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ORIGINAL RESEARCH

Measures of risk and their relationship to the relative size of a high-risk group: application to medical thromboprophylaxis

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Background: The aim of this study was to establish the meaning of "high-risk" when the subgroup so defined by risk factor analysis is a substantial proportion of the population. This is clinically important when patients, deemed to be at high risk as a result of risk factor analysis, become eligible for a clinical intervention to decrease the risk, especially if the intervention has adverse effects. One example in clinical practice is the assessment of eligibility for medical thromboprophylaxis.

Methods: Equations were derived relating risk and the proportion of the population (*F*) deemed to be at high risk on risk factor analysis, based on the formula for weighted average. The equations were validated for the population of medical inpatients at high- or low-risk of thromobembolic events using a spreadsheet model of thrombosis risk containing known risk factors for venous thromboembolism in this population.

Results: The validated equations define an upper limit of absolute and incremental risk (risk relative to the whole population) in the high-risk group that is a function of or equal to *1/F*, respectively. The added risk in the high-risk group declines to zero as *F* tends to 1, because it must be balanced by the diminishing risk in the progressively smaller low-risk group while maintaining the population average.

Conclusion: The results of this study have implications for the validity of the published eligibility criteria for medical thromboprophylaxis.

Keywords: population risk, relative risk, risk factors, subgroups, thromboprophylaxis

Introduction

Many medical conditions are associated with background factors that can be used to assess the likelihood of future disease in individuals. For example, thrombosis arising during a hospital admission has known risk factors, and these may be used to define eligibility for thromboprophylaxis. They include a previous history of deep vein thrombosis (DVT), comorbidities such as malignancy, and increasing age.[1,2] Though the factors are well defined, doubts have been expressed over the scientific basis of thromboprophylaxis when applied to medical patients.[3–7]

Under longstanding Australian guidelines,[8] which are similar to those from the UK[9] and US,[10] 82% of medical inpatients have at least one risk factor for thrombosis, and are thereby defined as being at "high-risk" and thus eligible for thromboprophylaxis.[11] Under newer guidelines[12] interpreted broadly, the figure for eligibility is even higher (88%, net of bleeding contraindications).[13] By contrast, the clinical condition to be prevented affects only 0.3%–1.6% of medical inpatients.[1,13–15] This paper explores the nature of this paradox and the implications for medical thromboprophylaxis, using an epidemiological approach based on risk factor modeling.

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Materials and methods

Derivation of equations

Equations were derived from the expression for weighted average risk in a population divided dichotomously into high-risk and low-risk subgroups according to the presence of risk factors. Thus, for absolute risk:

$$\text{Population average risk} = \bar{R} = F_H \cdot R_H + (1 - F_H) \cdot R_L \quad (1)$$

where $\bar{R}$, R_H, and R_L are the risks of thromboembolism in the total population and the two subpopulations, respectively, and F_H is the proportion of the population at "high risk". The expression for weighted average does not apply to relative risk (RR) as usually defined (the risk ratio in the high-risk and low-risk groups) but it does when the risk in the high-risk group is expressed relative to that in the population as a whole, where the standardized risk is 1. This measure of risk is defined as "incremental risk" (D). When the high-risk group is small, $D \approx RR$ because of the size of the complementary low-risk group approximates to the population as a whole. Using incremental risk:

$$\text{Population standardised risk } = 1 = F_H \cdot D_H + (1 - F_H) \cdot D_L \quad (2)$$

in which the subscripts have the same meaning as before (for D_L, the increment is negative).

Relationship of R_H and D_H to F_H

The maximum value of both R_H ($R_H^{\max}$) and D_H ($D_H^{\max}$) in Equations 1 and 2, respectively, are reached as R_L and D_L tend towards 0, the limiting minimum value in the low-risk subgroup. Thus from Eq. 1

$$R_H^{\max} = \frac{\bar{R}}{F_H} \quad (3)$$

and from Eq. 2,

$$D_H^{\max} = \frac{1}{F_H} \quad (4)$$

Validation of equations

Validation was required to check that the expression for weighted average applies to both Equations 1 and 2 and also to demonstrate the validity and accuracy of D_H as a proxy for RR. Risk factor contributions to venous thromboembolism in the population of medical inpatients was modeled using a spreadsheet (Microsoft Excel). Because thrombotic risk factor weights are reported variably in the literature as relative risk, odds ratios, or hazard ratios (Table 1), which cannot be compared directly or interchanged easily, empirical values of D_H were used for each factor, while maintaining the known relativities (Table 1). Values for D_H were also constrained by the need to ensure that the upper limit of incidence for clinical venous thromboembolism reported by Edelsberg et al (1.59%)[1] was maintained in the model.

Model operation

Each risk factor, the corresponding value for D_H, and the proportion of the population affected (F_H) were added to the model in order of decreasing statistical weight (Table 2). Finally, the factor "age > 60 years" was added to bring the final value of F_H to 0.82, as in the Australian guidelines.[11] The model output was thrombotic event numbers, which were calculated for each risk factor and cumulatively in both the high-risk and complementary low-risk groups. This provided estimates of event rates in both groups, and RR was calculated. D_H and RR for each risk factor were compared by linear regression analysis. The expression for weighted average was applied to the model output variables to confirm the validity of Equations 1 and 2 as above. For simplicity, the occurrence of more than one risk factor in individuals was ignored. Though patients with combinations of strong risk factors are at compounding risk of thrombosis, their exclusion does not affect the model outputs in terms of confirming the validity of Equations 3 and 4.

Data sources

Risk factors and their relative statistical weightings (variably expressed) were obtained from three studies,[1,2,16] as summarized in Table 1. Thrombotic event rates by subgroup were calculated based on a population average of 1.59%, representing the highest reported symptomatic venous thromboembolism rate in medical inpatients.[1] The model was populated with the number of adult medical patients across Australia who had an overnight hospital admission during the year 2010–2011 (n = 2,138,418), derived from data published by the Australian Institute of Health and Welfare.[13,17]

Results

Equations 1 and 2 remained valid at each stage of the accumulation of risk factors in the spreadsheet model (Table 3) and were independent of risk factor weighting and the proportion of the population affected by each risk factor. For both absolute and incremental risk, the relationship between risk

Table 1 Details of three studies reporting risk factors for venous thrombosis and pulmonary embolus in medical inpatients and the general population

	Heit et al[16]	Edelsberg et al[1]	Alikhan et al[2]
Study type	Retrospective nested case-control	Retrospective cohort	Clinical trial
Study setting	General population	Hospital inpatients	Hospital inpatients
Patients (n)	1250	92,162	575
Risk measure	OR	HR	RR, OR
Disease ascertainment	Records of "first lifetime definite DVT event" from 1976–1990 held by the Rochester Epidemiology project	Post-discharge morbidity coding using pharmacy records	Doppler ultrasound in all patients
Disease type	Clinical	Clinical	Subclinical
Comment	Not the population of interest but provides weightings for nonsurgical risk factors	Included ICU patients but otherwise is the population of interest	Patients selected for increased risk of developing DVT; OR probably derived from groups given placebo or 20 mg of enoxaparin (not explicitly stated)

Note: The studies reported thrombosis risk as different measures.
Abbreviations: ICU, intensive care unit; DVT, deep vein thrombosis; OR, odds ratio; HR, hazard ratio; RR, relative risk.

and F_H is one of simple reciprocity. Validity increases as F_H tends towards 1, because R_L and D_L increasingly approach zero. Values of $D_H^{\max}$ and $R_H^{\max}$ for medical thromboprophylaxis are shown in Table 4. $R_H^{\max}$ was calculated assuming $\bar{R} = 0.0159$ (see Materials and methods section).

There was a close linear relationship ($r^2 = 0.99355$) between D_H and RR for each factor considered individually (Figure 1). Hence $D_H \approx RR_H$ for each risk factor (Figure 1). However, the same measures of risk assessed cumulatively diverged progressively as F_H increased. Incremental risk declines towards one, but RR increases substantially (Table 3) to the point at which the known incidence of clinical events is reached, in this case (under the assumptions of the model) at $F_H = 0.89$. If 82% of medical inpatients are deemed to be at "high" risk, the maximum incremental risk is no greater than 1/0.82, or 1.22.

Discussion

The spur to this study was the question of the meaning and significance of a claim that over 82% of medical inpatients are at "high risk" of a thrombotic event during an admission.[11] On the surface, this claim seems plausible, but on deeper enquiry questions emerge. The problem lies in the way the risk factor analysis is carried out and applied without regard to the

Table 2 Risk factors and risk factor weights for thrombotic disease in the community (Heit et al[16]) and in hospital medical patients (Edelsberg et al[1] and Alikhan et al[2]) expressed in various measures after multivariate Cox proportional hazards (HR) or multivariate logistic regression analysis (OR) of candidate risk factors. Also shown are the empirical incremental risks (*D*) used on the modeling

Risk factors	Risk weights in above units (multivariate analysis only)			*D*, this study
	Heit et al	Edelsberg et al	Alikhan et al	
	OR	HR	OR	
Recent surgery	21	1.81		1.4
Neoplasm with chemotherapy	6.53			
Neoplasm without chemotherapy	4.05			
Neoplasia, but chemotherapy unspecified	Not reported	1.67	1.62	1.6
Prior central venous catheter or pacemaker	5.55			
Prior DVT or VTE	N/A	6.14	2.06	1.8
Prior superficial thrombosis	4.32			
Neurological disease with paresis	3.04	1.35		1.1
Varicose veins	0.88–4.19 (age dependent)			
CHF	1.36	1.72		1.15
Acute infectious disease			1.74	
Age > 75 years			1.03	1.01
Peripheral vascular disease		1.68		
COPD during admission		1.33		
Post-thrombotic syndrome		2.00		

Abbreviations: CHF, congestive heart failure; COPD, chronic obstructive pulmonary disease; DVT, deep vein thrombosis; OR, odds ratio; HR, hazards ratio; RR, relative risk; VTE, venous thromboembolism; D, incremental risk; N/A, not available.

Table 3 (columns 1–9) Absolute, incremental (see Materials and methods section), and relative risk in a subpopulation of medical patents at high risk of venous thrombosis, and the calculated corresponding risks in the complementary low-risk subgroup

Factor	High risk group								
	Incremental risk D_H	F_H	n	Cum F_H	Cum n	DVT	Cum DVT	Cum rate	Cum D_H
	Table 2	Nominal	Col2 × N	∑F	∑n	Col 3 × Col1 × R_T	∑DVT	Col7/Col5	Col8/R_T
DVT history	1.80	0.05	106921	0.05	106921	3060	3060	0.029	1.800
Cancer	1.60	0.09	192458	0.14	299379	4896	7956	0.027	1.671
Surgey within 30 d	1.40	0.01	21384	0.15	320763	476	8432	0.026	1.653
Peripheral artery disease	1.30	0.002	4277	0.152	325040	88	8521	0.026	1.649
CHF	1.15	0.147	314347	0.299	639387	5748	14268	0.022	1.404
Neurological paresis	1.10	0.1	213842	0.399	853229	3740	18009	0.021	1.327
Age > 60 alone	1.01	0.421	900274	0.82	1753503	14386	32394	0.018	1.162

Notes: The high-risk group was defined by cumulative application of risk factors as described by Edelsberg et al[1] in descending order of relative risk, plus the factor "age > 60 years" as in Australian[8] and UK[9] guidelines, to bring the total eligibility[8] to 82% (see text). Row 3 shows column reference numbers for calculations detailed in Row 4. The fraction of the population with each risk factor (F_H) and the cumulative F_H as each risk factor is added are shown. Calculations pertain to the total general medical inpatient admissions in Australia for 2010–2011 (n = 2,138,418)[13,17] where the absolute risk of a venous thrombotic event R_T is assumed to be 0.0159.[1] For this number of admissions, the total number of thrombotic events is estimated to be 34,001. Under the heading "Test", WAR = result of calculation of weighted average for subgroup risk by F_H, ie, $[F_H \cdot R_H + (1 - F_H) \cdot R_L]$; WAD = result of calculation of weighted average for subgroup incremental risk by D_H, ie, $[F_H \cdot D_H + (1 - F_H) \cdot D_L]$. The calculations result in $\overline{R} = 0.159$ and population RR = 1, respectively, at each stage of the cumulative addition of risk factors, thereby confirming the applicability of weighted average as the basis of Equations 1 and 2 (see text) and for deriving the relationship between R_H, D_H, and F_H. This result is independent of N, F_H, $\overline{R}$ or inclusion of alternative, additional, or combined risk factors, assuming that $\overline{R} = 0.0159$ and that $N_T = 34{,}001$ in the year under study. Columns 17 and 18 show calculated *RR* for each risk factor individually ("RR") and for the aggregate high-risk group at each stage of the development of the model ("RR_{cum}").
Abbreviations: CHF, congestive heart failure; cum, cumulative; DVT, deep vein thrombosis; RR, relative risk.

meaning of "high risk" or relative risk when applied to the majority of the population in question. "Relative risk" is the risk ratio of high-risk and low-risk subgroups. The reciprocal ratio has mathematical validity but is clinically meaningless, and the unstated implication is that the high-risk group is relatively small. When F_H becomes higher than 0.5, *RR* becomes increasingly dominated by the progressively smaller size and decreasing event numbers in the low-risk group, which is represented in the denominator. This problem is shown here as the widening discrepancy between incremental and relative risk as F_H tends towards one (Table 3). This study shows that at high levels of F_H, relative risk becomes an untenable concept and only incremental risk has clinical meaning. However, the value of incremental risk is constrained by the relationships described by Equations 3 and 4.

Established Australian guidelines for medical thromboprophylaxis[8] or new Australian National Health and Medical Research Council guidelines[12] interpreted broadly,[13] define

Table 4 Estimated maximum values of relative risk for thrombosis, and absolute risk where the population average risk of thrombosis is 0.0159, given by Equations 3 and 4 (see text), by the proportion of the population defined as being at high risk and hence eligible for thromboprophylaxis

Proportion at high risk and eligible	Incremental risk	Absolute risk (%)
0.2	5.00	7.95%
0.3	3.33	5.30%
0.4	2.50	3.98%
0.5	2.00	3.18%
0.6	1.67	2.65%
0.7	1.43	2.27%
0.8	1.25	1.99%
0.9	1.11	1.77%

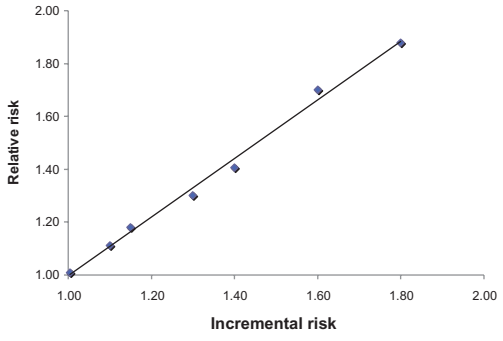

Figure 1 Linear regression of incremental risk of thrombosis (ie, risk in the high-risk group relative to the population of medical inpatients as a whole) on relative risk (risk ratio in the high-risk and low-risk groups) as risk factors for venous thrombosis are added to the spreadsheet model (see Materials and methods section).
Note: The values pertain to each risk factor individually, not the cumulative effect as each risk factor is added (see text).

Table 3 (columns 10–18)

Low risk group					Test		Other	
DVT	**n**	F_L	**Rate**	D_L	**WAR**	**WAD**	**RR**	RR_{Cum}
32,076 – Col7	**N – Col5**	**Col11/N**	**Col10/Col11**	**Col13/R_T**	**See legend**	**See legend**		
30941	2031497	0.95	0.0152	0.957895	0.0159	1	1.88	1.88
26045	1839039	0.86	0.0142	0.890698	0.0159	1	1.70	1.88
25569	1817655	0.85	0.0141	0.884706	0.0159	1	1.41	1.87
25480	1813378	0.85	0.0141	0.883726	0.0159	1	1.30	1.87
19732	1499031	0.70	0.0132	0.827889	0.0159	1	1.18	1.70
15992	1285189	0.60	0.0124	0.782612	0.0159	1	1.11	1.70
1606	384915	0.18	0.0042	0.262472	0.0159	1	1.01	4.43

about 82%–88% of the medical inpatient population as being at high risk and therefore eligible for low molecular weight heparin. These guidelines closely approximate the National Institute for Health and Clinical Excellence guidelines in the UK[9] and the American College of Chest Physician guidelines in the US,[10] so similar proportions are expected in these jurisdictions also. Equation 3 shows that the theoretical maximum possible incremental risks at $F_H = 0.82$ and 0.88 are 1.22 (1/0.82) and 1.14 (1/0.88), respectively. Therefore, when the population average risk is 1.59%, the maximum absolute risks given by Equation 3 are 1.94% (0.0194) and 1.81% (0.0181), respectively. This calculation uses the highest reported incidence of clinical thrombotic events in medical inpatients to avoid overstating the arguments made here against current thromboprophylaxis guidelines, but in fact most estimates using direct prospective observation or morbidity coding are in the range of 0.3%–0.5%. Absolute event rates for these lower incidence estimates can be derived similarly. The clinical validity of a guideline that provides for an almost universal intervention at low values of incremental and absolute risk is questionable. Within the so-called "high-risk" group, some individuals will be at higher than the average risk in that subgroup, because the factor they bear (eg, previous thrombosis) has greater than average statistical weight, but some will therefore be at lesser risk. Given that low molecular weight thromboprophylaxis involves hazard (major and minor bleeding),[18] it is more appropriate to restrict prophylaxis to a smaller subpopulation of patients with risk factors of greater weight.[13,19] On the basis of Equations 3 and 4, common risk factors which cause F to be > 0.5 must have low statistical weightings.

The numbers and risks but not the mathematical relationships described here change dramatically if asymptomatic thrombotic events discovered by ultrasound or venography (as in the clinical trials of efficacy) are the basis of the estimates. For medical patients, this risk is reported to be about 17%.[8,20] All medical thromboprophylaxis guidelines are based on and justified by subclinical event rates, but no rationale for using this datum has been published. Indeed, the House of Commons Report,[20] which underpinned the UK approach to thromboprophylaxis, quoted a 17% rate but omitted to state that this included asymptomatic events. That report, like the Australian[8] and American College of Chest Physicians[10] guidelines, which have also failed to explore this aspect in detail, may be reasonably considered to have exaggerated the problem of venous thrombosis in medical patients. Given the incidence of symptomatic DVT, the degree of exaggeration is 10–30-fold. This figure is similar to recent estimates provided

by Herzig and Rothberg.[7] To the author's knowledge, thromboprophylaxis is the sole example in medical practice where the need for drug prophylaxis is based on the incidence of an asymptomatic condition that proceeds to symptomatic disease in only a small proportion of patients. All symptomatic thrombi must form via an initial asymptomatic phase, but the rationale for prophylaxis rests on the incidence of the symptomatic disease, not its pathogenesis.

In the present modeling, "age > 60 years" was added as described in the Australian guidelines to the list of risk factors obtained from Edelsberg et al[1] to bring the final F_H to that found when the Australian guidelines are applied. However, age is a weak risk factor, with OR of only 1.03 (Table 2). The validity of "age > 60 years" (or any other age-related factor) as a criterion for thromboprophylaxis is questionable, especially because age is also a risk factor for bleeding during anticoagulant treatment.[21–23] Age contributes more than any other factor to the final tally of 82% eligibility under the Australian guidelines. Inclusion of this weak risk factor is likely to cause substantial misallocation of patients who are not at high risk, but who may suffer hemorrhagic complications of prophylaxis, to the high-risk group. Giving medical thromboprophylaxis on the grounds of age alone is hazardous and unnecessary. It has been shown[13] that when risk factors are applied according to statistical weighting, the eligibility for thromboprophylaxis falls to 20%–40%.

This study has a limitation in that it does not provide information on the actual values for incremental risk at high values for F_H. It merely shows that the value is subject to an upper limit. Because clinical events will occur occasionally in the low-risk as well as high-risk groups, R_L (and D_L) > 0. Thus $R_H = k \cdot R_H^{\max}$ where k is unknown but has a value between 0 and 1. Thus, by substitution in equation 4, $R_H = \bar{R} \cdot \frac{k}{F_H}$. Note that if $k < F_H$ then $R_H < \bar{R}$ which is not possible, hence $k \geq F_H$. Thus in the high-risk group defined by the Australian guidelines, where $F_H = 0.82$, R_H is no more than 18% different from $R_H^{\max}$.

Here it is shown that when a high proportion (F_H) of a population is deemed to be at "high" risk, the average level of incremental risk in that group diminishes according to the reciprocal of F_H, and that the absolute risk is the reciprocal multiplied by the population average risk. At 82% eligibility, the incremental risk cannot exceed 1.22, but the intrinsic hazard of major bleeding during prophylaxis remains.[18,19] The epidemiological approach adopted here casts further doubt on the validity of certain published medical thromboprophylaxis guidelines, provides support to authors who have questioned their scientific basis, and underlines the need for empirical guidelines or computer-based algorithms[24] in which thrombotic risk and its reversal are considered quantitatively.

Disclosure

The author reports no conflict of interest in this work.

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