Risk of testicular cancer after vasectomy: cohort study of over 73 000 men

Henrik Møller, Lisbeth B Knudsen, Elsebeth Lynge

Abstract

***Objective*—To confirm or refute reports that vasectomy may increase the risk of cancers of the testis and prostate.**

***Design*—Computerised record linkage study of cohort of men with vasectomy and comparison of cancer rates with those in the whole Danish population; manual check of all records of patients with testicular and prostate cancer diagnosed within the first year of follow up.**

***Setting*—Denmark 1977-89.**

***Subjects*—Cohort of 73 917 men identified in hospital discharge and pathology registers as having had a vasectomy for any reason during 1977-89.**

***Main outcome measures*—Observed incidences of testicular, prostate, and other cancers up to the end of 1989.**

***Results*—The overall pattern of cancer incidence in the study cohort was similar to that expected nationally. No increased incidence in testicular cancer was observed (70 cases; standardised morbidity ratio 1·01 (95% confidence interval 0·79 to 1·28)). The incidence during the first year of follow up was also close to that expected (nine cases; standardised morbidity ratio 0·80 (0·36 to 1·51)). The incidence of prostate cancer was not increased (165 cases; standardised morbidity ratio 0·98 (0·84 to 1·14)).**

***Conclusions*—The incidence of testicular cancer in men with vasectomy is no higher than in other men. Vasectomy does not cause testicular cancer and does not accelerate the growth or diagnosis of pre-existing testicular neoplasms. Data concerning a causal relation between vasectomy and prostate cancer were inconclusive.**

Introduction

Vasectomy is a simple and effective means of contraception which is commonly and increasingly being used in many parts of the world.[1-3] Several large cohort studies have failed to show any negative influence of vasectomy on overall mortality[4-6] or on the overall hospitalisation rate.[7-11]

Reports from Ireland and Scotland, however, have suggested that the risk of testicular cancer may be increased after vasectomy.[12 13] Furthermore, several studies have suggested that vasectomised men may have an increased incidence of prostate cancer.[14-20] By contrast, other studies have not found raised incidences of testicular or prostate cancer after vasectomy.[4-8 21-27]

There are difficulties in interpreting the results of available studies. These arise from the possibility of information bias in case-control studies,[21] from the use of self reports by cohort members or their wives to identify prostate cancer cases,[27] and from small numbers in studies finding an increased incidence of testicular cancer.[28] Our investigation attempted to overcome these difficulties by including a large enough cohort of vasectomised men to allow a detailed, quantitative assessment of the risk of cancer. Information on vasectomy was derived from hospital register data collected before the occurrence of cancer, thereby eliminating the possibility of information bias, and cancer cases were identified in a nationwide cancer register.

The study was designed primarily to investigate testicular cancer but, in order to provide overall documentation of cancer occurrence, results are presented for all sites of cancer for which 10 or more cases were observed.

It has been argued that vasectomy may accelerate the growth of an existing testicular cancer[12 13] or act at a late stage in carcinogenesis by facilitating the transition from non-invasive testicular carcinoma in situ to invasive testicular cancer.[29] For testicular cancer the study addressed two questions: is the incidence of testicular cancer increased in vasectomised men and is the increase (if any) particularly noticeable in the first years after vasectomy?

Subjects and methods

The study was based on a computerised linkage among four population based registers in Denmark. These registers use the same personal identifier which is unique to every resident in Denmark.

Since 1977 the Danish Hospital Discharge Register has recorded all hospital admissions in Denmark by dates of admission and discharge, diagnoses, and operations. The register is essentially complete from 1978 and includes all inpatient admissions regardless of the duration of stay—that is, from less than one day to several days. Treatment and other services provided on an outpatient basis are not recorded. In the period investigated vasectomies were usually performed during a one day admission and most departments reported these admissions to the register. Some departments, however, regarded vasectomy as an outpatient service and did not inform the register.

Computerised pathology registration was instituted from various dates in Danish counties. Pathology registers cover all specimens which have been analysed in hospital pathology departments within a county. It is routine at vasectomy to send the removed tissue for examination at the pathology department. In counties with pathology registers it is thus possible to identify all vasectomised men (whether treated as inpatients or as outpatients) from these registers.

The Danish Central Population Register is a computerised record of everyone who was alive in 1968 or who was born in or immigrated into Denmark thereafter and includes information about vital status and date of emigration or death. The Danish Cancer Register covers all cases of cancer in Denmark diag-

Danish Cancer Society, DK-2100 Copenhagen, Denmark
Henrik Møller, *epidemiologist*
Elsebeth Lynge, *epidemiologist*

Danmarks Statistik, DK-2100 Copenhagen, Denmark
Lisbeth B Knudsen, *epidemiologist*

Correspondence to:
Dr Elsebeth Lynge, Danish Cancer Society, Strandboulevarden 49, DK-2100 Copenhagen Ø, Denmark.

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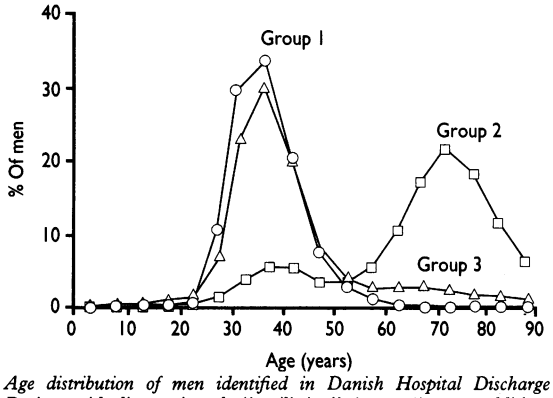
nosed since 1943, based on notifications from hospital departments, specialists, and necropsy reports. Additional case identification is from death certificates.

The Hospital Discharge Register for 1977 to 1989 was searched for all discharges which included the diagnostic code "male sterilisation" or the operation code "vasectomy." This procedure identified 64 817 men with valid identifiers. The pathology registers of five counties (Viborg and Frederiksborg (1977-89), Fyn (1979-89), and Storstrøm and Århus (1981-9)) were searched for all histological examinations of ductus deferens. By this means a further 9100 men were identified. The resulting list of 73 917 men was linked with the Central Population Register to provide vital status on 31 December 1989 or date of emigration or death. Cases of cancer occurring among the cohort members were identified by record linkage with the Danish Cancer Register. All records for men with testicular or prostate cancer diagnosed within the first year of follow up were checked manually.

Three groups of men were identified—men with a diagnostic code indicating male sterilisation (group 1; sterilisation), men with an operation code indicating vasectomy but with no diagnostic code for sterilisation (group 2; other vasectomy), and men identified only in the pathology registers with tissue code "ductum deferens" (group 3; pathology only). The age distribution of the three groups is shown in the figure. Men



Age distribution of men identified in Danish Hospital Discharge Register with diagnostic code "sterilistion" (group 1), men additionally identified in register with operation code "vasectomy" (group 2), and men additionally identified in pathology registers with tissue code "ductus deferens" (group 3)

in groups 1 and 3 had an identical age distribution with mode in the 30s, the predominant age range being 25-49 years. Most of these men had presumably been vasectomised for contraception. The age distribution in group 2 was bimodal with a small peak around 25-49 years of age and a larger peak after 60. The early peak probably represented men who were vasectomised for contraception. The later peak probably reflected use of vasectomy for other reasons, primarily in conjunction with transurethral prostate resection for benign prostatic hyperplasia, in which vasectomy may prevent epididymitis.

The incidence of cancer among cohort members was compared with the incidence in the Danish population as a whole by using indirect standardisation for age and period, both in five year intervals.[30] Observed cancer cases and person years at risk were counted from the date of hospital discharge or pathological examination to the date of death or emigration or 31 December 1989, whichever occurred first. Standardised morbidity ratios were estimated as the ratio of observed to expected numbers of cases and used as the measure of association. Confidence intervals (95%) were calculated assuming a Poisson distribution.

Results

Table I gives the follow up details of the cohort. The observed numbers of cancer cases and the calculated standardised morbidity ratios are presented in table II. Only a few standardised morbidity ratios were significantly increased or decreased.

TESTICULAR CANCER

The overall incidence of testicular cancer was as expected (70 cases; standardised morbidity ratio 1·01 (95% confidence interval 0·79 to 1·28)). In group 1 the incidence was also as expected (58 cases; standardised morbidity ratio 0·95 (0·72 to 1·23)). In group 2 only two cases of testicular cancer were observed. A slightly but non-significantly raised risk was found in group 3 (10 cases; standardised morbidity ratio 1·62 (0·77 to 2·98)).

The incidence of testicular cancer is analysed in more detail in table III. In group 1 the incidence was close to expected within the strata of age and time after operation. In the three to four years after entry the standardised morbidity ratio was 1·30, but this slight excess was not significant (95% confidence interval 0·76 to 2·08). In the period immediately after operation the incidence of testicular cancer was lower than expected (four cases; standardised morbidity ratio 0·42 (0·11 to 1·06)). In group 3 the observed number of cases was small in strata of age and time after pathological examination. An excess risk of testicular cancer seen in the first year of follow up did not reach significance (four cases; standardised morbidity ratio 3·05 (0·83 to 7·82)). For the three groups together there was no increased incidence in the first year of follow up (nine cases; standardised morbidity ratio 0·80 (0·36 to 1·51)).

PROSTATE CANCER

The incidence of prostate cancer (table II) was close to expected in group 1 (12 cases; standardised morbidity ratio 0·94 (95% confidence interval 0·49 to 1·65)) and group 2 (137 cases; standardised morbidity ratio 0·96 (0·80 to 1·13)). In group 3 a non-significant tendency was seen towards an increased incidence (16 cases; standardised morbidity ratio 1·29 (0·74 to 2·10)). Further analyses found no increase in incidence with time after entry (data not shown).

CANCER AT OTHER SITES

There were only a few, rather weak tendencies towards increased incidences of the other cancers listed

TABLE I—*Numbers of subjects and person years, mean duration of follow up, and observed numbers of cases of testicular cancer, prostate cancer, and cancer at all sites in men identified in Danish Hospital Discharge Register with diagnostic code "male sterilisation" (group 1), men additionally identified in register with operation code "vasectomy" (group 2), and men additionally identified in pathology registers with tissue code "ductus deferens" (group 3)*

Group	No of men	No of person years	Mean follow up (years)	Observed No of cases: Testicular cancer	Prostate cancer	All cancers
1 (Sterilisation)	57 931	397 099	6·9	58	12	698
2 (Other vasectomy)	6 886	42 804	6·2	2	137	964
3 (Pathology only)	9 100	42 510	4·7	10	16	149
Total	73 917	482 413	6·5	70	165	1811

TABLE II—*Observed numbers of cancer cases and standardised morbidity ratios (95% confidence intervals) in 73 917 men categorised in three groups based on hospital discharge and pathology register data, 1977-89*

Cancer site	Group 1 (sterilisation)		Group 2 (other vasectomy)		Group 3 (pathology only)		Total	
	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio
All sites	698	0·94 (0·87 to 1·01)	964	1·04 (0·98 to 1·11)	149	0·99 (0·84 to 1·16)	1811	0·99 (0·95 to 1·04)
Mouth and pharynx	20	0·61 (0·37 to 0·94)*	21	1·04 (0·65 to 1·60)	3	0·62 (0·13 to 1·80)	44	0·76 (0·55 to 1·02)
Oesophagus	3	0·37 (0·08 to 1·07)	6	0·63 (0·23 to 1·36)	1	0·58 (0·01 to 3·24)	10	0·51 (0·25 to 0·94)*
Stomach	19	0·84 (0·51 to 1·32)	58	1·25 (0·95 to 1·61)	4	0·73 (0·20 to 1·87)	81	1·09 (0·86 to 1·35)
Colon	31	0·83 (0·56 to 1·18)	87	1·13 (0·91 to 1·40)	6	0·61 (0·23 to 1·34)	124	1·00 (0·83 to 1·19)
Rectum	23	0·85 (0·54 to 1·27)	55	1·05 (0·79 to 1·37)	6	0·87 (0·32 to 1·90)	84	0·97 (0·78 to 1·21)
Liver	3	0·53 (0·11 to 1·54)	8	0·73 (0·32 to 1·44)	1	0·67 (0·02 to 3·71)	12	0·66 (0·34 to 1·16)
Gall bladder	3	0·89 (0·18 to 2·60)	7	1·02 (0·41 to 2·10)	1	1·14 (0·03 to 6·40)	11	0·99 (0·49 to 1·77)
Pancreas	17	1·13 (0·66 to 1·81)	34	1·14 (0·79 to 1·60)	7	1·81 (0·73 to 3·74)	58	1·19 (0·91 to 1·54)
Larynx	11	0·78 (0·39 to 1·40)	10	0·93 (0·45 to 1·71)	0	— —	21	0·77 (0·48 to 1·18)
Lung	76	0·85 (0·67 to 1·07)	150	0·94 (0·80 to 1·11)	26	1·12 (0·73 to 1·64)	252	0·93 (0·82 to 1·05)
Prostate	12	0·94 (0·49 to 1·65)	137	0·96 (0·80 to 1·13)	16	1·29 (0·74 to 2·10)	165	0·98 (0·84 to 1·14)
Testis	58	0·95 (0·72 to 1·23)	2	0·90 (0·11 to 3·25)	10	1·62 (0·77 to 2·98)	70	1·01 (0·79 to 1·28)
Kidney	28	1·14 (0·76 to 1·65)	31	1·20 (0·82 to 1·71)	4	0·86 (0·23 to 2·20)	63	1·15 (0·88 to 1·47)
Urinary bladder	46	1·00 (0·73 to 1·33)	103	1·25 (1·02 to 1·52)*	11	0·94 (0·47 to 1·68)	160	1·14 (0·97 to 1·33)
Skin melanoma	50	1·11 (0·82 to 1·46)	8	0·86 (0·37 to 1·69)	4	0·76 (0·23 to 2·20)	62	1·04 (0·80 to 1·33)
Non-melanoma skin cancer	135	1·07 (0·90 to 1·26)	125	1·01 (0·84 to 1·21)	26	1·14 (0·74 to 1·67)	286	1·05 (0·93 to 1·18)
Brain and nervous system	50	1.02 (0·76 to 1·35)	18	1·64 (0·97 to 2·59)	6	1·01 (0·37 to 2·20)	74	1·12 (0·88 to 1·41)
Non-Hodgkin's lymphoma	26	0·86 (0·56 to 1·27)	13	0·82 (0·44 to 1·41)	4	0·91 (0·25 to 2·32)	43	0·85 (0·62 to 1·15)
Hodgkin's disease	14	1·04 (0·57 to 1·74)	1	0·46 (0·01 to 2·54)	0	— —	15	0·87 (0·49 to 1.44)
Leukaemia	16	0·76 (0·43 to 1·24)	22	0·87 (0·54 to 1·31)	5	1·23 (0·40 to 2·86)	43	0·85 (0·62 to 1·15)
Multiple myeloma	6	0·95 (0·35 to 2·07)	10	0·96 (0·46 to 1·77)	0	— —	16	0·88 (0·50 to 1·43)

*95% Confidence interval does not include value of 1·00.

TABLE III—*Observed numbers of testicular cancer cases and standardised morbidity ratios (95% confidence intervals) in 73 917 men categorised in three groups based on hospital discharge and pathology register data, 1977-89, by age at diagnosis and time after hospital discharge*

Cancer site	Group 1 (sterilisation)		Group 2 (other vasectomy)		Group 3 (pathology only)		Total	
	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio	Observed	Standardised morbidity ratio
Age at diagnosis (years):								
0-24	0	— —	0	— —	0	— —	0	— —
25-39	29	0·84 (0·57 to 1·21)	1	2·13 (0·05 to 11·85)	7	1·97 (0·79 to 4·05)	37	0·96 (0·68 to 1·33)
40-54	29	1·12 (0·75 to 1·60)	1	1·64 (0·04 to 9·13)	3	1·28 (0·26 to 3·75)	33	1·14 (0·79 to 1·60)
≥55	0	— —	0	— —	0	— —	0	— —
Time after entry (years):								
0	4	0·42 (0·11 to 1·06)	1	2·71 (0·07 to 15·06)	4	3·05 (0·83 to 7·82)	9	0·80 (0·36 to 1·51)
1-2	13	0·78 (0·41 to 1·33)	1	1·61 (0·04 to 8·99)	2	0·98 (0·12 to 3·52)	16	0·83 (0·47 to 1·34)
3-4	17	1·30 (0·76 to 2·08)	0	— —	3	2·10 (0·43 to 6·13)	20	1·34 (0·82 to 2·06)
5-6	10	1·02 (0·49 to 1·88)	0	— —	0	— —	10	0·91 (0·44 to 1·67)
7-8	8	1·21 (0·52 to 2·40)	0	— —	1	2·54 (0·06 to 14·29)	9	1·25 (0·57 to 2·37)
≥9	6	1·16 (0·43 to 2·52)	0	— —	0	— —	6	1·09 (0·40 to 2·38)
Overall	58	0·95 (0·72 to 1·23)	2	0·90 (0·11 to 3·25)	10	1·62 (0·77 to 2·98)	70	1·01 (0·79 to 1·28)

in table II. Urinary bladder cancer occurred more frequently than expected in group 2 (standardised morbidity ratio 1·25 (95% confidence interval 1·02 to 1·52)) but no such tendency occurred in the other two groups. The incidence of brain cancer was slightly raised in group 2 (standardised morbidity ratio 1·64 (0·97 to 2·59)) and the incidence of pancreatic cancer was slightly raised in group 3 (standardised morbidity ratio 1·81 (0·73 to 3·74)). On the other hand, several cancers occurred less frequently than expected in the cohort—namely, cancer of the mouth and pharynx (standardised morbidity ratio 0·76 (0·55 to 1·02)), oesophageal cancer (standardised morbidity ratio 0·51 (0·25 to 0·94)), and liver cancer (standardised morbidity ratio 0·66 (0·34 to 1·16)). These effects were fairly consistent across the three groups.

Discussion

TESTICULAR CANCER

The primary objective of this study was to investigate whether the incidence of testicular cancer is increased by vasectomy and whether such an increase (if it exists) is particularly pronounced in the first years after vasectomy. The investigation was conceived to be of sufficient size and statistical power to settle the issue of testicular cancer and vasectomy conclusively.

The two studies which prompted the work were based on fairly small numbers. Thornhill *et al* reviewed 240 consecutive testicular cancer patients in Ireland and found three with a history of recent vasectomy (1·3%).[12] By using census information the expected prevalence of vasectomy was only 0·2%. This comparison was, however, based on few cases and uncertain assumptions. Cale *et al* reported a small cohort study from Scotland and prompted the recent interest in the association between vasectomy and testicular cancer. They observed eight cases of testicular cancer as against 1·9 expected among 3079 vasectomised men, giving a standardised morbidity ratio of 4·2 (95% confidence interval 1·8 to 8·2).[13] As in the study by Thornhill *et al*, the intervals between vasectomy and testicular cancer were short—three months to four years in the Scottish study and less than two months in the Irish study.

Our findings do not indicate an increased risk of testicular cancer in vasectomised men. A possible source of bias might arise from a systematic difference in fertility between the cohort members and the total male population. The incidence of testicular cancer is increased in men with reduced fertility, which is attributable to the higher prevalence of cryptorchidism in testicular cancer patients than in other men.[31] The prevalence of cryptorchidism in Danish men has been estimated in a case-control study of testicular cancer (unpublished data) and in reviews of records from medical examinations of schoolboys[32] (unpublished data). Both sets of data indicate a prevalence of around 2% for previous treatment of cryptorchidism and around 7% for a history of spontaneously descending testes.

The case-control analysis found that the increase of testicular cancer was restricted entirely to men with treated or persistent cryptorchidism (unpublished data), and a previous cohort study of men in Denmark with treated cryptorchidism gave a relative risk of 4·7 for testicular cancer.[33] If we assume that none of the 2% of men with treated or persistent cryptorchidism chose

to be sterilised because of their reduced fertility, then correction for a 2% prevalence of cryptorchid men with a relative risk of 5·0 reduces the expected number by a factor of 0·93 and increases the overall standardised morbidity ratio from 1·01 to 1·09 (95% confidence interval 0·85 to 1·37).

The comparison of incidence in the first year after vasectomy and the later period of follow up is not sensitive to the bias described above. There was no increase in the incidence in the first year (standardised morbidity ratio 0·80) compared with the incidence in the later period (standardised morbidity ratio 1·05).

It is therefore probable that no association exists between vasectomy and the risk of testicular cancer. But if such an association exists it is unlikely to be higher than the upper 95% confidence limits calculated above—namely, 1·28 without correction and 1·37 with correction for the possible influence of cryptorchidism. Furthermore, there is no indication of increased incidence shortly after vasectomy. Thus it is most likely that vasectomy neither induces testicular tumorigenesis nor accelerates the growth or diagnosis of non-invasive precursor lesions or clinically unrecognised testicular cancers. Several studies support this conclusion.

Strader *et al* reported an association between testicular cancer risk and vasectomy in a case-control study in western Washington State (odds ratio 1·5 (95% confidence interval 1·0 to 2·2)).[21] However, the association was present only in Catholic men and was attributed to bias arising from underreporting of vasectomy by Catholic controls. The odds ratio was 8·7 (95% confidence interval 2·8 to 27·1) in the Catholics but 1·0 (0·6 to 1·7) in Protestants and 1·3 (0·6 to 3·0) in people with other religions. The odds ratios (95% confidence intervals) for vasectomy in the case-control studies of Moss *et al*[22] and Swerdlow *et al*[23] were 0·6 (0·3 to 1·2) and 1·13 (0·63 to 2·04), respectively. A record linkage study from Oxford gave a relative risk of testicular cancer of 0·46 (95% confidence interval 0·1 to 1·4), based on four cases in 13 246 vasectomised men and 17 cases in 22 196 controls.[25]

PROSTATE CANCER

Other studies which have collected information on the incidence of prostate cancer by time since vasectomy have shown an increased incidence only after around 15 years.[14 16-20] Our study does not cover this period of risk and is based on comparatively few cases of prostate cancer in sterilised men. Thus with regard to male sterilisation and risk of prostate cancer our findings are inconclusive.

CANCER AT OTHER SITES

With the many associations examined (63 independent standardised morbidity ratios in table II) some are bound to be significant by chance. At the P=0·05 level some three or four spurious associations may be expected.

The observed association with urinary bladder cancer in group 2 was probably caused by increased medical attention of men with urological problems. The great majority of bladder cancers in this group occurred in men over 60. This resembles the increased risk of bladder cancer in multiple sclerosis patients, in whom urinary problems are a common complication.[34]

The decreased incidence of cancers of the mouth and pharynx, oesophagus, and liver may in part reflect the selection of men with a healthy lifestyle in the cohort. Cancers at these sites are associated with heavy drinking.[35] Such selection is not likely to have influenced the results for testicular cancer, which in Denmark is not associated with alcohol (unpublished data) and has only a weak association with social class.[36]

Clinical implications

- Vasectomy is a widely used method of contraception
- Small studies have suggested a possible risk of testicular cancer after vasectomy
- This study found no increased risk of testicular cancer in over 73 000 vasectomised men in Denmark
- It is concluded that vasectomy does not cause testicular cancer
- Vasectomy does not accelerate the growth or diagnosis of pre-existing testicular neoplasma

CONCLUSION

We found no increase in testicular cancer in our cohort of 73 917 vasectomised men. Based on our findings it is most likely that vasectomy neither induces testicular tumorigenesis nor accelerates the growth or diagnosis of non-invasive precursor lesions or clinically unrecognised testicular cancers. The incidence of prostate cancer was also close to expected, but owing to the short follow up we regard this finding as inconclusive.

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Comparison of efficacy and safety of low molecular weight heparins and unfractionated heparin in initial treatment of deep venous thrombosis: a meta-analysis

A Leizorovicz, G Simonneau, H Decousus, J P Boissel

Abstract

***Objective*—To compare the efficacy and safety of low molecular weight heparins and unfractionated heparin in the initial treatment of deep venous thrombosis for the reduction of recurrent thromboembolic events, death, extension of thrombus, and haemorrhages.**

***Design*—Meta-analysis of results from 16 randomised controlled clinical studies.**

***Subjects*—2045 patients with established deep venous thrombosis.**

***Intervention*—Treatment with low molecular weight heparins or unfractionated heparin.**

***Main outcome measures*—Incidences of thromboembolic events (deep venous thrombosis or pulmonary embolism, or both); major haemorrhages; total mortality; and extension of thrombus.**

***Results*—A significant reduction in the incidence of thrombus extension (common odds ratio 0·51, 95% confidence interval 0·32 to 0·83; P=0·006) in favour of low molecular weight heparin was observed. Non-significant trends also in favour of the low molecular weight heparins were observed for the recurrence of thromboembolic events (0·66, 0·41 to 1·07; P=0·09), major haemorrhages (0·65, 0·36 to 1·16; P=0·15), and total mortality (0·72, 0·46 to 1·4; P=0·16).**

***Conclusions*—Low molecular weight heparins seem to have a higher benefit to risk ratio than unfractionated heparin in the treatment of venous thrombosis. These results, however, remain to be confirmed by using clinical outcomes in suitably powered clinical trials.**

Service de Pharmacologie Clinique, BP 3041, 69394 Lyons Cedex 03, France
A Leizorovicz, *senior scientist*
J P Boissel, *professor of clinical pharmacology*

Service de Pneumologie, Hôpital A, Béclère, 92140 Clamart, France
G Simonneau, *professor of pneumology*

Hôpital Bellevue, 42023 St Etienne Cedex, France
H Decousus, *professor of clinical pharmacology*

Correspondence to:
Dr Leizorovicz.

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Introduction

Since the results of a trial performed in the early 1960s showing the clinical efficacy of treatment with heparin followed by oral anticoagulants for the management of pulmonary embolism[1] the conditions for optimum use of this treatment have not been determined. Initial treatment to establish rapid, adequate anticoagulation with unfractionated heparin (intravenous infusion or subcutaneous injection), however, with emphasis on an early, intense anticoagulation, is a widely used validated approach.[2-4]

Despite effective treatment, patients with deep venous thrombosis are still at high risk of recurrent venous thromboembolic events (5% to 10%), death in the months after the initial episode, and disabling chronic venous insufficiency in the subsequent years. High doses of unfractionated heparin and oral anticoagulants increase the risk of severe haemorrhages (5%), and heparin can induce severe thrombocytopenia (0·3%-1%). Also, frequent laboratory tests and adjustments of dose are needed.

In animal models low molecular weight heparins have been shown to induce haemorrhage less often than unfractionated heparin at equipotent antithrombotic doses.[5] They also have a longer half life than unfractionated heparin used at doses recommended for the treatment of deep vein thrombosis. After subcutaneous injection their bioavailability is close to 100% whereas that of unfractionated heparin is closer to 30%.[6] It has been suggested that similar efficacy to that of unfractionated heparin could be obtained with fewer injections and less laboratory monitoring. Although low molecular heparins are about four to five times more expensive than unfractionated heparin, the reduced number of injections and absence of the need for adjustment of dose could reduce the cost of care, and this may compensate for the higher price.

Recent meta-analyses of randomised clinical trials that compared low molecular weight heparins with unfractionated heparin in the prevention of postoperative deep vein thrombosis showed that low molecular weight heparins can significantly decrease the incidence of deep venous thrombosis with no difference in the incidence of major haemorrhages.[7,8]

Low molecular weight heparins and unfractionated heparin have been compared for the treatment of patients with deep vein thrombosis in several randomised trials. Individually, however, most of these trials do not have sufficiently high statistical power to enable meaningful differences on clinically relevant end points to be detected. We undertook a meta-analysis of all the available data to obtain a better estimate of the efficacy and safety of low molecular heparins compared with those of unfractionated heparin in patients with deep venous thrombosis.

Methods

DATA COLLECTION

We performed a manual and computed aided (Medline) literature search for randomised clinical