurrence is likely affected by multiple competing factors, hence

given the variable estimates of this risk, more information on which factors and to what extent they affect this risk is needed.

Few studies have assessed which risk factors are associated with increased risk of VTE recurrence in children. The previously noted study with the high recurrence risk of 21.3 % was done on 301 children with a first episode of VTE and no evidence of an acquired risk factor, and compared those with a thrombophilia (n=239) to those without thrombophilia (n= 62), and found that 61 of the 64 recurrences occurring in the group with thrombophilia. Multivariate logistic analysis in this study demonstrated that recurrence was only influenced by the presence of a thrombophilic defect but not by any acquired prothrombotic factors, nor gender.[90] Estepp and colleagues reviewed all incident VTE cases in patients under the age of 19 years at St. Jude Children's Research Hospital from 2004 to 2008. Subjects were followed for an average of 3.1 years and overall, 21% (31/149) developed a recurrence. Neither treatment with enoxaparin, duration of anticoagulation, gender, BMI, age, presence of a chronic condition, presence of a central venous line nor concurrent cancer diagnosis was associated with an increased risk of recurrence in this study. Interestingly, of the 21 recurrences that occurred in those treated with enoxaparin, 76% occurred in patients who were still on anticoagulation with therapeutic levels, perhaps indicating that some risk factors may be so strong that even anticoagulation can not prevent the recurrence of a thrombus.[91] A European multicentre cerebral venous thrombosis (CVT) cohort from 1995 to 2006 enrolled 396 consecutive cases of CVT. The 384 surviving subjects were followed for a median of 36 months and had a recurrence risk of 6% with approximately half of recurrences occurring outside of the cerebral venous system. Only children diagnosed with a CVT after the age of two had recurrences (n=115 children ≤2,

n=269 children >2 years of age).[92] The etiology of neonatal CVT is likely due to peripartum factors and this may explain the difference noted in recurrence between age groups. Both the Canadian Childhood Thrombophilia Registry and the Dutch registry showed an increased recurrence risk in children of older age groups, suggesting the risk of recurrence is likely age-dependent.[4,12]

The current literature on risk factors for recurrent VTE in children is sparse, with only increased age and presence of a thrombophilic defect showing some evidence of increased risk. In certain cases, prophylactic anticoagulation is thought to be able to decrease the risk of recurrence, however anticoagulation imparts its own risks with respect to bleeding.[87] Older aged children and those with thrombophilia still make up a large portion of children with VTE and further information therefore is needed as to which risk factors will allow us to better delineate who might benefit from prolonged anticoagulation after an incident episode of VTE.

2.2.5 Mortality Associated with Pediatric Venous Thromboembolism

Mortality in pediatrics remains a rare occurrence in developed countries. In 2010, the mortality risk for children under 5 in developed countries was approximately 7 per 1000 live births, with more specific rates for the United States demonstrating a mortality rate in those between the ages of 1-19 ranging from 1.4 to 6.2 per 10 000 children depending on the age group.[93,94] With so few children dying, any event or illness that increases this risk even modestly can be considered significant.

Epidemiological studies on pediatric VTE have rarely documented mortality, and for the few that have, follow up times were generally short. Of the larger studies, the Canadian Childhood Thrombophilia Registry documented an overall mortality of 16% (65 of 405) with a VTE-specific mortality risk of 2.2% (9 of 405).[12] Similar results were found by the Dutch group, with an overall mortality rate of 15% in neonates and 17% in older children.[4] Of the neonate specific registries, in the German registry all-cause mortality occurred in 4 of 60 neonates with venous thrombosis (6.7%) and in a multicentre international registry all-cause mortality risk was 5% for those with RVT (renal vein thrombosis) and 18% for other venous thrombosis among 60 registered patients.[14,50] The difference in mortality estimates in neonates with VTE seen between these two studies may be explained by the fact that the multicenter study only included patients admitted to level II and III neonatal intensive care units (NICU) whereas the German registry included neonates admitted to NICUs as well as other wards, who may not have been as ill as those admitted to intensive care units.[50,95] Other studies have found much lower mortality risks. Mortality in children under 15 years of age in the Hong Kong VTE study was between 0 and 0.01 per 10 000 persons, whereas a cross sectional study using an American discharge survey database documented an overall mortality of only 0.5%, and another American single centre study showed a 3% risk of mortality where only 1 of the deaths among 99 patients was directly attributed to the thrombotic state. [9,16,17] The methodology and type of participants in these studies likely explains their lower mortality estimates. The Hong Kong study only included in-hospital deaths over the two year period of the study, therefore may have missed deaths outside of the hospital and those that occurred after the study period, especially for those enrolled in the latter part of the study as

they had less follow up time. In addition, overall they only had approximately 30 cases of VTE in children less than 19 years of age in their study leading to a very small study population to calculate mortality occurrence.[9] The cross sectional study by Vu *et al*. inherently in its study design would only be able to pick up deaths at the point in time of analysis which likely explains their low estimate.[17] Finally, the American single centre study by Sandoval and colleagues may represent a unique patient demographic that may have different morbidity and mortality characteristics than a more general population type of study.[16]

Mortality risks thus vary widely, with some possible regional and age dependent differences. More information on factors that contribute to death in children with VTE as well as more precise estimates are needed.

2.3 WHY STUDY INCIDENCE TRENDS IN PEDIATRIC VENOUS THROMBOEMBOLISM AND FURTHER INVESTIGATE ITS EPIDEMIOLOGY?

There is currently a paucity of literature evaluating temporal trends in incidence of pediatric VTE. The low incidence of VTE in this age group, variable evaluation of risk factors and lack of consistent treatment strategies has made it difficult to conduct randomized controlled trials to study prophylactic and treatment regimens. Many studies that attempted address these issues were hampered by slow recruitment and were prematurely terminated.[96,97] The establishment of evidence-based pediatric treatment regimens has thus been limited and management of VTE is generally extrapolated from adult literature or observational studies.[61] Whether the incidence rate of pediatric VTE is

truly increasing as many authors have stated or not, it is clear from the current literature that VTE risk factors and the potential for much longer-term morbidity in children is different than in adults and therefore they should not be treated identically.

For the most part, the literature to date shows an increasing trend of pediatric VTE over the last several years in hospitalized patients. This increase is presumed to be secondary to advances in care and survival of critically ill children, increased use of indwelling catheters and increased awareness of VTE amongst pediatric care providers. Interestingly, the only two studies that estimated incidence trends at a population level rather than in hospitalized children exclusively showed no statistically significant change.[2,18] It is difficult to delineate whether the increasing trend in some studies is simply a result of a change in type of patients being hospitalized and their care or if overall in the pediatric population, VTE is becoming more common, either from increased awareness, improved diagnostic modalities, or a combination of factors.

2.4 WHY USE AN ADMINISTRATIVE DATABASE TO STUDY PEDIATRIC VENOUS THROMBOEMBOLISM?

Unlike adult VTE, pediatric VTE mostly is managed in the inpatient setting, most frequently in tertiary care centres. The Netherlands registry demonstrated that 76% of their cases were reported from tertiary care centres with 85% of VTE diagnosed during hospitalizations.[4] Using hospital discharge databases to estimate population incidence is therefore likely to capture most of the diagnosed cases of pediatric VTE so long as a comprehensive database of all hospitalizations within a defined population is used.

To date, much of the literature on pediatric VTE has calculated incidence either on the basis of events per hospital admissions, which are difficult to extrapolate to the general population risk, or based on estimated number of events from discharge surveys, which is then modeled to reflect the actual numbers in the population. By assessing the number of events from nationwide physician surveys and establishing population estimates, registries have tried to overcome this imprecision in both the numerator and denominator for calculating incidence of pediatric VTE. Nationwide surveys can be time consuming and may have inaccuracies due to non-response or incomplete sampling of all types of physicians caring for patients with VTE. Studies looking at trends in VTE incidence in children have had similar limitations.

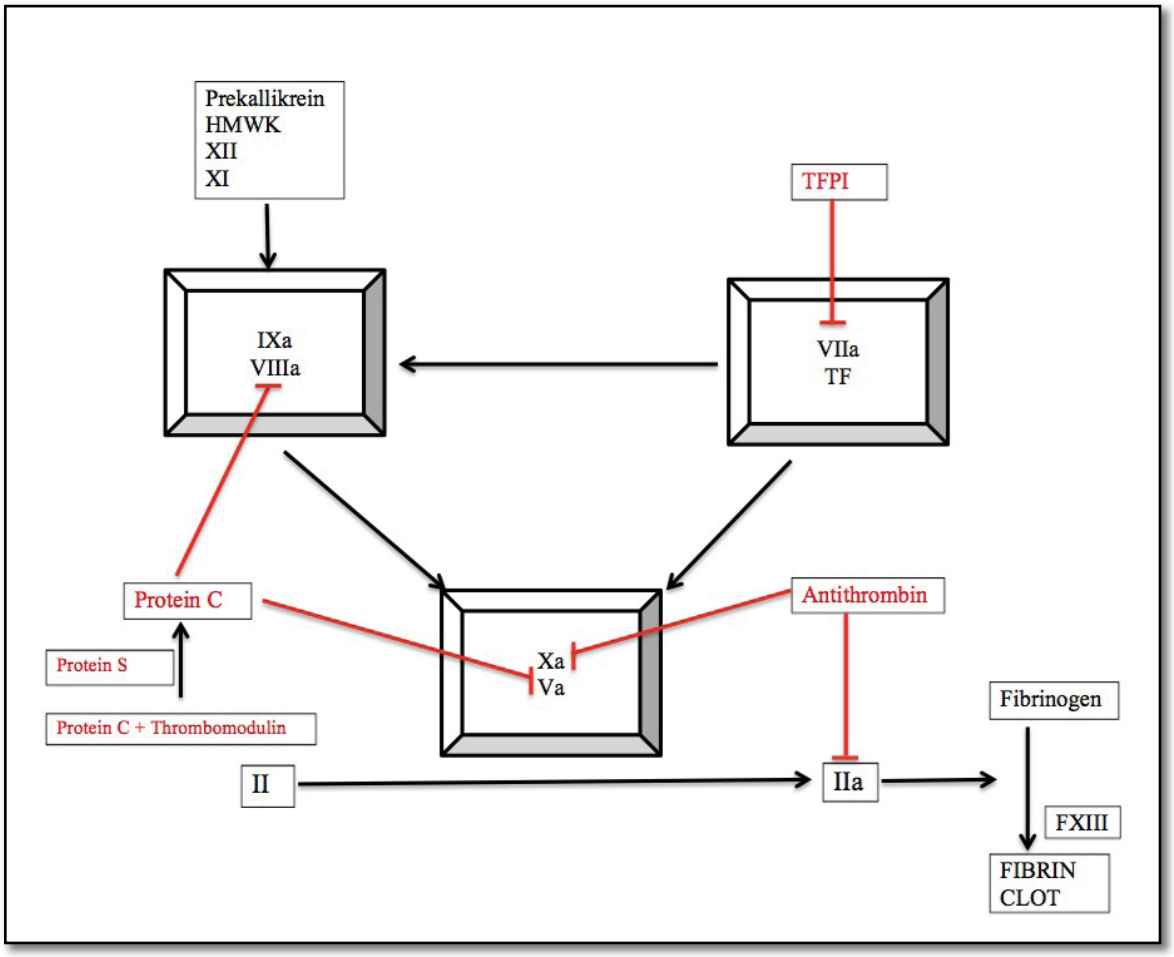
Use of a comprehensive, unselected database of all hospitalizations in the province of Quebec allows for an accurate estimate of incident pediatric VTE. Given that the database includes all children hospitalized in the province, there is no need for extrapolation of sample estimates to determine total number of events in the population. In addition, since the database includes all residents of the province, who are each covered by the universal healthcare plan and have a unique identifier number, cases of first time VTE can be assessed and separated from recurrent events so that both incident cases and rates of recurrence can be studied.

The use of Med-Echo (Quebec provincial hospitalization database) has been validated in the diagnosis of bronchopulmonary dysplasia in children. The specificity of this diagnosis when compared to medical chart records was 98% and the sensitivity was 52.4%.[98] Another study validated the diagnosis of a myocardial infarction based on Med-Echo claims with medical chart review and found a positive predictive value of 0.96 for

this diagnosis. They did however find decreased reporting of other comorbid illnesses during this study, hence the accuracy of Med-Echo coding may vary by illness.[99] Both Med-Echo and RAMQ databases (the latter includes all claims made to the universal health care system for a beneficiary in the province) in conjunction with prescription information were used to create an index of asthma severity and showed a statistically significant correlation between this database derived index and actual lung function measures.[100] Although validation of VTE codes in Med-Echo in children has not been done to date and was outside of the scope of this master's thesis, previous analysis of RAMQ coding has found it to be 87% and 78% sensitive diagnosis of DVT and PE, respectively, within a 60-day window period of the event in adults.[101]

Chapter 2: Tables and Figures

Figure 2.1* Coagulation Cascade[102,103]



High molecular weight kininogen (HMWK), Tissue factor (TF), Tissue factor plasminogen inactivator (TFPI)
*Simplified depiction of coagulation cascade. All factors in black contribute to the formation of fibrin. Factors in red are natural anticoagulants.

Table 2.1 Summary of Population-Based Incidence Studies of Pediatric Venous Thromboembolism

Study	Years of study	Age range	N (cases)	Numerator (VTE definition)	Denominator	Incidence
Grunt et al[10]	2000-2008	<16yo	65	Active surveillance of all neurologist for Switzerland (VTE=CSVT only)	Swiss population	0.056 CSVT per 10 000 children
Tuckuviene et al[18]	1994-2006	0-18yo	331	First time hospital discharge diagnosis of VTE from Danish National Patient Registry (VTE= all VTE except CNS)	Danish population	0.21 per 10 000 children
Gibson et al & Chalmers et al[3,8]	2001-2003	1mo-16yo	349	UK mail registry (VTE= all VTE excluding stroke and arterial TE)	Unclear, likely UK population	0.07 per 10 000 children
Stein et al[2]	1979-2001	0-17yo	75000	Estimates based on hospital discharge codes from NHDS (VTE=PE, DVT, obstetrical thrombosis)	US Census estimates	0.49 per 10 000 child/yr
Cheuk et al[9]	2000-2001	All ages	<50	VTE admissions at Hong Kong Hospital Authority (services 95% of population) (VTE= DVT and PE only)	Total population of Hong Kong	0.01-0.1 per 10 000 (< 15y)
Lee et al[11]	1995-2000	15d – 14.7yo	8	All VTE admissions Tuen Mun Hospital, Hong Kong (VTE=all VTE)	Population of hospital catchment area	0.07 per 10 000 child/yr
Van Ommen et al[4]	1997-1999	0-18yo	99	Dutch Registry (via mail) (VTE=all VTE)	Age distribution data-Netherlands	0.14 per 10 000 child/yr
Monagle et al[12]	1990-1996	1 mo-18 yo	405	Canadian Registry, active surveillance at 15 hospitals across Canada (VTE=extremity DVT and PE)	unclear, likely from census data	None recorded
Nowak-Gottl et al[14]	1992-1994	<4w	79	German Registry Surveillance results (VTE=all arterial and venous TE)	National Birth Register	0.51 per 10 000 births
Andrews et al[1]	1990-1992	1 mo-18yo	137	Same as Monagle et al[12], preliminary findings (VTE=extremity DVT and PE)	unclear, likely from census data	0.07 per 10 000 children (5.3 per 10 000 admissions)
Nordstrom et al[13]	1987	All ages	1	All confirmed hospitalized cases of VTE in Malmo, Sweden (VTE=DVT)	Population of Malmo	0-0.5 per 10 000 (<20yo)
Anderson et al[7]	1985-1986	All ages	615 (405 pts)	All discharge diagnosis from Worcester area hospital (VTE=DVT and PE)	Population of Worcester	0 per 10 000 (<9yo) 0.2-0.3 per 10 000 (10-19 yo)

Central nervous system (CNS), cerebral sinovenous thrombosis (CSVT), days (d), deep vein thrombosis (DVT), month (mo), patients (pts), pulmonary embolism (PE), thromboembolism (TE), United Kingdom (UK), United States (US), venous thromboembolism (VTE), weeks (w), year (yr), years old (yo).

Figure 2.2 Virchow's Triad and Risk Factors for Venous Thromboembolism in Children[5]

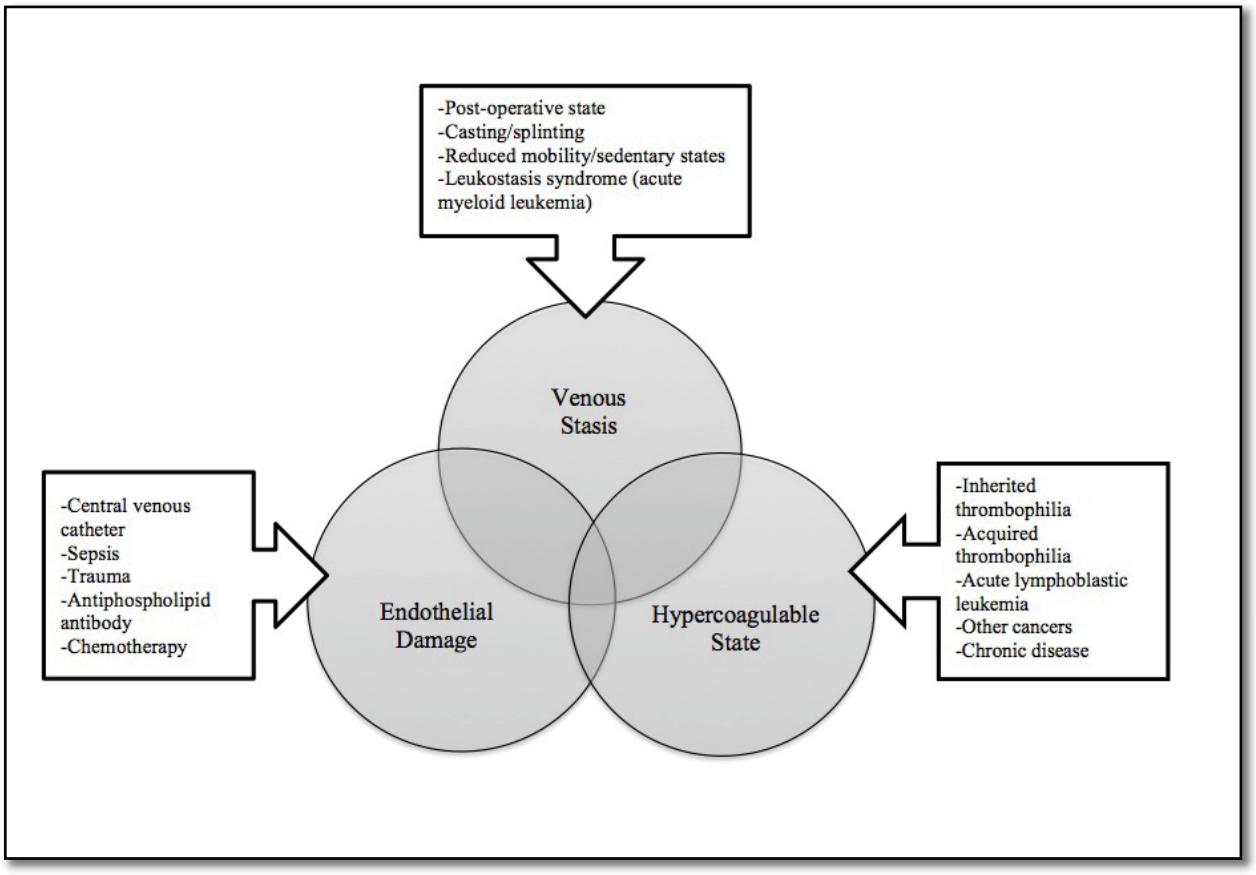


Table 2.2 Postulated Role of Components of Virchow's Triad within Venous Thromboembolic Risk Factors

Risk Factor	Hypercoagulability	Venous Stasis	Endothelial Injury
Inherited Thrombophilia	yes		
Age			
Central Venous Catheter		yes	yes
Congenital Heart Disease		yes	yes
Oral Contraceptive Pill	yes		
Surgery		yes	yes
Chronic Disease	yes		yes
Cancer/BMT*	yes		
Trauma		yes	yes
Infectious Disease			yes

*Bone marrow transplant (BMT)

Table 2.3 Summary of Inherited Thrombophilia Studies in Children with Venous Thromboembolism

Study	N	% tested	FVL tested	PT tested	PC tested	PS tested	AT tested	Lip(a) tested	Homocysteine tested	% with Inherited Thrombophilia
Andrew *et al.* 1994[1]	137	33% (partial testing)	**unclear**	**unclear**	**Yes**	**Yes**	**unclear**	**unclear**	**unclear**	8.8%
Hagstrom *et al.* 1998[41]	85	100%	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**No**	**No**	19%
Lawson *et al.* 1999[43]	30	87-100%	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	43%
Heller *et al.* 1999[42]	43	100%	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	40%
Ehrenforth *et al.* 1999[40]	285	100% (lip (a) only 32%)	**Yes**	**No**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	74%
Van Ommen *et al.* 2001[4]	99	57% (partial testing)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	16% (of tested patients)
Bonduel *et al*. 2002[39]	130	85%	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**No**	23%
Revel Vilk *et al.* 2003[36]	171	100% (lip (a) only 65%)	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	13%
Kuhle *et al.* 2004[104]	1312	5%	**Yes**	**unclear**	**Yes**	**Yes**	**Yes**	**unclear**	**unclear**	28% of tested patients
Wright *et al.* 2011[34]	92	32-53%	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**No**	**Yes**	5 % of all patients
Tuckuviene *et al.* 2011[18]	331	1-58%	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	**Yes**	~36%

Factor V Leiden (FVL), Prothrombin 20210A variant (PT), protein C (PC), protein S (PS), antithrombin (AT), lipoprotein (a) (Lip(a))

Table 2.4 Summary of Studies on Recurrence Risk after Venous Thromboembolism in Children

Study	Years of study	N	Age range	Follow-up Time: Range (median)	Definition of venous thromboembolism	Recurrence Risk during follow-up
Wright & Watts[34]	2006-2008	64	2 days-20yo	1 month-4.3 years (2 years)	DVT, PE, CSVT, RVT, PVT	14%
Estepp et al[91]	2004-2008	149	< 19yo	4 days-8 years (average 3.1 years)	DVT, PE, CSVT, RVT, PVT	21%
Young et al[89]	1994-2006	416	0-18yo	12-156 months (~58 months)	DVT, PE, CSVT, RVT, PVT	9.3% (Incidence rate of recurrence of 19.8 per 1000 person-year (95% CI 14.3–26.7)
Gibson et al & Chalmers et al[3,8]	2001-2003	200	1mo-16yo	(6 months)	All VTE excluding stroke and arterial TE	5.5%
Van Ommen et al[4]	1997-1999	99	0-18yo	1 month - 1 year	DVT, PE, CSVT, RVT, PVT	7%
Nowak-Gottl et al[90]	1985-1999	301	0-18yo	6 months-15 years (7 years)	DVT, PE, CSVT, RVT, PVT	21.3%
Monagle et al[12]	1990-1996	405	1 mo-18 yo	2 weeks - 6 years (2.86 years)	Extremity DVT, PE	8%
Andrews et al[1]	1990-1992	137	1 mo-18yo	6 months- 3 years (18 months)	Extremity DVT, PE	18.5%

* cerebral sinovenous thrombosis (CSVT), deep vein thrombosis (DVT), months old (mo), portal vein thrombosis (PVT), pulmonary embolism (PE), renal vein thrombosis (RVT), years old (yo).

Chapter 3: Hypothesis and Objectives

3.1 HYPOTHESIS

Recent improvements in the care of acutely and chronically ill children has led to the survival of children with complex medical conditions who have often undergone multiple medical procedures. This, in addition to increased awareness of VTE occurrence among children by pediatric care-providers, may be leading to an increased incidence of pediatric VTE. We therefore hypothesize that incidence rates of pediatric VTE, once adjusted for differences in age distribution within the population over time, will show an increasing trend over time. We also hypothesize that children with chronic medical conditions at the time of incident VTE will have a higher risk of recurrence than those with transient risk factors at time of their initial VTE.

3.2 OVERALL OBJECTIVE

To describe the epidemiology of pediatric VTE in Quebec, Canada.

3.2.1 Primary Objectives:

Among children aged 1-17 years in Quebec, Canada between 1994-2004:

1) To determine the age-standardized population-based incidence rate of first time VTE.

2) To determine the incidence rate of first time VTE by sex and for the following age groups: children: 1-5 years of age, and 6-10 years of age, pre-adolescents (11-14 years of age), and adolescents (15-17 years of age).

3) Employing different time frames, to determine the trend of VTE incidence during this eleven-year period (January 1, 1994 to December 31, 2004) for the whole population and for specific age groups.

3.2.2 Secondary Objectives:

Among all children aged 0-17 years in Quebec diagnosed with incident VTE between 1994-2004:

1) To describe the frequency of known risk factors, prescription medications and diagnostic modalities associated with VTE and to determine change in frequency of these factors over time. The frequency of prescription medication use will be based solely on data from those patients that are covered by the provincial prescription plan.

2) To estimate the overall and age-specific rate and timing of first recurrent VTE after incident VTE.

3) To determine the incidence of all-cause mortality following an incident VTE.

4) To assess the relation between the effect of demographic factors and known VTE risk factors (e.g. cancer, presence of indwelling catheter, surgery) and the risk of recurrence and all-cause mortality.

Chapter 4: Study Methods

4.1 OVERVIEW OF STUDY DESIGN

Using data from the Régie de l'Assurance Maladie Québec (RAMQ) database and the Maintenance et Exploitation des Données pour l'étude de la Clientèle Hospitalière (Med-Echo) database, we identified a cohort of all Quebec residents under the age of 18 (0-17 years of age inclusive) with an incident VTE diagnosed upon admission or during an admission to hospital (within the province) between January 1st, 1994 and December 31st, 2004 AND who had participated in the provincial health care plan for at least twelve months preceding the incident VTE. We then obtained information regarding VTE risk factors and demographic data for up to one year preceding the event as well as details regarding VTE-related outcomes from the time of the initial event until the end of the study period (December 31st, 2005), death or exit from cohort (emigration from the province). This study period was chosen as it represented the time period for which data was currently available from the linked databases of Med-Echo and RAMQ.

4.1.1 Ethics Approval

This study was approved by the Jewish General Hospital's Research Ethics Committee (please see appendix for copy of letter of approval). Permission for access to linked data from Med-Echo, Institut de la Statistique de Quebec and RAMQ was obtained from the Commission d'acces à l'information (CAI), who are responsible for maintaining

the act respecting access to documents held by public bodies and to maintain the protection of personal data. All data utilized for this research project were stripped of patient identifiers by the CAI prior to transfer to the research group.

4.1.2 Study Design

The study design was a population based retrospective cohort study of all children with an incident VTE identified from the Med-Echo provincial hospitalization database. The source population included all residents of the province of Quebec, Canada who were under the age of 18 and were members of the provincial medical insurance program at some point during the eleven-year study period.

4.1.3 Description of the Healthcare Databases Utilized

4.1.3.1 RAMQ databases

RAMQ is the provincial body that is responsible for managing the provincial healthcare insurance program in Quebec. Their computer database was started in 1983 and is compiled using three main sources of data: 1) the beneficiaries database, 2) the medical services database and 3) the prescription database. Since 1970 coverage by the provincial insurance plan is **compulsory** for all residents (permanent or temporary after they have been residing in the province for at least 3 months) in Quebec. Coverage by the plan ceases when a person dies or emigrates from the province. Every person within the

database has a unique identifier number, which allows for the linkage with other Quebec provincial databases (ISQ, Med-Echo).

The beneficiaries database contains demographic information for every member of the plan (date of birth, sex, postal code, and year of death). The medical services database includes information on all claims submitted by physicians in both the inpatient and ambulatory setting for members of the insurance plan. The prescription database includes information on all dispensed prescription medications to members of the provincial prescription plan, except for those prescriptions dispensed in hospital or in long term care facilities. The provincial prescription plan is only mandatory for those under 65 years of age without private prescription drug insurance or on welfare and covers all persons aged 65 and older in the province of Quebec. In 2004, 517 791 Quebec residents under the age of 18 were covered by the provincial prescription plan, which accounted for approximately 30% of children in the province at that time.[105] Since the prescription plan is not universal, data obtained from this source will be used to estimate the associations only within the group of children covered by the plan.

4.1.3.2 Med-Echo database

Med-Echo is a provincial database maintained since 1967 by the Quebec ministry of health with information on all hospital admissions within the province. Each person within the province has a unique identifier number (same as for RAMQ) and each hospitalization they experience is registered within this database. For each hospitalization the following is a sample of information recorded: length of stay, admission and discharge dates, primary discharge diagnosis, and up to 15 secondary

discharge diagnoses as classified using the International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) and up to 8 procedure codes using the Canadian classification of diagnostic therapeutic and surgical procedures (CCDTC).[106]

4.1.3.3 Institut de la Statistique du Québec

The Institut de la Statistique du Québec (ISQ) is in charge of maintaining Quebec's death registry. As mentioned previously, given that each resident of Quebec holds a unique identifier number, information within this database can easily be linked to that found in either Med-Echo or RAMQ databases. The ISQ was established in 1998, after an act was passed by the National Assembly of Quebec to create a new organization that would encompass four previously different independent administrative bodies in Quebec. These were the Bureau de la statistique du Québec, Institut de recherche et d'information sur la rémunération, Santé Québec and the personnel of the ministère du Travail. This act stated that the ISQ's mandate would be: *"The Institut de la statistique du Québec is the government body in charge of producing, analyzing and disseminating objective and high-quality official statistical information for Québec. This information enhances knowledge, enlightens debate and supports decision-making by the various players in Québec society."*[107]

4.1.3.4 Quebec Census Data

Official census data for the provinces is collected by Statistics Canada every 5 years. Statistics Canada is the branch of the Canadian government enlisted with the task of undertaking the national census. Information is available to the public via their website

in various aggregated forms.[108] The McGill University Libraries provided province-specific census data for the years 1991, 1996, 2001 and 2006 with description of the Quebec population by sex and age in years. For the census years 1996, 2001 and 2006, data were obtained from the McGill University Libraries Electronic Data Resources Service (EDRS) which acquires data directly from Statistics Canada's Data Liberation Program.[109] These data resources were accessed using the software program Beyond 20/20© (Beyond 20/20© release 6.0, Professional Browser, Beyond 20/20 Inc.). For the 1991 census year, data was obtained directly from the McGill University Library liaison personnel in Microsoft Excel© format (Microsoft Office Professional Plus 2010, version 14.0.6112.5000, Microsoft Corporation).

4.1.4 Construction of the Study Cohort

The study cohort was created from the source population of all residents of the province of Quebec, Canada who were under the age of 18 and were members of the provincial medical insurance program at some point during the study period. The study cohort included of all members of the provincial health insurance program with a diagnosis of VTE in the Med-Echo database, who were less than 18 years of age at time of their diagnosis, between January 1st, 1994 and December 31st, 2004 AND who were participants of the provincial health care plan for at least twelve months preceding this incident VTE.

The following subjects were excluded from the cohort: any subject with a diagnosis of VTE prior to January 1, 1994, dating back to the inception of the database in

1983. This allowed for only incident cases to be included in the cohort. Since the cohort included only subjects with at least twelve months of participation in the provincial health plan, we recognized that incident cases of VTE in children less than one year of age would not be captured. Twelve months of participation was required to ensure that we had sufficient information on all those in the cohort to determine the presence of risk factors for incident VTE. Previous administrative database studies looking at risk factors for VTE have used between 90 days and 12 months for various risk factors in order to attempt to have improved retrieval for possible contributing factors.[110,111] Consequently, any cases under the age of one at the time of incident VTE diagnosis that for unclear reasons were retrieved from the database and appeared in our cohort, were used only for assessment of outcomes (mortality and recurrence) and not in the calculation of population incidence rates as this likely reflected an incomplete sample in this age group.

The date of index VTE was defined as the date of admission for any VTE event that was coded as a primary discharge diagnosis. For those events classified as secondary discharge diagnosis the date of a diagnostic procedure for VTE diagnosis (e.g. Doppler ultrasound) was used as the index date, and in the case of no procedural code existing then the median day of hospitalization was used.

Exit from the cohort occurred at the earliest of the following: 1) death, 2) emigration from the province or 3) end of the study (December 31st, 2005). The end of study date was chosen to allow for at least 1 year of follow up data for those who entered the cohort in 2004.

4.1.5 Data Collection

For each member of the cohort the following data were collected:

- From the RAMQ Database:
    - Demographic data: Age, sex, date of birth and death were extracted from the beneficiaries database.
    - End of Service Date: For children who were no longer eligible for coverage from the provincial health care plan, the date of their cessation of coverage was retrieved.
    - Prescription information for specific medications:
        - Number of prescriptions for oral vitamin K antagonists, low-molecular weight heparin and intravenous heparin in the six months following incident VTE. These medications are used to prevent or treat VTE.[5]
        - In females, number of prescriptions for oral contraceptive pills (OCP) in the six months preceding incident VTE. OCPs are known to increase the risk of VTE occurrence.[5]

This information was extracted from the RAMQ prescription database for those individuals under the age of 18 covered by the plan (as previously stated, this represents approximately 30% of the population under 18 years of age)[105,108].

- From ISQ Database:
    - Date and cause (where documented) of death were extracted from the database.

- From the Med-Echo Database:
    - Information with respect to death, VTE-diagnostic modalities, VTE-risk factors and VTE-related outcomes from all hospitalizations within the twelve months preceding the index VTE and until exit from the cohort, was obtained.

4.1.6 Database Linkage

All data obtained from the Med-Echo, RAMQ and ISQ databases were provided in SAS© format files (SAS© proprietary software 9.2, by SAS Institute Inc.). Linkage of databases, extraction of study cohort individuals, and creation of risk factor and outcome variables were done using SAS©. While the CAI stripped individuals of their unique identifier numbers, individuals were each numbered in the databases with unique identifier numbers that were used to link the individuals with their corresponding information from the other databases without being traceable to their usual unique identifier numbers.

4.1.7 Definitions and Diagnostic Coding for Venous Thromboembolism, Venous Thromboembolism-related Risk Factors and Outcomes

4.1.7.1 Outcomes

Index VTE

The diagnosis of VTE was identified through the use of International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM). Of note, the ICD-10 was only introduced in the province of Quebec in 2007. Codes for deep-vein thrombosis (DVT) [ICD-9-CM codes 451.0, 451.1, 451.2, 451.8, 451.9, 453.1, 453.2, 453.4, 453.8, 453.9 excluding 451.28 which codes for superficial upper extremity thrombosis], obstetrical thromboembolism [ICD-9-CM codes 671.3, 671.4, 671.5, 671.9, 673.2, 673.8], renal vein thrombosis (RVT) [ICD-9-CM code 453.3], pulmonary embolism (PE) [ICD-9-CM codes 415.0, 415.1], portal vein thrombosis (PVT) [ICD-9-CM codes 452, 453.0], cerebral sinus venous thrombosis (CSVT) [ICD-9-CM code 325, 437.6], peripheral vasculature complication of a procedure [ICD-9-CM code 997.2], and lung vascular complication of a procedure [ICD-9-CM code 997.3]. All of the above events were classified as a VTE.

Recurrent VTE

Recurrent VTE was defined as a minimum 2-day re-hospitalization with a discharge diagnosis of VTE at least 30 days after discharge from initial incident VTE admission, which was modified from an adult recurrence definition.[112]

Cohort members were therefore assessed for recurrence starting from 30 days after their incident VTE and continuing for the length of their membership in the healthcare insurance program or until the end of study. A cut-off of thirty days was used to try to prevent the misclassification of early repeat admission for the incident event being classified as a recurrence.

Mortality

The following algorithm was used to establish date, cause and location of death:

- Individuals with a date of death in Med-Echo and in ISQ were considered as having died in hospital.
- Individuals with a death date in ISQ-only were considered to have died outside hospital.
- If a death date was recorded in Med-Echo and not confirmed in ISQ, but had a cause of death compatible with a fatal condition, these individuals were considered to have died if they had no further claims in the Med-echo, pharmacy or RAMQ outpatient claims 30 days after their death date.

All three databases (i.e. RAMQ, Med-Echo and ISQ) were used to extract information on mortality within the cohort so that each death could be validated using the three databases to decrease the risk of misclassification. If any individual had a claim more than 30 days after their death date in one of the other databases they were removed from the mortality list.

4.1.7.2 Diagnostic Modalities

Diagnostic modalities used for diagnosis of VTE are described in **Table 4.1**.

Table 4.1: Diagnostic Modalities for Venous Thromboembolism

Diagnostic Modality	Coding Manual	Coding	Diagnostic Purpose
V/Q scan	CCDTC	6.15	PE
CT Chest (thorax)	CCDTC	2.21	PE
MRI Head	CCDTC	3ER40.WA 3ER40.WC 3ER40.WE	CSVT
MRV Head	CCDTC	3JX40.WA 3JX40.WC 3JX40.WE	CSVT
CT Head	CCDTC	2.01	CSVT
Echocardiography	CCDTC	2.82	DVT/PE
U/S diagnostic limbs	CCDTC	2.87	DVT
Renal U/S	CCDTC	2.86	RVT
Other diagnostic U/S	CCDTC	2.89	DVT/PVT
Angiography site unspecified	CCDTC	50.80	DVT
Angiography cerebral vessels	CCDTC	50.81	CSVT
Angiography pulmonary vessels	CCDTC	50.83	PE
Angiography other intrathoracic	CCDTC	50.84	DVT/PE
Angiography renal vessels	CCDTC	50.85	RVT
Angiography intra-abdominal vessels	CCDTC	50.87	PVT
Angiography femoral vessels	CCDTC	50.88	DVT
Angiography other vessels	CCDTC	50.89	DVT

*Ventilation/Perfusion Scan (V/Q scan), Computed Tomography (CT), Magnetic resonance imaging (MRI), Magnetic resonance venography (MRV), Ultrasound (U/S), Canadian classification of diagnostic therapeutic and surgical procedures (CCDTC), Pulmonary Embolism (PE), Cerebral Sinus Venous Thrombosis (CSVT), Deep Vein Thrombosis (DVT), Renal Vein Thrombosis (RVT), Portal Vein Thrombosis (PVT)

4.1.7.3 Venous Thromboembolism-related Risk Factors

Risk factor codes and definitions are described in **Table 4.2.**

Table 4.2: Risk Factor Coding and definitions

Risk factor	**Coding**	**Coding Manual***	**Definition****
Bone marrow transplant	41.0	ICD 9CM	Bone marrow transplantation undertaken in the 12 months prior to index VTE date
Cancer	140-172, 174-209, 235-239***	ICD 9CM	Cancer diagnosis in the 12 months prior to index VTE date or 12 months post discharge date of index VTE date
Congenital Heart Disease	745- 748 ---------- 35-39 (surgeries)	ICD 9CM ---------- CCDTC	Diagnosis of congenital heart disease or procedure code for surgical repair of congenital heart disease in 12 months prior to index VTE date
Surgery	65-71 (gynecological), 76-84 (orthopedic), 55-64 (urologic), 30-34 and 42-54 (general surgery), 01-05 (neurosurgical)	CCDTC	Major surgery in previous 90 days prior to index VTE date
Indwelling Central Catheter	50.91 (umbilical arterial catheter), 50.92 (umbilical venous catheter), 50.93 (other venous catheter), 98.06 (Port-A-Cath)	CCDTC	Central line placed in last 12 months prior to index VTE date
Infection	036.0, 036.1, 036.2, 038.0, 038.1, 038.2, 038.3, 038.4, 0.38.8, 038.9, 383.00, 383.02, 383.9, 995.90, 995.92, 998.5	ICD 9CM	Major infection in 90 days prior to index VTE date

Table 4.2 continued…

Trauma	800.00 to 959.9 excluding 905-909; 910-924; 930-939****	ICD 9CM	Major Trauma in last 90 days prior to index VTE diagnosis
Inherited Thrombophilia	289.91	ICD 9CM	Inherited Thrombophilia diagnosis in the 12 months prior to index VTE date or 12 months post discharge date of index VTE date
Pregnancy	6713, 6714, 6715, 6719, 6732 (secondary diagnosis) OR v22, v23, v27, v30, 634, 635, 636, 637, 638, 639, 650-669 (primary diagnosis) ---------- 84, 85, 86	ICD 9CM -------- CCDTC	Pregnancy related if occurred within 38 weeks following index VTE or within 91 days postpartum
Cystic Fibrosis	277.0	ICD 9CM	Cystic fibrosis coded in 12 months prior to index VTE date
Inflammatory Bowel Disease	555.0, 555.1, 555.2, 555.9, 556	ICD 9CM	IBD coded in 12 months prior to index VTE date
Sickle Cell Disease	282.6, 282.41 and 282.42	ICD 9CM	SCD coded in 12 months prior to index VTE date
Systemic Lupus Erythematosus	710.0	ICD 9CM	SLE coded in 12 months prior to index VTE date
Nephrotic Syndrome	581.0, 581.2, 581.3, 581.8, 581.9	ICD 9CM	Nephrotic syndrome coded in 12 months prior to index VTE date

*International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM), Canadian classification of diagnostic therapeutic and surgical procedures (CCDTC)

** Venous thromboembolism (VTE), inflammatory bowel disease (IBD), sickle cell disease (SCD), systemic lupus erythematosus (SLE)

***Except 173: non-melanoma skin cancer, as the odds of thrombosis with this type of cancer has been found to be low[113,114]

****Codes as proposed by the American College of Surgeons National Trauma DataBank).[115]

4.2 STATISTICAL ANALYSES

4.2.1 Precision & Missing Values

All rates were calculated with 95% confidence intervals. Although we have census data for the population of Quebec, given that this data was only available every 5 years, linear interpolation was utilized in order to estimate the total person-years in the cohort. Given this estimation we included confidence intervals for our estimates to account for residual uncertainty. Where hypothesis testing was used, a p-value<0.05 was used to denote statistical significance unless otherwise noted.

Linkage of the three databases (Med-Echo, RAMQ, ISQ) allowed for retrieval of demographic information from an alternate database if it was missing in one of the three. Duration of follow up was missing in a few patients. Unless a death date or end of RAMQ coverage date was available, it was assumed that subjects remained covered by the RAMQ plan even if they had no subsequent hospitalizations after their incident VTE and thus were considered as being followed until end of study period (December 31st, 2005). If the date of end of RAMQ coverage was prior to their actual index VTE date, it was assumed that information regarding those subjects was only accurate until the end of their index VTE hospitalization.

4.2.2 Population Based Incidence Density of Pediatric Venous Thromboembolism

With respect to the first primary objective of this study, the overall population based crude incidence of incident VTE was calculated using all individuals with a discharge diagnosis consistent with incident VTE retrieved from the Med-Echo database between January 1st, 1994 and December 31st, 2004 as the numerator and census estimates of the annual pediatric population of Quebec during this 11 year period as the denominator. The Med-Echo database used for this study was comprised of all hospital admissions for subjects with an incident VTE in the province of Quebec between 1994 and 2004. Only individuals between the ages of 1 and 17 years of age inclusive were included in the incidence calculations.

For the second primary objective, yearly estimates of VTE incidence in all children greater than one year of age and less than 18 years of age as well as within the specific age ranges (1-5, 6-10, 11-14, 15-17) were calculated. Rates were calculated using yearly incidence of incident VTE as the numerator and the estimated mid-year population of that calendar year as denominator.

4.2.2.1 Census Estimates

Official census data from the Canadian 1991, 1996, 2001 and 2006 censuses were obtained. Census data was retrieved for the province of Quebec and divided by year of age and sex for each census year. Person-year estimates were calculated using linear interpolation for each age (by individual years) for children ages one to seventeen inclusive and for each calendar year (1994-2004). Estimates were calculated as follows:

- Average annual change in population of each age was calculated by taking the total number of persons for each age year in the earlier census and subtracting it from the corresponding number of persons now 5 years older (i.e. following the birth cohort) in the subsequent census. This was done by obtaining the average annual increase or decrease in population at that age between censuses, then dividing this difference by five (time between censuses).
- We assumed that individuals who entered (immigration) or exited the cohort (emigration or death) did so at the mid-point of the year and therefore contributed only 0.5 person-years for the year in which they entered or left the cohort.
- For age groups that did not have data from a preceding census because they were not yet born (example: those born in 1993), the number of persons from the most accessible census year was used as the number of persons contributing for each year until that census (for current example, the number of persons who were three years of age in 1996 census was used as the number of person aged one or two in 1994 and 1995 respectively)
- These calculations were performed for each age year (1-17) and for each calendar year between 1994 and 2004.

4.2.2.2 Age Standardization

In order to account for changes in age distribution of the population throughout the study period, all incidence rates were directly standardized based on the overall population age distribution throughout the whole cohort period as calculated using census estimation as detailed above. Age standardized incidence rates were reported as an overall rate for the entire study period and then by calendar year, by the following age groups: 1-5, 6-10, 11-14 and 15-17 years of age, and also by the following time periods: 1994-1995, 1996-2000 and 2001-2004.

4.2.2.3 Sex Specific Incidence Rates

Estimates for overall population size by sex were calculated and used to assess the sex distribution of pediatric VTE, and to evaluate if sex was associated with VTE occurrence in children. The rate ratio for pediatric VTE comparing females to males was calculated, stratified by age group, as age was a likely confounder since incidence in females is known to be higher in certain pediatric age groups than males (teenage).[2] Using the Stata command 'ir VTE gender pyrs, by(agecat)', methods similar to the Mantel-Haenszel test were used to estimate the incidence rate ratio (IRR) but in this case with count data for each stratum, with the H_0 assumed to be following a chi-squared distribution.[116] The overall rate ratio was then estimated by calculating a weighted average of the stratum specific IRRs. A chi-squared test for homogeneity across all strata of IRRs was used to test whether the estimation of a common IRR was appropriate.

4.2.2.4 Incidence Trend Analysis

Poisson log-linear regression was used to evaluate if trends in incidence rates for the whole cohort over this eleven-year period showed evidence of statistically significant change. Incidence rate trends were also analyzed using Poisson log-linear regression for changes within the previously stated age groups and time periods. Age standardized rates were used to evaluate these trends to ensure that if changes existed, they were not simply due to differences in the age distribution of the population during the different time periods or years.

4.2.3 Cohort Characteristics

With respect to the secondary objectives of this study, the distribution of demographic factors (age and sex) and ICD-9-CM codes for known risk factors such as presence of indwelling catheter, diagnosis of cancer or bone marrow transplant and type of cancer, recent major surgery, presence of congenital heart disease, infection, inherited thrombophilia, trauma, pregnancy, systemic lupus erythematosus, inflammatory bowel disease, cystic fibrosis, sickle cell disease, and nephrotic syndrome within the cohort was analyzed. Prescription data and CCDTC codes for imaging modality for those individuals for whom it was available were analyzed. The total number of patients prescribed oral vitamin K antagonists versus heparin-based anticoagulants was calculated, although as previously mentioned only information for the approximately 30% of the population under 18 that is covered by the Quebec prescription plan was available. To try to establish possible associations with trends in incidence, concurrent

changes in frequency of risk factors within the cohort were evaluated along with changes in the utilization of various diagnostic modalities during this time period.

4.2.4 Recurrence Rate

With respect to the second secondary objective of this study, the recurrence rate of VTE after incident VTE was calculated for all individuals in the cohort who had follow-up data available. Therefore the recurrence cohort included any child less than eighteen years of age (including those less than one year of age that were not previously included in the incidence cohort) with an incident VTE retrieved from the database for analysis as part of the recurrence cohort. The numerator in the recurrence rate calculation was the occurrence (yes/no) of a recurrent episode of VTE as previously defined in any individual in the cohort. The denominator used was time to event recurrence in those with recurrence, and in those without recurrence, the time that they were observed in the cohort (time of the initial VTE to the earliest of end of plan coverage, death or end of study). Recurrence risk was also calculated as the number of subjects with a recurrence divided by the number of subjects evaluable for recurrence (survival greater than 30 days after incident VTE).

4.2.5 Mortality Rate

For the third secondary objective, all-cause mortality rates were calculated using the mortality data as described earlier as the numerator and total person-years in the

cohort (time from index VTE to death, exit from health plan or end of study, whichever was earlier) as the denominator. Mortality risk was calculated as the number of deaths divided by the total number of subjects in the cohort.

4.2.6 Role of Risk Factors on Adverse Outcomes

VTE recurrence rates were then analyzed separately by age, age group and sex. Given that the rate of recurrence is unlikely constant over time (e.g., it is highest in the first 6-12 months following incident VTE in adults)[88], Poisson regression could not be used. Hence, survival analysis methods were used to study associated risk factors. A Cox proportional hazards model was used to estimate the role of sex, age group, age as a continuous variable, type of initial incident VTE (e.g. PE vs. DVT vs. CSVT), surgery, cancer and BMT, indwelling catheter, infection, inherited thrombophilia, trauma, congenital heart disease and presence/absence of a chronic disease (SLE, SCD, IBD, CF, nephrotic syndrome). A separate analysis was performed in females that included pregnancy as a risk factor. Univariate analysis using either log rank test for equality of survivors for each categorical risk factor or Cox proportional hazard for a single continuous predictor variables was used to determine which variables would be kept in the model by assessing their chi squared p-value; a cut off of $p<0.25$ was used. We chose to include a priori known risk factors in order to ensure confounding was controlled to the best of our knowledge, and then added only those that showed statistical significance on univariate analysis as this provides a conservative approach to model building. Although this may create a large model, it is unlikely to introduce bias, but may introduce

some statistical inefficiency.[117] Variables that satisfied this cut off were incorporated into the final Cox proportional hazards model. A p-value<0.05 was used to denote statistical significance in the multivariate Cox proportional hazards model. A priori, both age and chronic disease were included in the models as prior literature supports their role in VTE recurrence.[4,8,12,48,92,118] The Stata command "estat phtest" was used to ensure that the proportionality assumption was not being violated, this is assessed on the basis of Schoenfeld residuals of a Cox fitted-model.[119]

These steps were then repeated using mortality rates. Based on the previous literature, our goal was to have no less than 6 events per risk factor included in the models.[120]

An analysis of accuracy of the risk factor central line was performed to identify the correctness of central line placement reporting in the database. All patients who receive a bone marrow transplant require a central line for infusion of peripheral blood stem cells or bone marrow. Therefore, all patients who underwent bone marrow transplantation were analyzed for reporting of central line placement.

4.2.7 Sample Size Estimates

Preliminary evaluation of the data set gave an estimate of ~480 cases of incident pediatric VTE during this eleven year period. Given an estimate of 480 cases we expected to see at least 77 deaths (based on a previously reported mortality risk of 16%[12]) and approximately 38 cases of recurrence (based on a published recurrence risk of 8%[12]).

Chapter 4: Tables & Figures

Figure 4.1 Cohort Extraction

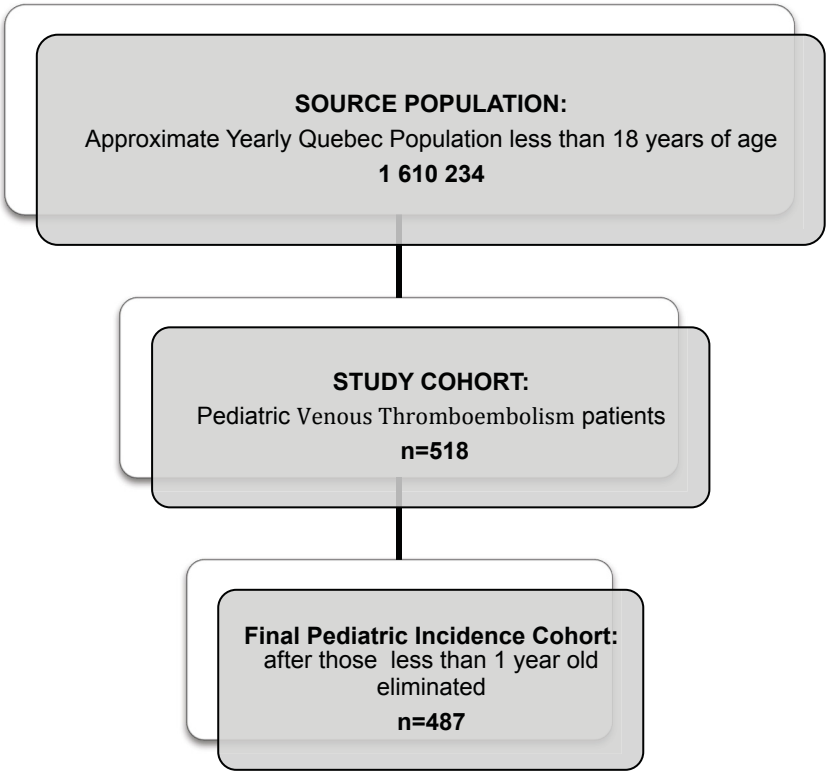


Table 4.3. Types of Incident Venous Thromboembolism

Variable Description	Database Name	Coding	Type
Type of Incident VTE	VTE_Type2	DVT=1 PE=2 DVT&PE=3 PVT=4 RVT=5 CSVT=6 DVT&CSVT=7 DVT&RVT=8 DVT&PVT=9	Categorical

Venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT).

Table 4.4 Outcome Variables

Variable Description	Database Name	Coding	Type
Recurrent VTE	EVENT_Recur	No=0 Yes=1	Dichotomous
Death	Death	No=0 Yes=1	Dichotomous

Venous thromboembolism (VTE)

Table 4.5 Demographic Information

Variable Description	Database Name	Coding	Type
Age	CohortH_IndexVTE_AGE	Age in years	Continuous
Age Category	Agecat	<1=0 1-5=1 6-10=2 11-14=3 15-17=4	Categorical
Sex	SEXE	Female=0 Male=1	Dichotomous
Year of incident VTE	Year	Calendar year	Continuous

Venous thromboembolism (VTE)

Table 4.6 Modifiable Risk Factors

Variable Description	Database Name	Coding	Type
Central Line (arterial or venous)	CVL1 ArtL1	Presence=1 Absence=0	Dichotomous
Surgery	Surgery	Presence=1 Absence=0	Dichotomous
Trauma	Trauma	Presence=1 Absence=0	Dichotomous
Pregnancy	Pregnancy	Presence=1 Absence=0	Dichotomous
Cancer or bone marrow transplant	cancerBMT	Presence=1 Absence=0	Dichotomous
Hematological Malignancy*	HEME_CANCER1	Presence=1 Absence=0	Dichotomous
Central Nervous System Malignancy*	CNS_CANCER1	Presence=1 Absence=0	Dichotomous
Other Malignancy*	OTHER_CANCER1	Presence=1 Absence=0	Dichotomous
Bone Marrow Transplant*	BMT1	Presence=1 Absence=0	Dichotomous

* Included in major variable group Cancer or bone marrow transplant

Table 4.7 Other Risk Factors

Variable Description	Database Name	Coding	Type
Congenital Heart Disease	CHD1	Presence=1 Absence=0	Dichotomous
Inherited Thrombophilia	IT	Presence=1 Absence=0	Dichotomous
Chronic Diseases	Chronicdisease	Presence=1 Absence=0	Dichotomous
Nephrotic Syndrome*	NEPHROTIC1	Presence=1 Absence=0	Dichotomous
Cystic Fibrosis*	CF1	Presence=1 Absence=0	Dichotomous
Systemic Lupus Erythematosus*	SLE1	Presence=1 Absence=0	Dichotomous
Inflammatory Bowel Disease*	IBD1	Presence=1 Absence=0	Dichotomous
Sickle Cell Disease*	SCD1	Presence=1 Absence=0	Dichotomous

* Included in major variable group Chronic Diseases

Chapter 5: Results

Results are presented separately for VTE incidence, VTE recurrence and mortality.

5.1 INCIDENCE OF FIRST-TIME VENOUS THROMBOEMOBLISM IN CHILDREN

5.1.1 Description of Incidence Cohort

The study period for inclusion of incident VTE cases began on January 1st, 1994 and ended on December 31st, 2004. Subjects were followed from the time of their admission into the cohort (at time of incident VTE), until their first recurrence, death, emigration from the province or end of the study period (December 31st, 2005), whichever came first.

In total, 487 incident cases of VTE in children between the ages of 1 and 17 inclusive were documented. Median age was 15 years (range 1-17), **Figure 5.1** shows the age distribution of incident cases. A description of the demographic characteristics of the incidence cohort is shown in **Table 5.1.** Due to the lack of retrieval of inherited thrombophilia information, a decision was made to not include this risk factor in any further calculations or models, as at a minimum we would have expected to see the baseline population distribution of this risk factor in our cohort, which we did not.

Figure 5.1 Distribution of Incident Venous Thromboembolism in Children (1-17 years of age)

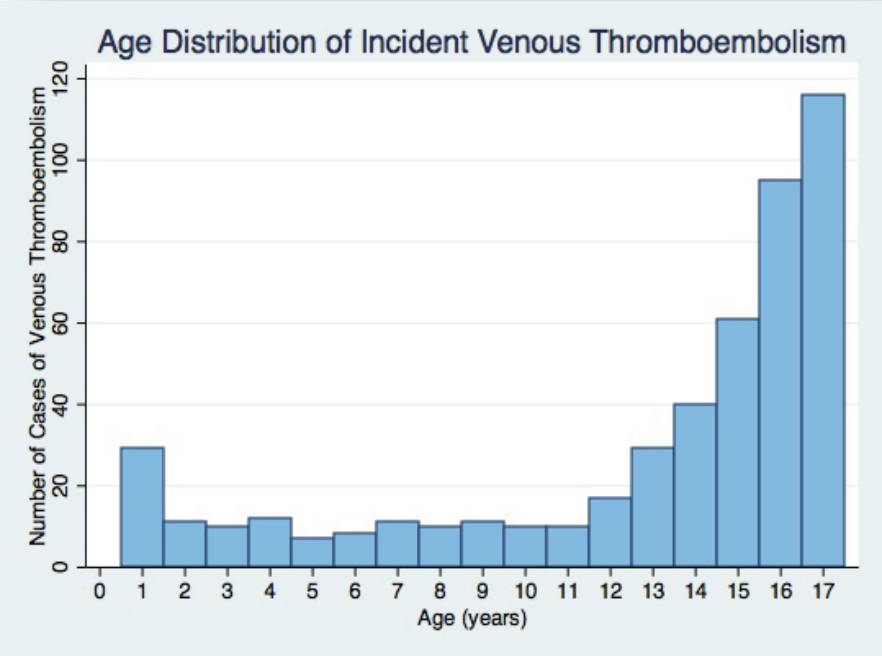


Table 5.1 Demographic and Clinical Features of Incidence Cohort

Variable	Number (%) [Total N=487]
Age	
(Median year +/- SD*)	15 +/- 5.7
Age Category	
1-5 years	69 (14%)
6-10 years	50 (10%)
11-14 years	96 (20%)
15-17 years	272 (56%)
Sex	
Male	182 (37%)
Female	305 (63%)
Venous Thromboembolism Type**	
DVT	319 (66%)
PE	80 (16%)
DVT & PE	36 (7%)
PVT	12 (2%)
RVT	2 (<1%)
CSVT	32 (7%)
DVT & CSVT/PVT/RVT	6 (1%)
Risk Factors***	
Surgery	87 (17.9%)
Infection	1 (0.2%)
Trauma	41 (8.4%)
Congenital Heart Disease	22 (4.5%)
Chronic Disease	36 (7.4%)
Central Line	93 (19.1%)
Cancer/BMT	45 (9.2%)
Inherited Thrombophilia	0 (0%)
Pregnancy (female only)	8 (2.6%)

* Standard deviation (SD)

**Deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT)

***Categories are not mutually exclusive. For surgery, trauma, and infection having occurred in prior 90 days; for congenital heart disease, chronic disease, BMT and central line having occurred in prior 12 months, for cancer and inherited thrombophilia having occurred in 12 months preceding or after index VTE and for pregnancy having occurred during 38 weeks of pregnancy or within 91 days post-partum

Prescription usage information was retrieved from the RAMQ prescription database, however no code existed to identify which subjects were covered by the RAMQ prescription plan. Thus, we were unable to differentiate between those who did not receive a prescription versus those who were not a member of the prescription plan and may have received prescriptions that were not documented in the RAMQ prescription database. Available prescription information on type of anticoagulant prescribed is shown in **Table 5.2**.

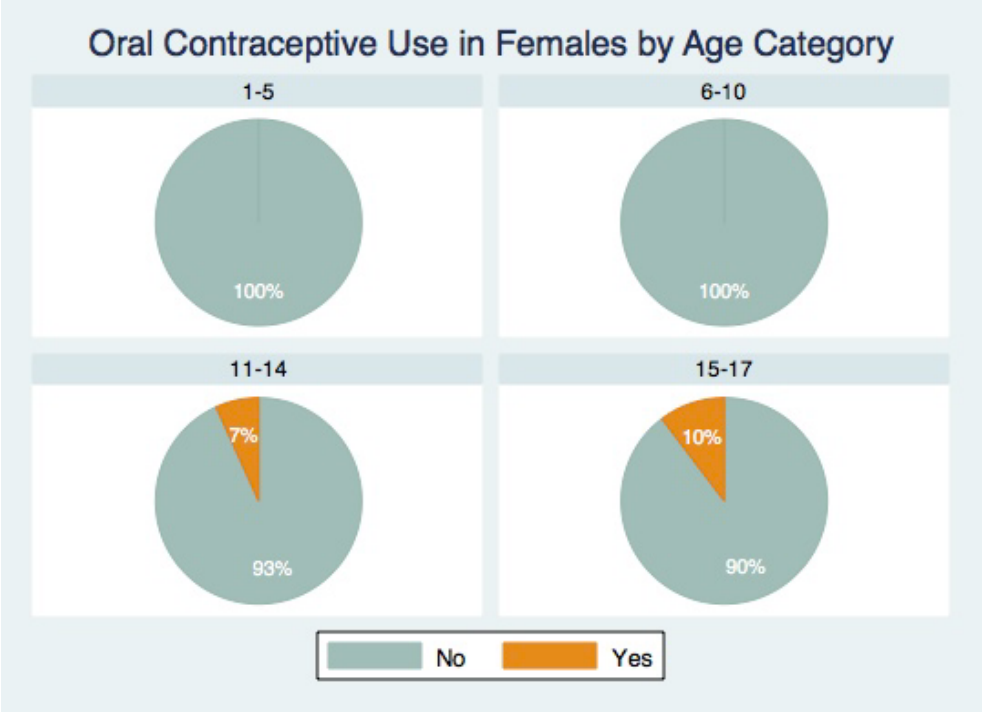
Table 5.2 Prescription Information on Type of Anticoagulation Prescribed

Anticoagulant	**N* [Total N-487]**
Vitamin K Antagonist	90
Unfractionated Heparin	7
Low Molecular Weight Heparin	31
Missing/Not Prescribed**	377

* Numbers add up to >487 as some individuals had prescriptions of more than one drug
** This category includes missing, not prescribed, and subjects who were not eligible for RAMQ coverage therefore may have received anticoagulation but data is not available

Overall, 23 out of 305 females were prescribed the oral contraceptive pill (OCP) within 6 months prior to their incident VTE. Distribution of prescriptions of OCP divided by age category is described in **Figure 5.2** and **Table 5.3**.

Figure 5.2 Oral Contraceptive Use by Age Category*



*Percentages calculated based on n=305 females

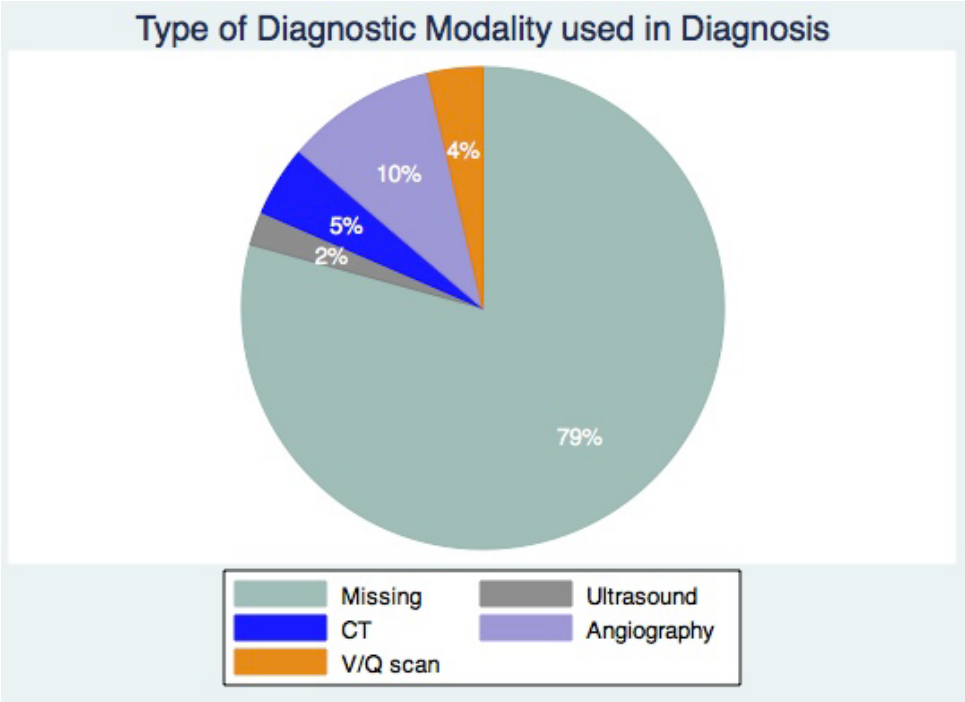
Table 5.3 Distribution of Oral Contraceptive Pill use by Age Category*

Age Category (years)	Number (users of OCP)	Percent of OCP usage
1-5	0	0
5-10	0	0
11-14	4	7%
15-7	19	10%

Oral contraceptive pill (OCP)
*Percentages calculated based on n=305 females

Information on diagnostic modality used for incident VTE was more often than not missing as shown in **Figure 5.3** and **Table 5.4**.

Figure 5.3 Diagnostic Modality Used for Incident Venous Thromboembolism*



***Of note, some subjects had more than one diagnostic modality utilized per event.**
Computed Tomography (CT), Ventilation Perfusion Scan (V/Q)

Table 5.4 Documented Type of Diagnostic Imaging used in Venous Thromboembolism Diagnosis

Imaging Modality	Number	Percent
CT	23	5%
V/Q scan	18	4%
Ultrasound	11	2%
Angiography	49	10%
Missing	386	79%

Computed Tomography (CT), Ventilation Perfusion Scan (V/Q)

Due to the large amount of missing information for prescription and diagnostic modality data, as well as the lack of data on baseline population usage of these diagnostic

tools and medications, it was decided that analysis of trends in their usage would not be appropriate and therefore was not pursued.

5.1.2. Incidence Rate of Pediatric Venous Thromboembolism

Based on the estimated population person-years over the study period (16 919 827 person-years) the crude incidence rate (IR) was 0.29 VTE per 10 000 person-years. The age-standardized IR was 0.29 VTE per 10 000 person-years (95% confidence interval (CI) 0.26-0.31). The age-standardized IR of DVT and/or PE (excluding RVT, PVT and CSVT exclusively) was 0.26 per 10 000 person-years (95% CI 0.24-0.29). When analyzed as separate age groups, the age-standardized IRs were as follows: for 1-5 year olds, 0.04 VTE per 10 000 person years (95% CI 0.03-0.05); for 6-10 year olds, 0.03 VTE per 10 000 person years (95% CI 0.02-0.04); for 11-14 year olds, 0.06 VTE per 10 000 person years (95% CI 0.05-0.07); and for 15-17 year olds, 0.16 VTE per 10 000 person years (95% CI 0.14-0.18).

5.1.3 Incidence Rate by Sex

Females had a significantly higher age-standardized VTE incidence rate than males, 0.37 VTE per 10 000 person-years (95% CI 0.33-0.41) vs. 0.21 VTE per 10 000 person-years (95% CI 0.18-0.24), respectively. The incidence rate ratio comparing the incidence in females to males, adjusted for age group, was 1.75 (95% CI 1.46-2.10). Since incidence in females is known to be higher in certain age groups than males

(adolescents), age group was adjusted for.[2] This difference can be seen in our comparison of incidence rates in females and males as shown in Table 5.5.

Table 5.5 Age Standardized Incidence Rates in Males and Females by Age Group

Age Category	Incidence Rate Female*	Incidence Rate Male*	Incidence Rate Ratio
1-5 years old	0.047	0.035	1.34
6-10 years old	0.028	0.031	0.90
11-14 years old	0.071	0.043	1.65
15-17 years old	0.222	0.102	2.18

*per 10 000 person-years, age-standardized

5.1.4 Analysis of trends in incidence rates over time

Poisson regression analysis of the age-standardized incidence rates over the 11-year study period showed no significant change in incidence rates when assessed using time as continuous variable (yearly) or time as a categorical variable (time period; time-period 1:1994-1995, time-period 2: 1996-2000, time-period 3: 2001-2004). The β coefficient for year was 0.0081 with a 95% CI that crossed the null (95% CI -11 to 11). The β coefficient comparing time-period 2 to time-period 1 was -0.13 (95 % CI -162 to 162) and time-period 3 to time-period 1 was -0.06 (95 % CI -159 to 159). Yearly and time-period specific rates are shown in **Figures 5.4** and **5.5**.

Figure 5.4 Age Standardized Incidence Rate of Venous Thromboembolism by Calendar Year

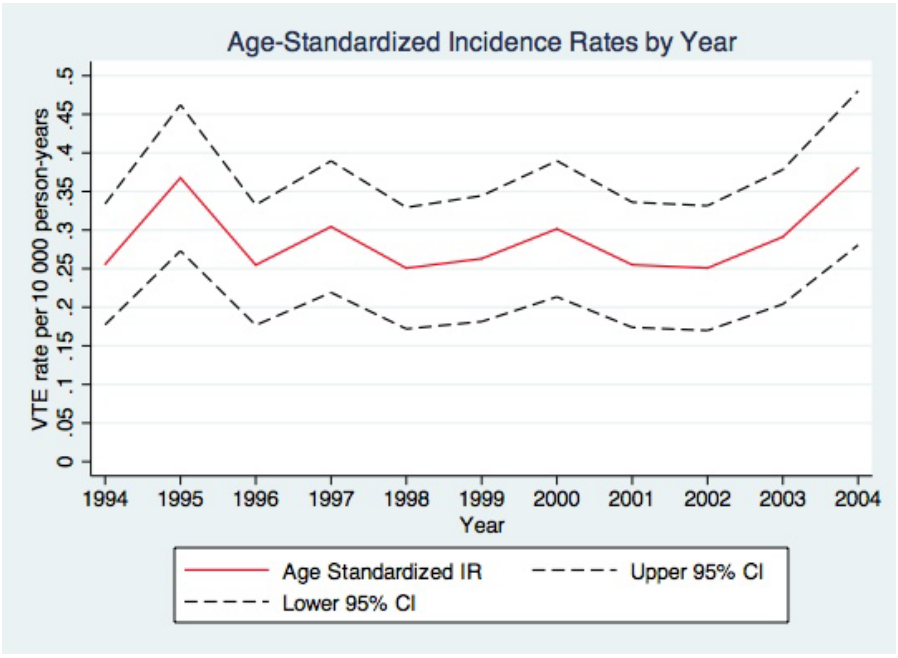
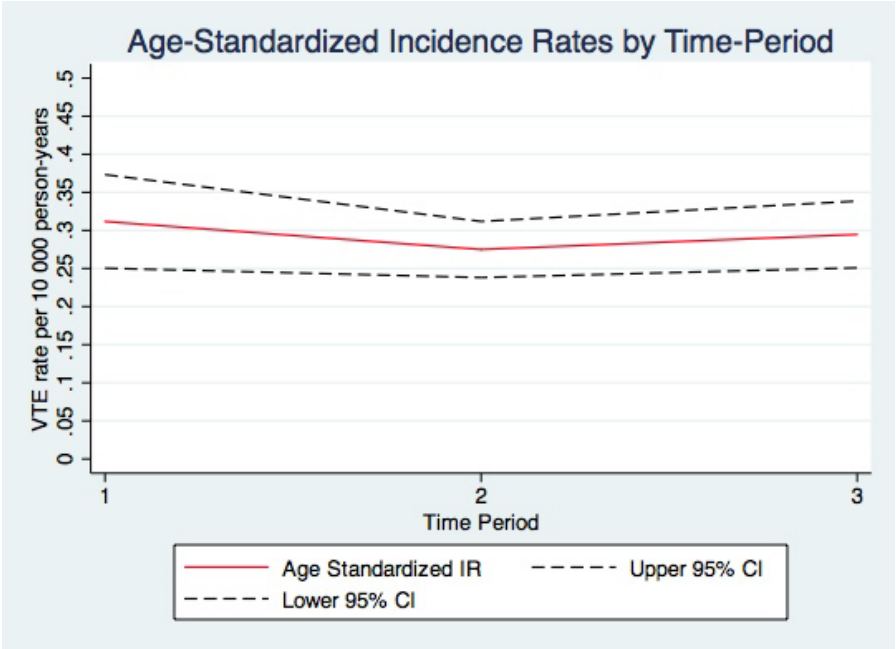


Figure 5.5 Age Standardized Incidence Rate of Venous Thromboembolism by Time Period



Time-period 1:1994-1995, time-period 2: 1996-2000, time-period 3: 2001-2004

When assessing trends in IR by age groups, there was no statistically significant change in rates over the 11-year study period by year or by time period. The β coefficient for year for age group 1 (1-5 yo (years old)) was 0.14 (95% CI -30-31); age group 2 (6-10 yo) was 0.06 (95% CI -35-35); age group 3 (11-14 yo) was 0.002 (95% CI -25-25); and age group 4 (15-17 yo) was -0.03 (95% CI -15-15), with respective incidence rate ratios of 1.15, 1.06, 1.0, and 0.97. The β coefficients for time periods by age group were similar and non significant with p-values between 0.997-1.00 (see appendix for exact output). **Figure 5.6** and **5.7** shows age-standardized incidence rates of VTE by calendar year and by time period, respectively, for each age group.

Figure 5.6 Age Standardized Yearly Incidence Rate of Venous Thromboembolism by Age Group

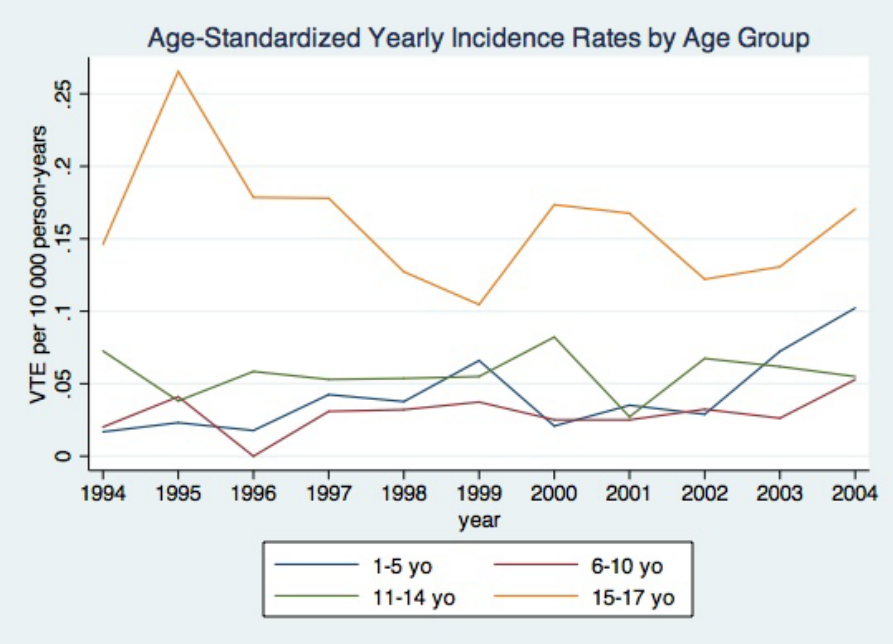
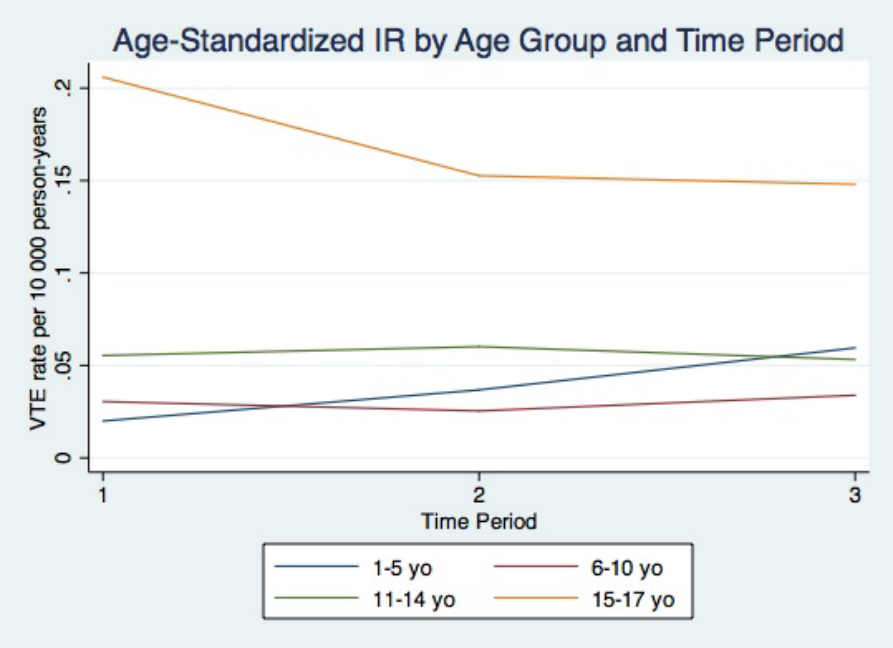


Figure 5.7 Age Standardized Time Period Incidence Rate of Venous Thromboembolism by Age Group



All of the Poisson models were assessed for dispersion. Within a Poisson distribution the expected value and the variance should be equal, when this does not occur there is said to be dispersion.[116,121] For all of our models, the variance was not equal to the mean, indicating overdispersion. Robust standard errors were used to address this overdispersion (using the Stata command "VCE robust"), yet the point estimates for the β coefficients remained identical to those from standard Poisson modeling. Of the two methods, the more conservative confidence intervals were reported, which was in all cases the standard Poisson modeling.[121]

5.2 RECURRENCE OF VENOUS THROMBOEMBOLISM IN CHILDREN

5.2.1 Description of Recurrence Cohort

The cohort evaluated for recurrence was larger than the cohort for the incidence calculations as 31 subjects under the age of one were available for recurrence assessment (n=518). As discussed in the methods section on p. 61, patients under the age of one (n=31) were excluded from incidence calculations. All children with follow-up data after an incident VTE were included in the recurrence cohort. Further clinical data on subjects less than one year of age are depicted in **Table 5.6**. Description of the demographic characteristics of the recurrence cohort is presented in **Table 5.7**.

Table 5.6 Description of Subjects Less Than One Year of Age

Variable	Number (%)
Sex	Male 18 (58%) Female 13 (42%)
Length Of Hospital Stay	Median 24 days (range 1-193d)
Death	4 (13%)
Age	Median 4 months (range 0-11 months)
VTE Type*	
DVT	22 (71%)
PE	0
DVT&PE	0
PVT	1 (3%)
RVT	0
CSVT	5 (16%)
DVT & CSVT/PVT/RVT	3 (10%)

*Venous Thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT).

Table 5.7 Demographics Characteristics of Recurrence Cohort

Variable	Number (%) [Total N=518]
Age	
(Median year +/- SD*)	15 +/- 5.7
Follow-Up Time	
Median (Range)	4.4 years (1 day to 12 years)
Age Category	
<1 year	31 (6%)
1-5 years	69 (13%)
6-10 years	50 (10%)
11-14 years	96 (19%)
15-17 years	272 (53%)
Sex	
Male	200 (39%)
Female	318 (61%)
VTE Type**	
DVT	341 (66%)
PE	80 (16%)
DVT & PE	36 (7%)
PVT	13 (3%)
RVT	2 (<1%)
CSVT	37 (7%)
DVT & CSVT/PVT/RVT	9 (2%)
Risk Factors***	
Surgery	99 (19.1%)
Infection	2 (0.4%)
Trauma	41 (7.9%%)
Chronic Disease	36 (7%)
Central Line	107 (20.7%)
Cancer/BMT	49 (9.5%)
Congenital Heart Disease	34 (6.6%)
Pregnancy (female only)	8 (2.5%)

* Standard deviation (SD)

**Venous Thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT)

***Categories are not mutually exclusive. For surgery, trauma, and infection having occurred in prior 90 days; for congenital heart disease, chronic disease, Bone Marrow Transplant (BMT) and central line having occurred in prior 12 months, for cancer having occurred in 12 months preceding or after index VTE and for pregnancy having occurred during 38 weeks of pregnancy or within 91 days post-partum

5.2.2 Recurrence Rate Analysis

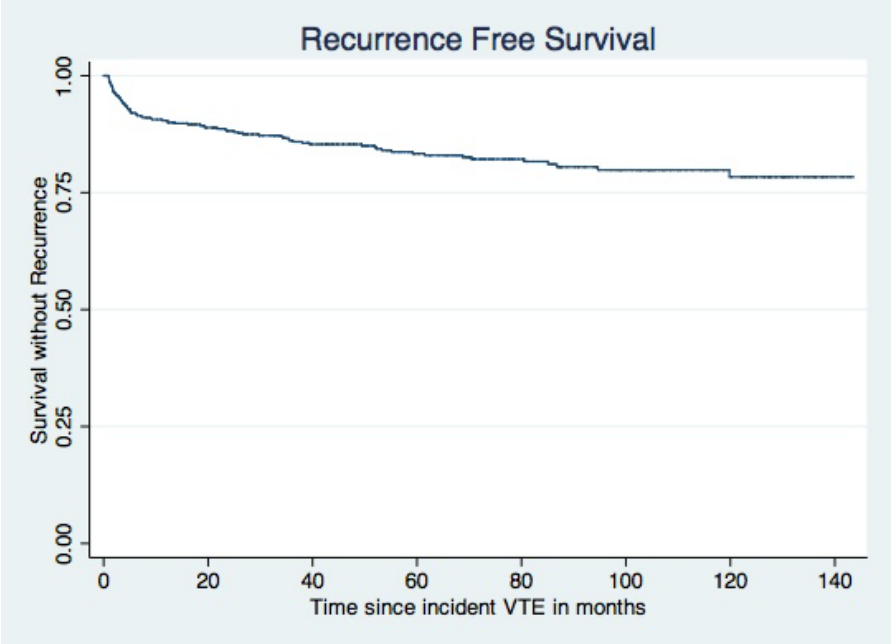
Assessment of the cohort for recurrence demonstrated an overall recurrence rate of 2.8 VTE recurrences per 1000 person-months (95% CI 2.2, 3.4). Males had a higher recurrence rate of 3.7 VTE recurrences per 1000 person-months (95% CI 2.7, 5.1) as compared to females who had a recurrence rate of 2.3 VTE recurrences per 1000 person-months (95% CI 1.7, 3.0). Recurrence rate was highest in the 1-5 and 11-14 year old age categories. The rates of recurrence by age group are shown in **Table 5.8**.

Table 5.8 Recurrence Rate by Age Group

Age Group (years)	Recurrence Rate (per 1000 person-months)	95 % Confidence Interval
<1	2.4	0.7-7.3
1-5	3.8	2.2-6.7
6-10	3.5	1.8-6.8
11-14	3.8	2.4-5.8
15-17	2.2	1.6-3.0

There were a total of 83 recurrences among the 508 subjects that were evaluable for recurrence (those that survived ≥ 30 days post incident VTE), for a recurrence risk of 16.3%. Kaplan Meier estimate of recurrence-free survival are shown in **Figure 5.8**.

Figure 5.8 Venous Thromboembolism Recurrence Free Survival



5.2.3 Analysis of Accuracy of Central Venous Catheter Reporting in Database: an analysis of accuracy

To determine the accuracy of recorded information in Med-Echo, we performed an analysis of the accuracy of the procedure codes related to insertion of a central vascular catheter. Insertion of a central venous catheter is necessary when performing a bone marrow transplant in order to infuse into the patient the bone marrow or peripheral blood stem cells, and for technical reasons this cannot be done via a peripheral catheter. For this reason we chose to evaluate if all patients within the cohort who were coded as having undergone a bone marrow transplant were also coded as having had a central venous catheter inserted. The procedure codes for central venous catheter insertion

include 50.92 (umbilical venous catheter), 50.93 (other venous catheter including peripherally inserted central catheter [PICC]), and 98.06 (Port-A-Cath).

In total, 6% (n=32) of subjects in the cohort were coded as having previously undergone a bone marrow transplant; of these, 18 (56%) had a concomitant diagnosis of central line placement. Although it is possible that some patients coded as having undergone bone marrow transplant may have been coded as such in error, the retrieval of central line placement at least within the bone marrow transplant group seems to be incomplete.

5.2.4 Hazard Model for Recurrence

The results of the univariate analysis, as shown in **Table 5.9** and **Figure 5.9**, informed our decision of which factors to include in the multivariate Cox proportional hazards model.

Table 5.9 Univariate Risk Factor Assessments for Recurrence After Incident Venous Thromboembolism

Variable*	P-value	Keep Yes/No for Cox Hazards Model (p<0.25)
Sex	0.066	YES
Age (continuous)**	0.3379	YES***
Central Line	0.0094	YES
Major Surgery	0.5846	NO
Major Infection	0.1412	YES
Trauma	0.3429	NO
Pregnancy (female only)	0.2349	YES
Cancer or BMT	0.2341	YES
Chronic Disease****	0.0050	YES
Type of VTE*****	0.0135	YES
Congenital Heart Disease	0.1174	YES

* Venous thromboembolism (VTE), bone marrow transplant (BMT)
** Age Category was not included because of collinearity with age (continuous)
***Continuous Age was kept in model based on a priori information
****Chronic diseases included: sickle cell disease, nephrotic syndrome, inflammatory bowel disorder, cystic fibrosis, and systemic lupus erythematosus
***** Type of VTE included deep vein thrombosis (DVT), pulmonary embolism (PE), DVT and PE, portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinus venous thrombosis (CSVT), DVT and RVT/PVT/CSVT

Figure 5.9 Recurrence-Free Survival by Categorical Risk Factor

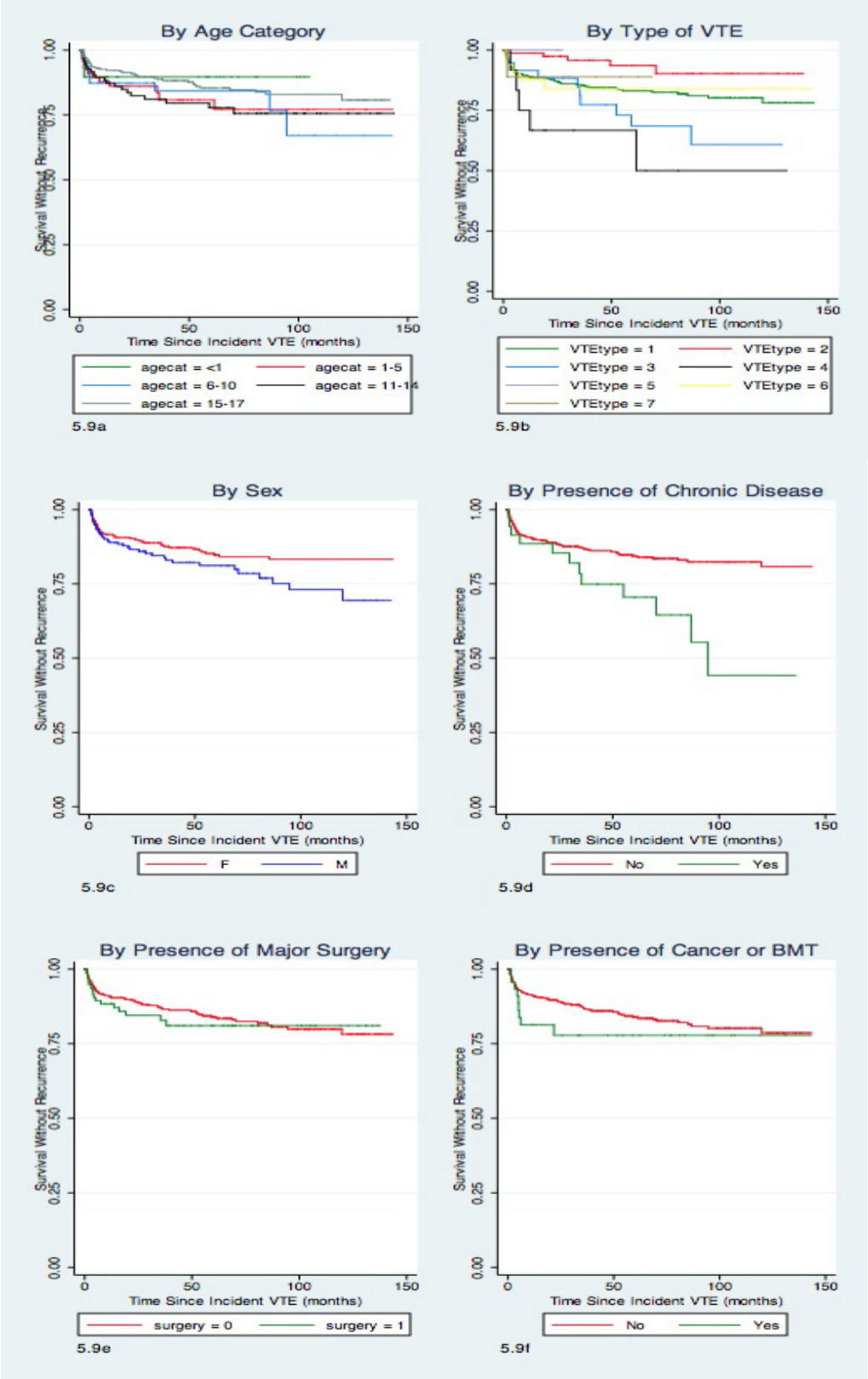
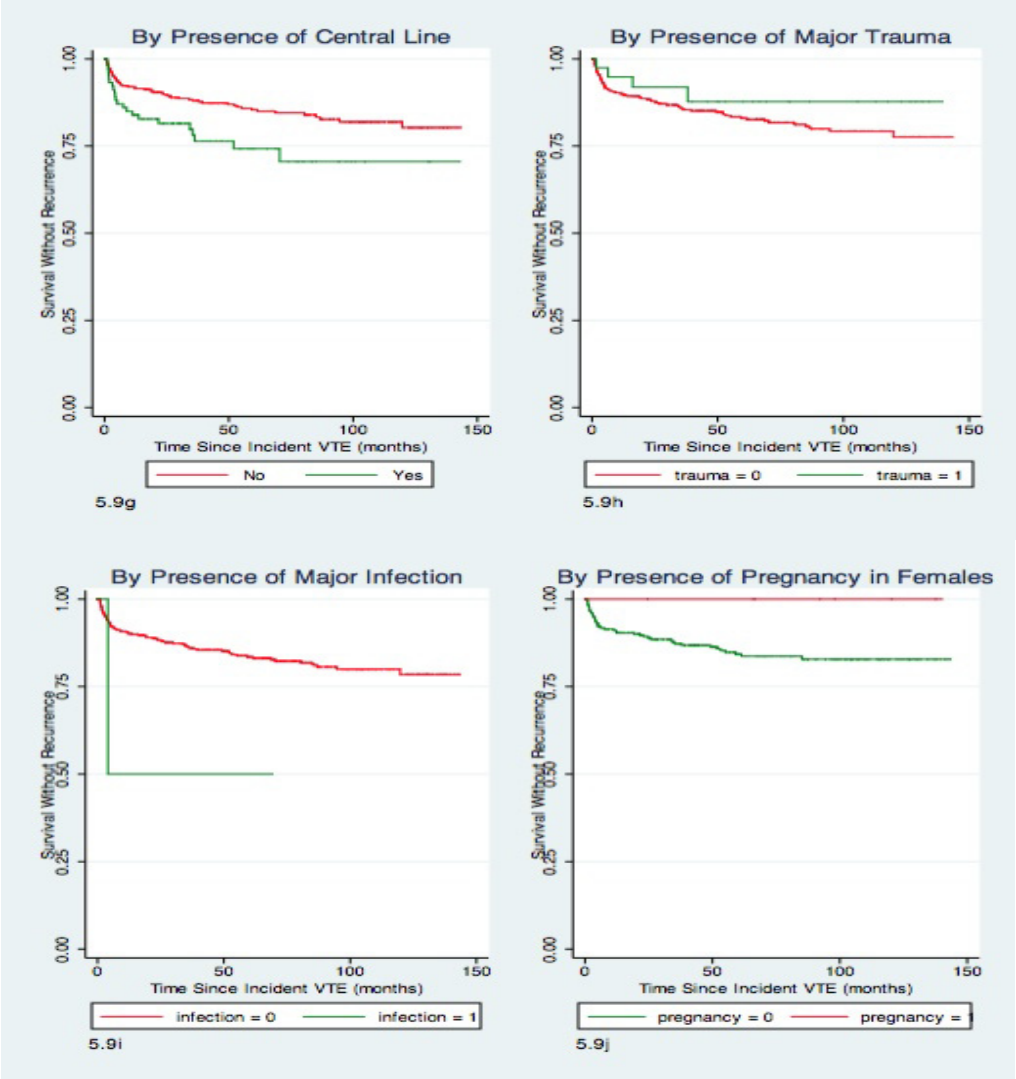


Figure 5.9 Recurrence Free Survival by Categorical Risk Factor continued…



Male (M), Female (F), Bone Marrow Transplant (BMT)
Chronic diseases included: sickle cell disease, nephrotic syndrome, inflammatory bowel disorder, cystic fibrosis, and systemic lupus erythematosus
Type of VTE are as follows: Type 1:deep vein thrombosis (DVT), Type 2: pulmonary embolism (PE), Type 3: DVT and PE, Type 4: portal vein thrombosis (PVT), Type 5: renal vein thrombosis (RVT), Type 6: cerebral sinus venous thrombosis (CSVT), Type 7: DVT and RVT/PVT/CSVT

The final multivariate Cox proportional hazards model for recurrence of VTE included sex, age, central line, infection, cancer-BMT, chronic disease, VTE type and congenital heart disease. Prior studies have shown that VTE recurrence seems to be

higher in older children.[8,12,32] Many of the VTE risk factors are also associated with age. For chronic diseases (e.g. lupus, inflammatory bowel disease), pregnancy and cancer, increasing age of children is associated with a higher incidence of their occurrence[122-124], whereas for VTE type, some types, such as renal vein thrombosis are much more common in younger than older children.[8] For this reason, age was included in the model a priori, as it was known to be a probable confounder. The final multivariate model included 13 variables. Hazard risk for recurrence was statistically higher in those with a prior diagnosis of a chronic disease (HR 2.3; 95% CI 1.2-4.3)[panel 5.9d], PVT as initial VTE diagnosis (HR 4.1; 95% CI 1.5-11.0) [panel 5.9b] and presence of a central line at time of initial VTE (HR 1.9; 95% CI 1.0-3.3)[panel 5.9g] Of note, both univariate and multivariate Cox proportional hazards modeling, as shown in **Table 5.10**, showed similar hazard risks. The global test for proportionality was not statistically significant (p-value= 0.15), showing no violation of the proportionality assumption. For both the whole cohort and for females only, Cox proportional hazards models for certain VTE subtypes and for pregnancy had too few observations, and the coefficient for this term did not converge (95% confidence intervals were from zero to infinity). However, we fit the model excluding these categories and the results for all other variables were nearly identical (as shown in appendix).

Table 5.10 Univariate and Multivariate Cox Proportional Hazards Recurrence Risks

Variable*	Univariate HR [95% CI]	Multivariate HR [95% CI]
Sex	1.50 [0.97-2.31]	1.51 [0.97-2.36]
Age Category Baseline <1 year old		----------
1-5 years old	1.67 [0.47-5.93]	----------
6-10 years old	1.63 [0.44-6.03]	----------
11-14 years old	1.77 [0.53-5.97]	----------
15-17 years old	1.12 [0.35-3.66]	----------
Age (continuous)	0.98 [0.95 1.02]	1.04 [0.99-1.09]
Central Line	1.88 [1.16-3.05] ¶	1.87 [1.04-3.33] ¶
Major Surgery	1.16 [0.67-2.01]	----------
Major Infection	3.94 [0.55-28.36]	4.30 [0.55-33.42]
Trauma	0.62 [0.23-1.69]	----------
Pregnancy (female only)	4.43×10^{-15} [0-∞]	----------
Cancer or BMT	1.52 [0.76-3.04]	1.18 [0.56-2.47]
Chronic Disease	2.34 [1.27-4.31] ¶	2.28 [1.20-4.35] ¶
Type of VTE (baseline DVT only)		
PE	0.36 [0.14-0.89]	0.40 [0.16-1.00]
DVT & PE	1.70 [0.87-3.34]	1.56 [0.78-3.12]
PVT	3.01 [1.20-7.52] ¶	4.12 [1.54-11.02] ¶
RVT	2.81×10^{-14} [0-∞]	2.14×10^{-15} [0-∞]
CSVT	0.97 [0.39-2.43]	0.95 [0.37-2.45]
DVT & PVT/RVT/CSVT	0.84 [0.12-6.10]	0.67 [0.09-5.01]
Congenital Heart Disease	1.78 [0.86-3.69]	1.91 [0.85-4.28]

* Hazard Risk (HR), confidence interval (CI), venous thromboembolism (VTE), Deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT), bone marrow transplant (BMT)

¶ Statistically significant HR

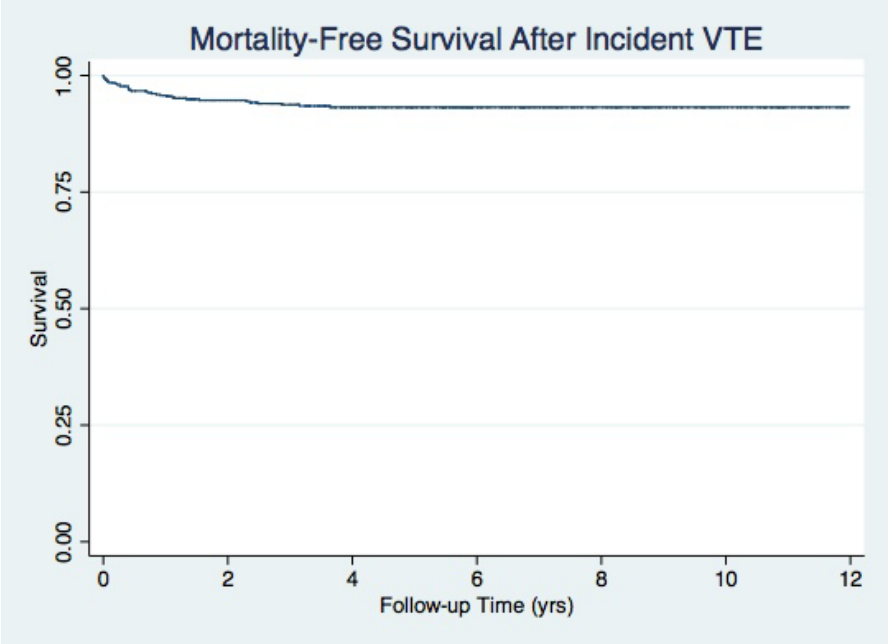
A separate Cox proportional hazards model was constructed for females only to assess the role of pregnancy in VTE recurrence, with the rest of the risk factors remaining in the model except for sex. In females only, there was no statistically significant effect of pregnancy on hazard of recurrence. The 95% confidence interval for the effect of pregnancy did not converge (was very wide) likely due to the small number of pregnant subjects within the cohort. The global test for proportionality was not statistically significant (p-value=0.85), showing no violation of the proportionality assumption.

5.3 MORTALITY

5.3.1 Mortality Rate Assessment

There were 33 deaths in the cohort for an overall all-cause mortality risk of 6.4%. Evaluation of all databases for death verification showed a total of 26 claims (for 14 subjects) in either the Med-Echo or RAMQ databases after the date of death. All claims were within 30 days of the date of death; therefore based on our pre-decided criteria we elected to not remove any of the death cases. The mortality rate after incident VTE was found to be 11.4 deaths per 1000 person-years (95% CI 8.1-16.1). **Figure 5.10** shows the Kaplan Meier mortality-free survival curve after incident VTE.

Figure 5.10 Kaplan Meier Survival After Incident Venous Thromboembolism



Mortality varied by age category, as presented in **Table 5.11**. The highest mortality was observed in the youngest age groups. With respect to sex, males had a mortality rate of 11.1 deaths per 1000 person-years (95% CI 10.7-27.6), compared to females who had a mortality rate of 8.4 per 1000 person-years (95% CI 5.2-13.8). Age-controlled mortality rates for males and females were evaluated in the multivariate Cox proportional hazards model.

Table 5.11 Mortality Rate by Age Category

Age Group (years)	Mortality Rate (per 1000 person-years)	95 % CI
<1	33.6	12.6-89.5
1-5	34.2	18.4-63.5
6-10	20.5	8.6-49.4
11-14	10.5	4.7-23.4
15-17	4.8	2.4-9.6

5.3.2 Hazard Model for Mortality

The results of the univariate analysis, as shown in **Table 5.12**, informed our decision of which factors to include in the multivariate Cox proportional hazards model for mortality.

Table 5.12 Univariate Risk Factor Assessments for Mortality After Incident Venous Thromboembolism

Variable*	P-value	Keep Yes/No for Cox Hazards Model (p<0.25)
Sex	0.093	YES
Age (continuous)**	0.000	YES
Central Line	0.000	YES
Major Surgery	0.0696	YES
Major Infection	0.707	NO
Trauma	0.749	NO
Pregnancy (female only)	0.512	NO
Cancer or BMT	0.000	YES
Chronic Disease***	0.812	NO
Type of VTE******	0.973	NO
Congenital Heart Disease	0.158	YES

* Bone marrow transplant (BMT), venous thromboembolism (VTE)
** Age Category was not included because of collinearity with age (continuous)
***Chronic diseases included: sickle cell disease, nephrotic syndrome, inflammatory bowel disorder, cystic fibrosis, and systemic lupus erythematosus
**** Type of VTE included deep vein thrombosis (DVT), pulmonary embolism (PE), DVT and PE, portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinus venous thrombosis (CSVT), DVT and RVT/PVT/CSVT

The final multivariate Cox proportional hazards model for mortality after incident VTE included sex, age, central line, surgery, cancer-BMT, and congenital heart disease. Therefore, the final model included a total of 6 variables. Hazard risk for mortality was higher in those with a prior diagnosis of a cancer/BMT (HR 4.66; 95% CI 2.22-9.80), those with a central line at time of incident VTE (HR 2.53; 95% CI 1.13-5.64) and was lower with increasing age (HR 0.93; 95% CI 0.87-0.99). Again, both univariate and multivariate Cox proportional hazards modeling for mortality risk, as shown in **Table 5.13**, showed similar hazard risks. The only exception was that the oldest age category was statistically significant in univariate analysis but not included in final model because of collinearity with age as a continuous variable. The global test for proportionality was of borderline statistical non-significance (p-value=0.055), showing no definitive violation of the proportionality assumption. However, given the borderline significant results for the global test, the validity of the proportional assumption was further evaluated by plotting Schoenfeld residuals for each variable that had a statistically significant test result for the proportionality assumption (congenital heart disease: p-value 0.02 and central line: p-value 0.03), as shown in **Figures 5.11** and **5.12**. Based on this, it remains difficult to strongly support or refute the proportionality assumption as both plots show very little deviation from a zero slope. Results for this Cox proportional hazards model must therefore be interpreted with caution.

Table 5.13 Univariate and Multivariate Cox Proportional Hazards Mortality Risks

Variable*	Univariate HR [95% CI]	Multivariate HR [95% CI]
Sex	1.78 [0.90-3.52]	1.37 [0.68-2.74]
Age Category Baseline <1 year old		----------
1-5 years old	1.05 [0.33-3.35]	----------
6-10 years old	0.71 [0.19-2.64]	----------
11-14 years old	0.41 [0.12-1.47]	----------
15-17 years old	0.19 [0.06-0.64] ¶	----------
Age (continuous)	0.89 [0.85-0.94] ¶	0.93 [0.87-0.99] ¶
Central Line	5.74 [2.88-11.46] ¶	2.53 [1.13-5.64] ¶
Major Surgery	1.96 [0.93-4.13]	1.42 [0.66-3.06]
Major Infection	1.26×10^{-14} [0-∞]	----------
Trauma	0.79 [0.19-3.31]	----------
Pregnancy (female only)	1.64×10^{-15} [0-∞]	----------
Cancer or BMT	7.23 [3.59-14.55] ¶	4.66 [2.22-9.80] ¶
Chronic Disease	0.84 [0.20-3.51]	----------
Type of VTE (baseline DVT only)		----------
PE	0.77 [0.26-2.23]	----------
DVT & PE	1.30 [0.39-4.33]	----------
PVT	1.28 [0.17-9.48]	----------
RVT	5.58×10^{-19} [∞-∞]	----------
CSVT	0.93 [0.22-3.94]	----------
DVT & PVT/RVT/CSVT	2.15 [0.29-15.95]	----------
Congenital Heart Disease	2.09 [0.73-5.95]	0.92 [0.30-2.78]

* Hazard Risk (HR), confidence interval (CI), venous thromboembolism (VTE), deep vein thrombosis (DVT), pulmonary embolism (PE), portal vein thrombosis (PVT), renal vein thrombosis (RVT), cerebral sinovenous thrombosis (CSVT), bone marrow transplant (BMT)

¶ Statistically significant HR

Figure 5.11 Scaled Schoenfeld Residuals (Lowess Smooth) for Congenital Heart Disease

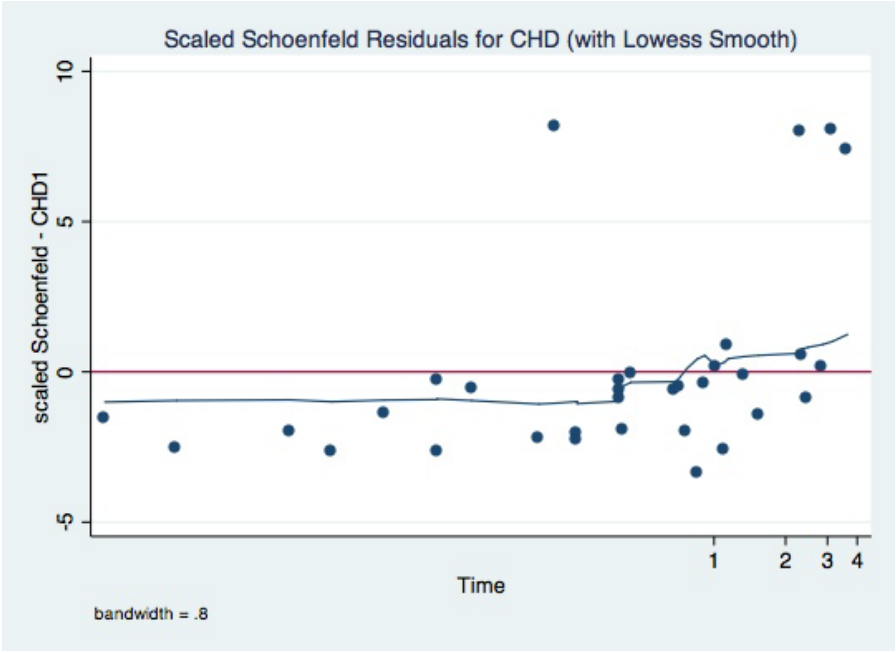
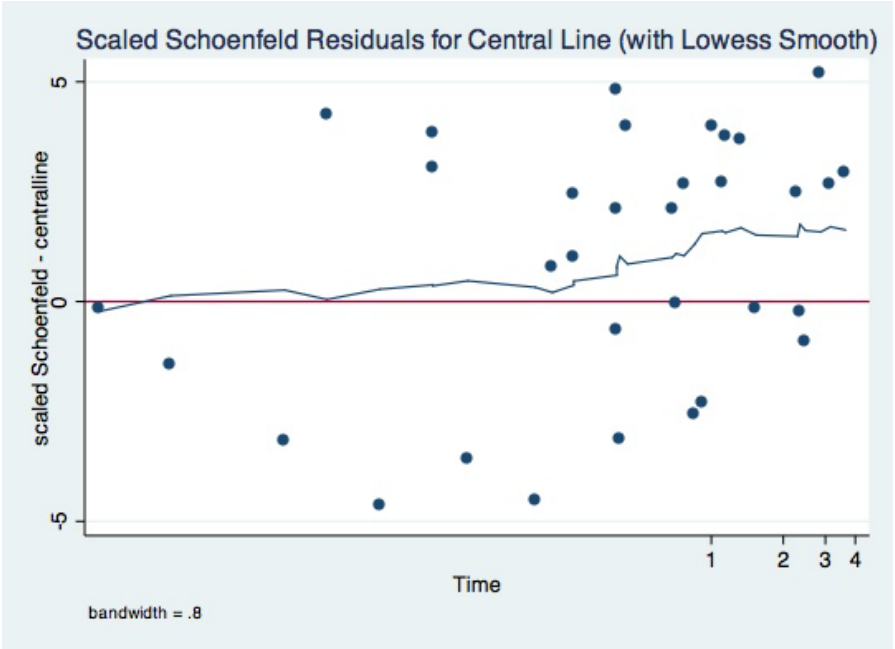


Figure 5.12 Scaled Schoenfeld Residuals (Lowess Smooth) for Central Line



Chapter 6: Discussion

6.1 DISCUSSION

Pediatric VTE, although rare, has significant sequelae including recurrence, post-thrombotic syndrome, and even death from pulmonary embolism. Individuals who suffer from an episode of VTE at a young age may be susceptible to these adverse outcomes for the greater part of their life. Although information regarding the duration of risk for children with VTE, especially later in life, is lacking. Many chronic or severe illnesses, as well as the procedures that are often associated with them, are known to predispose to VTE. Given the many recent advancements in the care of acutely and chronically ill children, it is quite possible that with their improved survival, as well as increased awareness of VTE occurrence by pediatric care-providers, we could see an increase in the incidence rates of pediatric VTE and their sequelae.

In order to better establish the incidence trends of pediatric VTE, this study used a comprehensive administrative database to calculate incidence rates over an eleven-year period and evaluate the time trends in incidence. In addition, recurrence and mortality rates were assessed and hazard risks for possible predictors of recurrence or death were evaluated in order to provide future information for trials on secondary prophylaxis for pediatric VTE.

Similar to prior studies, the age distribution of VTE in this retrospective cohort study showed a bimodal peak. Given that children under the age of one were excluded from the incidence calculations, it was not surprising that the initial peak (usually in the

youngest children) was less pronounced than in other studies.[1,4,12] Interestingly, we were able to show that the incidence in late adolescence continues to rise. Prior studies have often showed a drop off or plateau in the late teen years which is likely explained by the fact that pediatrician led registries may miss cases in older adolescents who may be cared for by non-pediatricians.[1,4] Moreover, we may have missed older adolescents who may have been treated for their VTE exclusively as outpatients since we used Med-Echo to define VTE cases. However, the number of older children treated as outpatients is likely to be small since in the Dutch Registry study 85% of children less than 18 years of age with VTE were diagnosed while in hospital.[4] Although beyond the scope of this thesis, it would be interesting in a future study to determine from the VTE-coded RAMQ medical acts the setting of patient care (in- vs. outpatient) so as to determine if any children (especially adolescents) are cared for solely in the outpatient setting.

The distribution of types of VTE showed a strong predominance of DVT and PE, with 90% of incident events in this cohort having one of these two types alone or in combination. This finding was similar to the recent Danish cohort study, which showed that 96% of their venous sites involved would be classified as a DVT or PE by our definition, although it is important to note that they excluded cerebral thrombosis.[18]

Overall, only 51% of our subjects had an identifiable risk factor for their VTE. This is much lower than prior studies that have shown that upwards of 85% of VTE in children have an identifiable precipitant.[4,12,18] Based on the results of our analysis of accuracy, the completeness of our risk factor extraction was likely inadequate. Improper coding and coding omissions are a frequent problem with administrative databases. Based on our analysis of accuracy, any conclusions based on the accuracy of all risk factors

extracted from the Med-echo database must be made with caution. In addition, our inability to retrieve data on inherited thrombophilic conditions and complete prescription data on the whole cohort (therefore lacking complete information on oral contraceptive use) could explain why we had such a high number of seemingly spontaneous events.

With respect to prescription medication as a risk factor for VTE recurrence or death, the limited data on prescription medication made its inclusion in any of the hazard risk models impossible. Twenty-three of 243 females aged 11-17 years had been prescribed the oral contraceptive pill in the 6 previous months prior to their VTE. Based on the estimated 30% of children covered by the RAMQ plan, we can estimate that approximately 32%* of VTE cases in adolescent females in Quebec are associated with OCP use.

Current estimates of population based incidence rates of pediatric VTE range between 0-0.49 events per 10 000 children-years. Most recently, population level incidence rates were evaluated in a nationwide comprehensive database in Denmark. The noncerebral VTE incidence rate in children was found to be 0.21 per 10 000 children-years.[18] Our finding is quite similar to this Danish report, with a population based incidence rate of 0.29 VTE per 10 000 children-years, and an incidence rate of DVT+/- PE of 0.26 per 10 000 children-years. The incidence of DVT+/- PE in our study was much higher than the published incidence of extremity VTE and PE of 0.07 events per 10 000 children, published from the original Canadian Childhood Thrombophilia Study

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**(243 females 11-17 years of age X 30% covered by RAMQ = 73 on RAMQ plan) → 23 OCP users 11-17 years of age, of 73 on RAMQ plan= 32%.*

although they included children starting at 1 month of age.[12] To our knowledge, our study is the first North American study to establish an incidence rate based on a comprehensive database as opposed to sampled hospital databases, single-centre databases (as was used in the American studies) and registries (as was used in the prior Canadian study).[1,2,12,15-17,34] Based on our results, the population based incidence rate of pediatric VTE in a North American region is much higher than previously published.

In our study, females were found to have a higher age-adjusted incidence of VTE compared to males, similar to the Tuckuviene study.[18] The incidence rate ratio of 1.75 for females compared to males when adjusted for age group is unlike older published reports that suggest similar rates in male and female children.[1,4] Therefore, although factors such as pregnancy and oral contraceptive use may play a role in the higher incidence in some females less than 18 years, other factors, especially in younger girls, should be evaluated that may play a role in this higher incidence.

Our study showed that whether we compared incidence rates yearly or during different time frames over the 11 years of the study (1994-2004) there was no statistically significant change in the incidence rate. As previously mentioned, studies to date that have assessed incidence rate trends of VTE in children have been varied in their outcomes. Analyses based on events per hospital discharge have shown increasing trends whereas the two studies to date using population based estimates of VTE incidence have shown a lack of significant trend in the last 10-30 years.[2,12,15-18] The reason for these very different findings is difficult to explain. Incidence rates based on per-hospital discharge rather than person-years may, in certain databases, fail to differentiate between patients being admitted and discharged with multiple recurrent events. Given the low incidence

and recurrence rates it is hard to explain all differences based on this. In addition, this issue was addressed in some of the administrative databases (especially single-centre), as they were able to identify hospitalization by unique identifier numbers and therefore avoid this issue. Another possible explanation could be that the type or severity of patients being admitted to hospitals has changed significantly over the past several years and that only much sicker individuals are now being admitted, therefore decreasing the denominator in the calculations with similar overall number of events occurring over the time period. An alternative possible explanation may be that the hospitals sampled in the per-hospitalization incidence rates do not reflect the overall incidence rate of VTE in the general population. From a standpoint of public health and assessment of burden of disease on the population that can be more easily extrapolated to other areas, most evidence to date, including ours, suggests that although the overall rate of VTE in children is likely higher than previously published, the burden of disease does not seem to be increasing at a rapid pace.

The recurrence rate for children with an incident VTE was 2.77 VTE recurrences per 1000 person-months. Kaplan Meier assessment showed a recurrence-free survival of 90.4% at 1 year, 83.4% at 5 years and recurrence occurring as late as 10 years after the incident event. The highest recurrence rates were found in children 1-5 years of age and 11-14 years of age. It is likely that the risk factors associated with events in these age groups play a larger role in recurrence than in the infants who overall have higher incident events but fewer recurrent events. Prior studies have shown that adolescents usually have a higher recurrence rate than other children.[4,12] Our study may have missed recurrences in the older adolescent group as their recurrences were more likely to occur

after the age of 18, at which point they would have been treated at an adult institution where VTE is often treated on an outpatient basis and therefore would not be found in Med-Echo. These differences should be more thoroughly evaluated in future studies.

We found that recurrence rates in males were higher than in females, which is similar to findings in adults.[88,110] Using multivariate Cox proportional hazard modeling we were able to demonstrate that the risk of recurrence after incident VTE was higher in those with a chronic disease (HR 2.3; 95% CI 1.2-4.3), central vascular line (HR 1.9; 95% CI 1.0-3.3) or portal vein thrombosis (PVT) (HR 4.1; 95% CI 1.5-11.0) at incident VTE diagnosis. Little data exists on the accuracy of PVT reporting in administrative databases, therefore it is hard to draw conclusions from this finding. Theoretically, since PVT often has more long-term sequelae (e.g. portal hypertension), it may be included in the discharge diagnoses for any hospitalization in the future related to the initial PVT. This may lead to a perceived increased risk of recurrence when it is merely the same event being coded on multiple occasions. This is unfortunately a shortcoming of administrative database studies. Chronic disease, however, has previously been found to be associated with an increased risk of recurrence.[48,118] This information could help to identify which subjects should be considered for prolonged anticoagulation after incident VTE in order to decrease the risk of recurrence. Presence of a central vascular line may very well lead to recurrence if the line remains *in situ* or if concurrent risk factors at the time of incident VTE are still present at the time of recurrence. Based on the current guidelines for anticoagulation in children, it is recommended that those with a VTE and a central venous line remain on prophylactic anticoagulation as long as the central venous line remains in place.[61] How closely these recommendations are followed is unclear.

Central vascular lines may also serve as a proxy for other complex medical conditions that may independently be associated with risk of recurrence.

We found an all-cause mortality rate after incident VTE of 11.4 deaths per 1000 person-years. This represented an overall all-cause mortality risk of 6.4%. Mortality was highest in those under 5 years of age. Several studies have consistently shown in adults that VTE occurrence increases risk of death compared to non-VTE occurrence. For example, among adults with cancer, VTE increases the risk of all-cause death by 3-4 fold.[125] Prior studies have demonstrated variable all-cause mortality risks in children with VTE ranging from 0.5-17%. Given that most prior studies reported all-cause mortality we also reported our mortality risk in this manner and found that our results are on the lower end compared to these previous studies.[4,9,12,16,17] Although likely a rare occurrence, if a child within our cohort died outside of Quebec, without being recorded by the province as having left, they would be missed. It would seem more probable that improved management of co-existent diseases that are often associated with VTE is likely the explanation for this lower risk.

Using a multivariate Cox proportional hazards model we found that the hazard risk for mortality was higher in those with a prior diagnosis of a cancer or BMT (HR 4.66; 95% CI 2.22-9.80), those with a central vascular line at time of incident VTE (HR 2.53; 95% CI 1.13-5.64) and decreased with increasing age (HR 0.93; 95% CI 0.87-0.99). Results from this model must be interpreted with caution as there may have been violation of the proportionality assumption. The fact that cancer or BMT and central vascular line placement, which are often associated with more complex medical problems, showed an increased hazard risk of death seems reasonable. Increasing age as a

decreased hazard for mortality is likely due to the fact that VTE that occurs in in younger children often occurs in the setting of critical illness.

6.2 LIMITATIONS

Several limitations of our study design should be discussed, as these may influence the validity and generalizability of our study results. In our retrospective cohort study, data from an existing database allowed for trends in incidence of VTE to be analyzed, but the overall population changes in risk factors leading to any change in VTE incidence could not be delineated as we lacked a control group of children without VTE to compare the frequency of these risk factors in the general pediatric population. With the use of a retrospective database, one is limited by the information that is available within the database and no supplemental information can be obtained. Administrative databases are compiled for administrative use and not necessarily research use, therefore there is often a lag in time before new data are available. For this reason, we were only able to obtain data from the period of 1994-2004 and newer data was unfortunately not available for this analysis.

In addition, the information from the database itself is subject to misclassification, omissions, and loss to follow up through emigration or death outside of the database's catchment area. In this study, since diagnostic coding was used not only to extract cases of VTE but also to extract risk factor data, death and recurrence data, there was the potential for substantial misclassification, depending on the quality of coding.

Numerous studies were conducted using this administrative VTE database and data extraction was limited to subjects with at least 12 months of membership in the provincial health care system. For this reason, children 0-1 years of age were not included. It was unclear from the data obtained how some cases of VTE in children less than 12 months ended up in our database. It is therefore possible that these cases are not representative of all children less than twelve months with a VTE. Misrepresentation may therefore have occurred if those that made it in the study database were somehow different than those in the source population. However, when comparing baseline sex distribution and mortality risk in our subjects less than one year of age these were similar to published characteristics in other neonatal cohorts, therefore we elected to keep this group in our recurrence calculations and analysis.[14,50]

Information on VTE events in the database was obtained with person-time details. Although the general population of Quebec was the denominator for most of our incidence calculations, in order to not lose information on timing of events, person-years of population at each age level was estimated using linear interpolation between census figures, which were only available every five years. Because the number of events was so small compared to the person-years in the province, the effect of estimation of person-years was unlikely to affect the incidence rates calculated. Also, when time trend analysis was done for categorical year periods, these categories were divided based on census years so that the least amount of variability cause by the estimation would play a role in the trend analysis.

Although prior studies showed variable association between VTE and presence of inherited thrombophilias, its role in recurrence has been shown in prior

studies.[1,4,18,34,36,40-43,89,90,104,126] The difficulty in obtaining data on this important risk factor made it impossible for us to assess the role of this risk factor as a cause of VTE or as a confounder in association with other predictor variables.

The results of our analysis of accuracy to determine database capture of VTE risk factors showed that among children who underwent bone marrow transplant, a code for central venous lines was found in about half of cases, assuming that the diagnostic codes for bone marrow transplant were used in the correct circumstances. As a result, we assume that at least for the risk factor of CVL, as well as perhaps for some or all of the risk factors studied, that administrative data were incomplete which may lead to misclassification.[127] It is unclear from our analysis if this misclassification was differential or non-differential, however since risk factor data were extracted at baseline (time of incident VTE), it is more likely that the misclassification was non-differential (as the outcome, recurrence or death, had not yet occurred).

Subjects within this study were censored at time of death, end of study period or emigration from the province (or at time of first recurrence, in the case of the recurrence cohort). Subjects may have been falsely censored at the end of study if they had left the province without change of their permanent address and/or had a recurrence or died outside of the province. This could lead to differential misclassification if children left the province temporarily for more specialized care at other institutions and had adverse events outside the province.

The definition of recurrence used in this study was re-admission for at least two days duration with a VTE diagnosis, at least 30 days after the incident VTE admission. No information could be obtained from this database on resolution of initial VTE or

verification of discharge diagnosis to ensure those who were classified as having a recurrence actually recurred. If certain types of VTE were more likely to be included in the discharge diagnoses from future hospitalizations or less likely to resolve, this could lead to differential misclassification, which may have occurred in the case of portal vein thrombosis.

Previous analysis of RAMQ coding has found it to be 87% and 78% sensitive diagnosis of DVT and PE, respectively, within a 60-day window period of the event in adults.[101] Due to the lack of information on sensitivity of coding for renal vein thrombosis (RVT), portal vein thrombosis (PVT) and cerebral sinus venous thrombosis (CSVT) within the Med-Echo database it is possible that the retrieval of these types of VTE was less optimal. However, the distribution of VTE subtypes was similar to other pediatric VTE studies.

Our study results showed that central vascular lines were a risk factor for both recurrence and mortality. Although it is possible that central lines truly lead to recurrent VTE and death via complications of VTE, it is more probable that they serve as a proxy for complex medical conditions that lead to VTE and death, despite the lack of evident collinearity in the Cox proportional hazards models. It is possible that characterization of medical conditions into many subdivisions (e.g. chronic disease, cancers, surgeries) led to an inability to assess for true collinearity between these small subcategories and central vascular line placement which is often associated with many of these factors.

As previously mentioned, the RAMQ prescription database only contains information on outpatient prescriptions and only covers approximately 30% of the Quebec population.[105,108] Therefore, precise information on type and duration of

anticoagulation if the patient was hospitalized for a prolonged period of time was not obtainable and any medications given while in hospital prior or following VTE that may have prevented or caused a recurrence was also not accessible. For this, reason prescription data could not be included in our hazards models.

In terms of generalizability of these findings to the rest of Canada, the initial Canadian Childhood Thrombophilia Registry showed that of pediatric VTE cases in Canada most were admitted to either the Hospital for Sick Children in Toronto, Ontario or the Ste. Justine Hospital in Montreal, Quebec. Overall 20% of cases in that registry were from Quebec, and 16% of all general pediatric admissions in Canada were from Quebec.[1] These proportions are consistent with the percent of the Canadian population that lives within Quebec. Based on this it would seem reasonable to expect similar incidence rates to ours would be found amongst children in the rest of the country. Therefore the results of our study are likely generalizable from a population standpoint to the rest of Canada.

However, the question remains whether the results of a study completed in a country with universal healthcare is be applicable to countries that have private healthcare, due to differences in access to medical care, quality of coding, and access to treatments. Although one would hope that access to care for children is equivalent throughout at least North America, the results from this study should be extrapolated with caution to countries or regions that may not have similar healthcare, as different risk factors and competing illnesses may affect rates of VTE, VTE recurrence and mortality.

6.3 CONCLUSIONS

This province-wide evaluation of the burden of pediatric VTE from a comprehensive administrative database, although limited by a number of issues inherent to administrative database research, was nevertheless able to provide many important findings. The overall population-based incidence rate of VTE in children is much higher than previously cited reports, and the incidence rate seems to be stable. Females are more prone to VTE than males. The rate of recurrence, much like in adults, is highest in the first year after incident VTE and continues to occur steadily for several years thereafter. Risk factors such as presence of a central vascular line, chronic diseases, and certain types of VTE may be associated with a higher recurrence rate. Finally, our study showed a lower than expected risk of death in children with VTE.

Our findings highlight the need for future studies to address sex differences in the incidence of pediatric VTE to help determine effective primary thromboprophylaxis strategies in children at high risk for VTE, as well as to determine effective secondary prophylaxis strategies in children at high risk for VTE recurrence.

Chapter 7: References

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APPENDIX

STATA Output For β-Coefficients For Incidence Rate Trends For Time Periods By Age Group

```
-> agecat = 1
Poisson regression                                Number of obs   =          3
                                                  LR chi2(2)      =       0.00
                                                  Prob > chi2     =     1.0000
Log likelihood = -.00121958                       Pseudo R2       =     0.0084
------------------------------------------------------------------------------
    Adjusted |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  timeperiod |
           2 |   .6114505   278.0633     0.00   0.998    -544.3826    545.6055
           3 |   1.093023   258.6995     0.00   0.997    -505.9487    508.1347
             |
       _cons |  -10.82225   223.8835    -0.05   0.961    -449.6259    427.9814
------------------------------------------------------------------------------
-> agecat = 2
Poisson regression                                Number of obs   =          3
                                                  LR chi2(2)      =       0.00
                                                  Prob > chi2     =     1.0000
Log likelihood = -.00097299                       Pseudo R2       =     0.0006
------------------------------------------------------------------------------
    Adjusted |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  timeperiod |
           2 |  -.1825734   268.6684    -0.00   0.999    -526.7629    526.3978
           3 |   .1076427    249.527     0.00   1.000    -488.9563    489.1716
             |
       _cons |  -10.39836   181.1237    -0.06   0.954    -365.3944    344.5977
------------------------------------------------------------------------------

-> agecat = 3
Poisson regression                                Number of obs   =          3
                                                  LR chi2(2)      =       0.00
                                                  Prob > chi2     =     1.0000
Log likelihood = -.00172296                       Pseudo R2       =     0.0001
------------------------------------------------------------------------------
    Adjusted |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  timeperiod |
           2 |   .0831628   186.1906     0.00   1.000    -364.8437      365.01
           3 |  -.0399565   191.9468    -0.00   1.000    -376.2488    376.1689
             |
       _cons |  -9.801112   134.3644    -0.07   0.942    -273.1506    253.5484
------------------------------------------------------------------------------
-> agecat = 4
Poisson regression                                Number of obs   =          3
                                                  LR chi2(2)      =       0.00
                                                  Prob > chi2     =     1.0000
Log likelihood = -.00460869                       Pseudo R2       =     0.0013
------------------------------------------------------------------------------
    Adjusted |      Coef.   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
  timeperiod |
           2 |  -.2997929   106.8049    -0.00   0.998    -209.6336     209.034
           3 |  -.3305784   107.7596    -0.00   0.998    -211.5356    210.8745
             |
       _cons |  -8.487772   69.67808    -0.12   0.903    -145.0543    128.0788
------------------------------------------------------------------------------
```

STATA Output for Cox Proportional Hazard Models and Estat phtest

Recurrence Risk Overall (including non-convergent variables)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
gender	1.512601	.3419616	1.83	0.067	.9711559	2.355917
centralline	1.865632	.5520788	2.11	0.035	1.044571	3.332069
infection	4.301166	4.499636	1.39	0.163	.553487	33.4245
chronicdisease	2.284487	.7502372	2.52	0.012	1.200189	4.348381
CHD1	1.910875	.7873177	1.57	0.116	.8521595	4.284932
cancerBMT	1.177998	.4444596	0.43	0.664	.5623229	2.467764
VTEtype						
2	.3960306	.1869786	-1.96	0.050	.1569819	.9990977
3	1.556755	.5527965	1.25	0.213	.77618	3.122324
4	4.120676	2.06757	2.82	0.005	1.541253	11.01699
5	2.14e-15	7.36e-08	-0.00	1.000	0	.
6	.9485957	.4594047	-0.11	0.913	.3671507	2.450857
7	.673575	.6894277	-0.39	0.699	.0906048	5.007497
CohortH_IndexVTE_AGE	1.036899	.0258728	1.45	0.146	.9874098	1.08887

Recurrence Risk Overall (excluding non-convergent variables)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
gender	**1.512601**	**.3419616**	**1.83**	**0.067**	**.9711559**	**2.355917**
centralline	**1.865632**	**.5520788**	**2.11**	**0.035**	**1.044571**	**3.332069**
infection	**4.301166**	**4.499636**	**1.39**	**0.163**	**.553487**	**33.4245**
chronicdisease	**2.284487**	**.7502372**	**2.52**	**0.012**	**1.200189**	**4.348381**
CHD1	**1.910875**	**.7873177**	**1.57**	**0.116**	**.8521595**	**4.284932**
cancerBMT	**1.177998**	**.4444596**	**0.43**	**0.664**	**.5623229**	**2.467764**
VTEtypea						
2	**.3960306**	**.1869786**	**-1.96**	**0.050**	**.1569819**	**.9990977**
3	**1.556755**	**.5527965**	**1.25**	**0.213**	**.77618**	**3.122324**
4	**4.120676**	**2.06757**	**2.82**	**0.005**	**1.541253**	**11.01699**
6	**.9485957**	**.4594047**	**-0.11**	**0.913**	**.3671507**	**2.450857**
7	**.673575**	**.6894277**	**-0.39**	**0.699**	**.0906048**	**5.007497**
CohortH_IndexVTE_AGE	**1.036899**	**.0258728**	**1.45**	**0.146**	**.9874098**	**1.08887**

```
estat phtest, log detail
------------------------------------------------------------
                  |       rho           chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      gender      |      0.17549         2.61        1         0.1062
      centralline |      0.10175         0.86        1         0.3526
      infection   |      0.03424         0.10        1         0.7474
      chronicdis~e|      0.20062         3.66        1         0.0558
      CHD1        |      0.13320         1.62        1         0.2036
      cancerBMT   |     -0.06144         0.36        1         0.5501
      1b.VTEtype  |            .            .        1              .
      2.VTEtype   |      0.14722         1.86        1         0.1731
      3.VTEtype   |      0.16350         2.24        1         0.1349
      4.VTEtype   |      0.17818         2.89        1         0.0889
      5.VTEtype   |      0.15089         0.00        1         1.0000
      6.VTEtype   |     -0.01733         0.03        1         0.8664
      7.VTEtype   |     -0.10024         0.89        1         0.3462
      CohortH_In~E|      0.22861         4.53        1         0.0334
      ------------+-----------------------------------------------------
      global test |                     18.20       13         0.1500
      ------------------------------------------------------------
```

Recurrence Risk in Females ONLY (including non-convergent variables)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
chronicdisease	2.047006	.9040976	1.62	0.105	.8613316	4.864832
cancerBMT	.9111258	.5309992	-0.16	0.873	.2907386	2.855315
centralline	2.538784	1.042212	2.27	0.023	1.135517	5.676202
pregnancy	2.98e-17	5.43e-09	-0.00	1.000	0	.
infection	3.050249	3.245922	1.05	0.295	.3789039	24.55508
VTEtype						
2	.2161673	.1587193	-2.09	0.037	.0512626	.9115464
3	1.176986	.5787874	0.33	0.740	.4489417	3.085694
4	2.690835	2.056497	1.30	0.195	.6016559	12.03445
5	9.15e-18	6.44e-09	-0.00	1.000	0	.
6	.7616269	.5666609	-0.37	0.714	.177189	3.273769
7	1.25e-17	3.06e-09	-0.00	1.000	0	.
CohortH_IndexVTE_AGE	1.063462	.0371342	1.76	0.078	.9931153	1.138792
CHD1	1.859351	1.186123	0.97	0.331	.5325499	6.49176

Recurrence Risk in Females ONLY (excluding non-convergent variables)

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
centralline	2.575569	1.06279	2.29	0.022	1.147179	5.782495
infection	3.077083	3.275741	1.06	0.291	.3819299	24.79104
chronicdisease	2.076217	.9191379	1.65	0.099	.8718611	4.944226
CHD1	1.872963	1.19604	0.98	0.326	.5357567	6.547732
cancerBMT	.923816	.5393213	-0.14	0.892	.2942092	2.900779
VTEtypeb						
2	.2110652	.1549554	-2.12	0.034	.050061	.8898845
3	1.206161	.5937355	0.38	0.703	.4596208	3.165273
4	2.739044	2.095144	1.32	0.188	.611645	12.26587
6	.7756244	.5773226	-0.34	0.733	.1803326	3.33602
CohortH_IndexVTE_AGE	1.06138	.0370914	1.70	0.088	.9911161	1.136625

```
. estat phtest, log detail
      Test of proportional-hazards assumption
      Time:  Log(t)
      ------------------------------------------------------------------
                  |       rho           chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      chronicdis~e|      0.12879         0.82        1         0.3663
      cancerBMT   |     -0.01463         0.01        1         0.9197
      centralline |      0.09543         0.42        1         0.5147
      pregnancy   |     -0.09796         0.00        1         1.0000
      infection   |      0.02907         0.04        1         0.8420
      1b.VTEtype  |            .            .        1              .
      2.VTEtype   |      0.04019         0.08        1         0.7815
      3.VTEtype   |      0.18141         1.45        1         0.2281
      4.VTEtype   |      0.29034         3.85        1         0.0499
      5.VTEtype   |      0.24013         0.00        1         1.0000
      6.VTEtype   |     -0.06797         0.22        1         0.6369
      7.VTEtype   |     -0.10835         0.00        1         1.0000
      CohortH_In~E|      0.24333         2.18        1         0.1402
      CHD1        |      0.09292         0.37        1         0.5443
      ------------+-----------------------------------------------------
      global test |                      7.91       13         0.8496
      ------------------------------------------------------------------
```

Mortality Risk

_t	Haz. Ratio	Std. Err.	z	P>|z|	[95% Conf.	Interval]
gender	1.368176	.4841906	0.89	0.376	.6837634	2.73765
surgery	1.416529	.555919	0.89	0.375	.656402	3.056897
cancerBMT	4.663982	1.767717	4.06	0.000	2.218907	9.803354
centralline	2.529448	1.03598	2.27	0.023	1.133447	5.644824
CohortH_IndexVTE_AGE	.929289	.0307605	-2.22	0.027	.8709137	.9915772
CHD1	.9157236	.5191667	-0.16	0.877	.3014243	2.781958

```
. estat phtest, log detail
      Test of proportional-hazards assumption
      Time:  Log(t)
      ------------------------------------------------------------------
                  |       rho            chi2       df       Prob>chi2
      ------------+-----------------------------------------------------
      gender      |     -0.04592          0.07        1          0.7843
      surgery     |     -0.24376          2.04        1          0.1535
      cancerBMT   |     -0.07806          0.21        1          0.6465
      centralline |      0.31442          4.75        1          0.0293
      CohortH_In~E|      0.22827          2.61        1          0.1060
      CHD1        |      0.41771          5.34        1          0.0209
      ------------+-----------------------------------------------------
      global test |                      12.36        6          0.0545
      ------------------------------------------------------------------
```