

Main morbidities recorded in the women's international study of long duration oestrogen after menopause (WISDOM): a randomised controlled trial of hormone replacement therapy in postmenopausal women

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ABSTRACT

Objective To assess the long term risks and benefits of hormone replacement therapy (combined hormone therapy versus placebo, and oestrogen alone versus combined hormone therapy).

Design Multicentre, randomised, placebo controlled, double blind trial.

Setting General practices in UK (384), Australia (91), and New Zealand (24).

Participants Postmenopausal women aged 50-69 years at randomisation. At early closure of the trial, 56 583 had been screened, 8980 entered run-in, and 5692 (26% of target of 22 300) started treatment.

Interventions Oestrogen only therapy (conjugated equine oestrogens 0.625 mg orally daily) or combined hormone therapy (conjugated equine oestrogens plus medroxyprogesterone acetate 2.5/5.0 mg orally daily). Ten years of treatment planned.

Main outcome measures Primary outcomes: major cardiovascular disease, osteoporotic fractures, and breast cancer. Secondary outcomes: other cancers, death from all causes, venous thromboembolism, cerebrovascular disease, dementia, and quality of life.

Results The trial was prematurely closed during recruitment, after a median follow-up of 11.9 months (interquartile range 7.1-19.6, total 6498 women years) in those enrolled, after the publication of early results from the women's health initiative study. The mean age of randomised women was 62.8 (SD 4.8) years. When combined hormone therapy (n=2196) was compared with placebo (n=2189), there was a significant increase in the number of major cardiovascular events (7 v 0, P=0.016) and venous thromboembolisms (22 v 3, hazard ratio 7.36 (95% CI 2.20 to 24.60)). There were no statistically significant differences in numbers of breast or other cancers (22 v 25, hazard ratio 0.88 (0.49 to 1.56)), cerebrovascular events (14 v 19, 0.73 (0.37 to 1.46)), fractures (40 v 58, 0.69 (0.46 to 1.03)), and overall deaths (8 v 5, 1.60 (0.52 to 4.89)). Comparison of combined hormone therapy (n=815) versus oestrogen therapy (n=826) outcomes revealed no significant differences.

Conclusions Hormone replacement therapy increases cardiovascular and thromboembolic risk when started many years after the menopause. The results are consistent with the findings of the women's health initiative study and secondary prevention studies. Research is needed to assess the long term risks and benefits of starting hormone replacement therapy near the menopause, when the effect may be different. **Trial registration** Current Controlled Trials ISRCTN 63718836

INTRODUCTION

Although the use of hormone replacement therapy for control of moderate to severe menopausal symptoms is well established, its long term use for disease prevention in postmenopausal women is in dispute.

The US women's health initiative study, which began in 1997, was designed to assess the prevention of cardiovascular disease in women aged 50-79 years taking combined oestrogen and progestogen or, in women who had had a hysterectomy, oestrogen only. In those taking combined oestrogen and progestogen it found a significantly increased risk of stroke, pulmonary embolism, and breast cancer and a decreased risk of hip fracture and colorectal cancer compared with women taking placebo.¹ This study found that combined oestrogen and progestogen therapy might increase coronary events in older women (aged 70-79) in their first year of treatment.² The combined oestrogen and progestogen arm of the trial was closed prematurely after a mean of 5.2 years of follow-up. Later, the oestrogen only arm of the trial also closed prematurely, after an average of 6.8 years of follow-up, as it showed an increased risk of stroke but no overall difference in cardiovascular disease or breast cancer.³

The women's international study of long duration oestrogen after menopause (WISDOM), began recruitment in 1999.^{4,5} It was originally designed to investigate a younger age group (45-60 years old) to ensure the data were relevant to the normal use of hormone replacement therapy, but this was later modified

to 50-69 years.⁵ The aim was to assess the balance of long term risks and benefits of hormone replacement therapy with particular emphasis on cardiovascular disease and dementia.

Recruitment began in the UK in 1999 and in Australia and New Zealand in 2000. Recruitment was still under way when the trial was stopped after the first results of the combined oestrogen and progestogen arm of the women's health initiative study were published in 2002. This paper presents the main clinical outcomes for WISDOM after 6498 person years of follow-up for a median of 11.9 months.

METHODS

Participants

Recruitment took place in general practice. Details are published elsewhere.⁶ In each country we identified women aged 50-69 years from practice registers. Postmenopausal women (no menstrual period in the past 12 months or had undergone hysterectomy) were eligible for the trial. See bmj.com for exclusion criteria. The strategy was to recruit the oldest women first. Women completed a screening questionnaire, were provided with written information, and, if, after consideration for two weeks, they were willing to participate, entered a 12 week run-in period (figure).

Interventions

The oestrogen therapy was conjugated equine oestrogens 0.625 mg orally daily. The combined therapy was conjugated equine oestrogens as above plus medroxyprogesterone acetate 2.5 mg orally daily. Women with a uterus and within three years of their last period, those aged 50-53, and older women with unacceptable breakthrough bleeding took 5.0 mg medroxyprogesterone acetate. Women with a uterus who experienced unacceptable spotting or bleeding with the combined therapy containing 5.0 mg medroxyprogesterone acetate were offered open label Premique cycle (Premarin 0.625 mg orally daily plus medroxyprogesterone acetate 10 mg orally for the last 14 days of a 28 day cycle).

The planned median treatment duration of the trial was 10 years (range 9-12), with treatment being co-terminous in all participants. As far as possible, the trial was conducted in a double-blind manner, though full blindness could not be maintained when vaginal bleeding triggered investigation.

Data collection

Women were to be seen at 4, 14, 27, 40, and 52 weeks after start of treatment and then at six month intervals. A final visit took place as soon as possible after the closure of the trial. At the start of treatment and at each follow-up visit, information was collected on all outcomes, adverse events, and other medical history to check that patients remained eligible. All information was sent to the coordinating centre within one week of collection. A member of the study team, blinded to treatment allocation, obtained any data needed to confirm a clinical event.

Main clinical outcome measures

Primary outcomes were major cardiovascular disease (defined as one or more of unstable angina requiring hospitalisation, fatal or non-fatal myocardial infarction, or sudden coronary death), osteoporotic fractures (all fractures other than of the skull, face, cervical spine, fingers, or toes), and breast cancer. Secondary outcomes were breast cancer mortality, other cancers, death from all causes, venous thromboembolism (deep vein thrombosis, pulmonary embolism, or retinal vein occlusion), cerebrovascular disease, and dementia. Quality of life and psychological wellbeing were measured and are reported separately. All outcomes were reviewed blind to treatment allocation. All cardiovascular and cancer outcomes and 10% of fractures were reviewed by independent assessors.

Sample size

WISDOM was originally designed to detect a 25% reduction in the number of cases of coronary heart disease (excluding unstable angina) and stroke over 10 years comparing combined oestrogen and progestogen therapy with placebo in women aged 50-64 years at randomisation. The primary outcome was subsequently changed to exclude stroke and to include unstable angina, and the age range at randomisation was extended to 69 years. Other assumptions were modified. The expected maximum recruitment of 22 300 (16 000 for combined therapy versus placebo) provided 80% power at the 5% significance level to detect a 29% reduction from an expected probability of a primary outcome event in the placebo group during the trial period of 39 per 1000 women randomised. This sample size also had the power to detect a 20% reduction, from an expected probability of 95 per 1000 women, in all osteoporotic fractures and a 40% increase, from an expected probability of 36 per 1000 women, in breast cancer. See bmj.com for details.

Statistical methods

Follow-up time for each participant was calculated for each outcome separately from date of randomisation until the date of outcome, of death, of loss to follow-up, or of trial closure, whichever occurred first. We calculated event rates (per 10 000 women-years) assuming a Poisson regression (constant hazards) model. We calculated hazard ratios under the Cox proportional hazards model. The results are reported as, respectively, rates and hazard ratios for the effect of combined therapy versus either placebo or oestrogen therapy. See bmj.com for details.

RESULTS

Recruitment

A total of 284 175 women aged 50-69 years were registered at the participating practices, of whom 226 282 were potentially eligible for the trial (figure).

Baseline data

The participants' mean age was 62.8 years (SD 4.8), reflecting the strategy of recruiting older women first. Women who had undergone a hysterectomy were, on average, slightly younger and were more likely to have ever used hormone replacement therapy and to have used it for a longer time than those women with a uterus. Women who were not willing to accept placebo randomisation (stratum 2) were more likely to have used hormone replacement therapy and to be using it at screening (82%). Other characteristics were similar for the three strata. See [bmj.com](#).

In the main treatment comparison (combined therapy versus placebo) 8% in each group were using hormone replacement therapy at screening and 46-47% of those screened were past users of hormone

replacement therapy for a median of 3.8-4 years. Data from the screening interviews indicate that, with regard to major risk factors for the primary outcomes, WISDOM participants were similar to women screened in the participating practices. See [bmj.com](#).

Follow-up

With the early closure of the trial the median follow-up time was 11.9 months (interquartile range 7.3-19.6), with a total follow-up time of 6498 women years. In women randomised to combined therapy or placebo, median follow-up was 12.8 (7.5-20.4) months, with a total of 5214 person-years; for women randomised to combined therapy or oestrogen therapy the figures were 10.3 (6.4-16.8) months and 1688 years, respectively.

The treatment code was unblinded in only two of the 1971 women who had undergone hysterectomy, but in women with a uterus the proportion unblinded was high, mostly as a result of vaginal bleeding in those randomised to combined therapy, where 712/1862 (38%) were unblinded, compared with 66/1859 (4%) of those randomised to placebo (hazard ratio 13.4 (95% confidence interval 10.4 to 17.3), $P < 0.001$).

Clinical outcomes

The total number of events for all trial outcomes was low because the trial was stopped early and there are no follow-up data on dementia.

Combined oestrogen and progestogen therapy versus placebo

Compared with those taking placebo, women taking combined therapy had significantly increased rates of cardiovascular events and venous thromboembolism and a non-significant reduction in the rate of osteoporotic fractures (table). Rates for cerebrovascular disease, breast cancer, and other cancers were not significantly different in the two groups.

Oestrogen and progestogen versus oestrogen alone

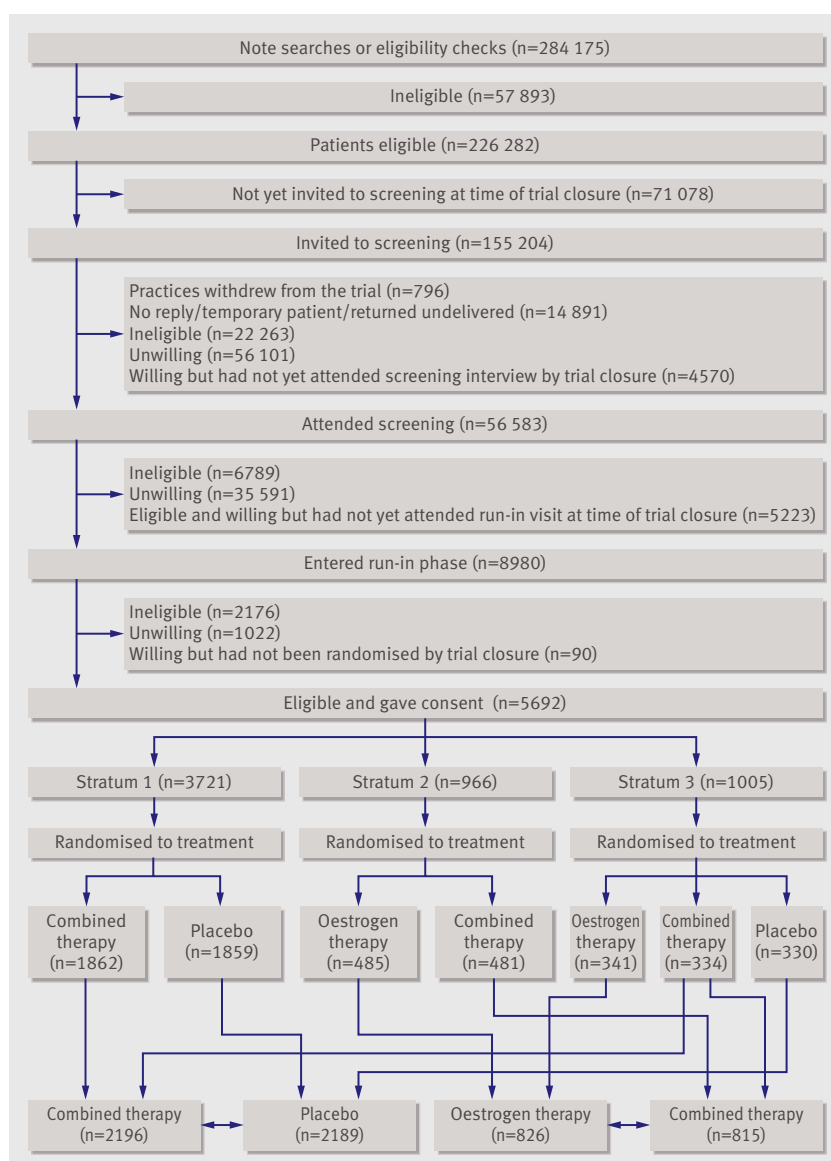
The numbers of participants and the number of events in this comparison are much smaller than for the comparison of combined oestrogen plus progestogen versus placebo (table). There is a suggestion in the combined therapy group of an increase in cardiovascular events and in venous thromboembolism.

Adverse events

There were 15 deaths during the trial, with a non-significant increase in the rate in the combined therapy group compared with placebo (30.7 *v* 19.2 per 10 000 women-years, hazard ratio 1.60 (0.52 to 4.89)). There was no excess of serious adverse events in either of the randomised comparisons. See [bmj.com](#).

DISCUSSION

Data from WISDOM suggest that women starting or restarting combined oestrogen and progestogen therapy an average of 15 years after menopause are at increased risk of cardiovascular disease and venous



Flow of patients through the women's international study of long duration oestrogen after menopause (WISDOM). (Trial closure was on 22 October 2002. Combined therapy=conjugated equine oestrogen 0.625 mg + medroxyprogesterone acetate 2.5 mg orally daily. Oestrogen therapy=conjugated equine oestrogen 0.625 mg orally daily)

thromboembolism, at least in the early years of treatment. We found a trend towards a decreased risk of osteoporotic fracture and no difference in the risk of stroke or cancers. The small numbers of events and the brief follow-up periods inevitably mean that some of the results cannot be confidently interpreted. However, we

can comment on the results for early cardiovascular and thromboembolic disease. In a direct comparison with combined oestrogen and progestogen therapy, oestrogen only therapy may have similar, but smaller, short term effects. These results are consistent with the findings of the combined oestrogen and progestogen

Primary and secondary clinical outcomes in WISDOM by time of follow-up and randomised treatment*

Outcomes	All (n=5692)	Combined therapy v placebo		Combined therapy v oestrogen therapy	
		Combined therapy (n=2196)	Placebo (n=2189)	Combined therapy (n=815)	Oestrogen therapy (n=826)
Cardiovascular disease					
Unstable angina	6	3	0	3	1
Non-fatal myocardial infarct	6	4	0	1	2
Fatal myocardial infarct	0	0	0	0	0
Sudden coronary death	1	0	0	0	1
Any of the above	11	7	0	4	2
Rate (95% CI)†	17.0 (9.4 to 30.6)	26.9 (12.8 to 56.4)	0	47.8 (18.0 to 127.5)	23.6 (5.9 to 94.4)
Hazard ratio (95% CI); P value		NA; 0.016		2.03 (0.37 to 11.09); 0.40	
Cerebrovascular disease					
Non-fatal	36	13	19	4	4
Fatal	1	1	0	0	0
Fatal or non-fatal	37	14	19	4	4
Rate (95% CI)†	57.2 (41.4 to 78.9)	53.8 (31.9 to 90.9)	73.4 (46.8 to 115.0)	47.9 (18.0 to 127.6)	47.1 (17.7 to 125.6)
Hazard ratio (95% CI); P value		0.73 (0.37 to 1.46); 0.38		1.01 (0.25 to 4.04); 0.99	
Venous thromboembolism					
Deep vein thrombosis	18	13	1	5	3
Pulmonary embolism	14	10	2	2	1
Fatal thromboembolism	3	2	0	0	1
Any of the above	30	22	3	7	3
Rate (95% CI)†	46.4 (32.4 to 66.3)	85.1 (56.0 to 129.2)	11.5 (3.7 to 35.7)	84.3 (40.2 to 176.9)	35.3 (11.4 to 109.5)
Hazard ratio (95% CI); P value		7.36 (2.20 to 24.60); <0.001		2.39 (0.62 to 9.24); 0.19	
Osteoporotic fractures					
Hip	5	2	3	1	0
Other	108	38	55	11	8
Any	113	40	58	12	8
Rate (95% CI)†	176.1 (146.5 to 211.8)	155.3 (114.0 to 211.8)	226.2 (174.9 to 292.6)	144.5 (82.1 to 254.4)	94.4 (47.2 to 188.8)
Hazard ratio (95% CI); P value		0.69 (0.46 to 1.03); 0.07		1.52 (0.62 to 3.72); 0.35	
Cancer					
Breast	16	5	7	3	2
Colorectal	6	2	2	1	2
Other	37	15	16	4	3
Any	59	22	25	8	7
Rate (95% CI)†	91.3 (70.7 to 117.8)	84.8 (55.8 to 128.7)	96.5 (65.2 to 142.8)	96.0 (48.0 to 192.0)	82.8 (39.5 to 173.6)
Hazard ratio (95% CI); P value		0.88 (0.49 to 1.56); 0.65		1.16 (0.42 to 3.20); 0.78	
Death					
Breast cancer	0	0	0	0	0
Colorectal cancer	1	1	0	1	0
Other cancer	5	2	3	0	0
Cardiovascular	1	0	0	0	1
Cerebrovascular	1	1	0	0	0
Venous thromboembolism	3	2	0	0	1
Other causes	4	2	2	0	0
All death	15	8	5	1	2
Rate (95% CI)†	23.1 (13.9 to 38.3)	30.7 (15.3 to 61.3)	19.2 (8.0 to 46.1)	11.9 (1.7 to 84.7)	23.5 (5.9 to 94.0)
Hazard ratio (95% CI); P value		1.60 (0.52 to 4.89); 0.40		0.51 (0.05 to 5.58); 0.57	
Any event	242	99	104	35	23
Rate (95% CI)†	382.7 (337.4 to 434.0)	390.9 (321.0 to 476.1)	410.9 (339.0 to 497.9)	429.9 (308.6 to 598.7)	274.6 (182.5 to 413.2)
Hazard ratio (95% CI); P value		0.95 (0.72 to 1.25); 0.72		1.56 (0.92 to 2.64); 0.09	

*Some events appear in both comparisons.

†Rate is per 10 000 women-years.

therapy arm of the women's health initiative study and with secondary prevention trials, and support the conclusion that combined oestrogen and progestogen therapy should not be given for cardiovascular disease prevention in older postmenopausal women.

Value of study

Despite the fact that WISDOM did not run to completion, this trial makes an important contribution to the body of knowledge about hormone replacement therapy started in older postmenopausal women of a mean age of 63 years. A strength of the study is that participants are likely to be representative of the general population of women of this age and the results applicable to this older age group. Comparing the population in the women's health initiative study, many of the women in WISDOM were similarly overweight or obese and had many similar cardiovascular risk factors.¹³ The mean age at entry was also similar. However, previous use of hormone replacement therapy was higher in WISDOM than in the women's health initiative study (45% compared with 26% in women with a uterus).

Comparison of results

Venous thromboembolism—The event rate in women taking combined oestrogen and progestogen therapy in WISDOM was higher than that reported in the early years of the women's health initiative trial, despite the exclusion in WISDOM of those with previous events. The reason for this is not clear but, in view of the small number of events, may be a chance finding. The increased rate of venous thromboembolism with combined therapy was greatest in the first year of the women's health initiative trial.¹ It is possible that those with genetic predisposition to thrombosis have early vulnerability to hormone replacement therapy.⁷

Cardiovascular disease—Although the number of cardiovascular events observed was small, all occurred in the hormone replacement therapy groups, at a rate of 27 per 10 000 women-years in the combined therapy arm of WISDOM. This rate was smaller than the rate of 51 per 10 000 women-years in the first year of the combined therapy arm of the women's health initiative study. The early increased risk of cardiovascular events in both trials is compatible with the hypothesis that administration of hormone replacement therapy, particularly combined oestrogen and progestogen therapy, to women many years after menopause, who are likely to have established atherosclerosis, may cause disruption of the plaque surface, with subsequent platelet adhesion, clotting, and further arterial narrowing.⁸ Most of the events in WISDOM occurred in women over the age of 64, many of whom had cardiovascular risk factors.

Fractures—The non-significant trend toward a reduced risk of fractures after an average follow-up period of only one year is in keeping with the significant reduction of fractures seen in the women's health initiative study.¹³ Neither WISDOM nor the women's health initiative study required an increased risk of fracture as an inclusion criterion, and so the results suggest a potent preventive effect in an unscreened population. As in the

women's health initiative study, we found no apparent difference between combined therapy and oestrogen therapy in their effect on fracture prevention.

Cancer—We found no effect on cancer rates, including breast cancer, but this must be interpreted with caution as the maximum follow-up was three years (median one year).

Death—The short follow-up time and small number of deaths recorded in WISDOM do not allow robust conclusions.

Implications of results

Most women who start hormone replacement therapy do so near the menopause to reduce menopausal symptoms and improve their quality of life. Clinical and animal studies suggest that the effect of oestrogen on the cardiovascular system and possibly the brain may be very different and probably beneficial when used at or near the time of menopause.⁹⁻¹¹ In particular, a recent meta-analysis of 23 randomised controlled trials of hormone replacement therapy showed that it significantly reduced coronary heart disease in women starting therapy younger than 60 years or within 10 years of menopause.¹² The early termination of WISDOM before large numbers of recently menopausal women could be recruited, means that the "critical window hypothesis" could not be examined to see if oestrogen has cardio-protective and neuroprotective effects.^{7,13} The risk:benefit equation for a younger menopausal woman may be different from that seen in the mainly older women in WISDOM and the women's health initiative study.

Conclusions

The women's health initiative study and WISDOM have not answered the question about long term benefits and risks of hormone replacement therapy in the large majority of women who start therapy around menopause for symptom control. However, they have shown that there is no overall disease prevention benefit, and some potential risk, for women with few or no oestrogen deficiency symptoms who start hormone replacement therapy many years after menopause. If there is a menopausal window of therapeutic benefit its upper limit has not been well defined and is likely to vary with arterial health and associated risk factors such as obesity and metabolic syndrome.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

Combined oestrogen and progestogen hormone replacement therapy initiated many years after menopause in asymptomatic women reduces fracture risk but increases thromboembolic, breast cancer, and possibly cerebrovascular risk

Oestrogen only hormone replacement therapy started near the menopause may decrease the risk of coronary heart disease, breast cancer, diabetes, and osteoporotic fractures

WHAT THIS STUDY ADDS

This study confirms an early increase in thromboembolic and cardiovascular risk in women starting hormone replacement therapy at a mean of 63 years and 15 years after the menopause

These uncommon serious events must be weighed against more common improvements in quality of life

These results cannot be applied to symptomatic women starting hormone replacement therapy near menopause, for whom cardiovascular benefits have recently been described

Zealand monitored local progress and received reports on progress from the UK steering committee. The principal investigators from Australia and New Zealand were non-voting members of the UK steering committee.

Competing interests: WISDOM was run and funded independently of industry. The funding bodies had no influence on the results except for the early curtailment of the trial by the MRC. Wyeth Ayerst provided active drugs and matched placebo but had no other involvement in the trial. All authors have declared no direct conflicts of interest. AHM and BL have received research grants and lecture honoraria from a variety of industry sources not associated with WISDOM.

Ethical approval: UK approval was granted by the South Thames Regional Health Authority Multicentre Research Ethics Committees and by the relevant local research ethics committees. Australian approval was given by the human research ethics committees for the universities of Adelaide, Newcastle, and Monash and by the Royal Australian College of General Practitioners' National Research and Evaluation Ethics Committee. New Zealand approval was given by the Wellington Regional Ethics Committee and the Auckland and Canterbury ethics committees.

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Dressings for venous leg ulcers: systematic review and meta-analysis

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ABSTRACT

Objective To review the evidence of effectiveness of dressings applied to venous leg ulcers.

Design Systematic review and meta-analysis.

Data sources Hand searches of journals and searches of electronic databases, conference proceedings, and bibliographies up to April 2006; contacts with dressing manufacturers for unpublished studies.

Studies reviewed All randomised controlled trials that evaluated dressings applied to venous leg ulcers were eligible for inclusion. Data from eligible studies were extracted and summarised independently by two reviewers using a data extraction sheet. Methodological quality was assessed independently by two reviewers.

Results The search strategy identified 254 studies; 42 of these fulfilled the inclusion criteria. Hydrocolloids were no more effective than simple low adherent dressings used beneath compression (eight trials; relative risk for healing with hydrocolloid 1.02, 95% confidence interval 0.83 to 1.28). For other comparisons, insufficient

evidence was available to allow firm conclusions to be drawn. None of the dressing comparisons showed evidence that a particular class of dressing healed more ulcers. Some differences existed between dressings in terms of subjective outcome measures and ulcer healing rates. The results were not affected by the size or quality of trials or the unit of randomisation. Insufficient data were available to allow conclusions to be drawn about the relative cost effectiveness of different dressings. **Conclusions** The type of dressing applied beneath compression was not shown to affect ulcer healing. The results of the meta-analysis showed that applying hydrocolloid dressings beneath compression produced no benefit in terms of ulcer healing compared with applying simple low adherent dressings. No conclusive recommendations can be made as to which type of dressing is most cost effective. Decisions on which dressing to apply should be based on the local costs of dressings and the preferences of the practitioner or patient.

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