RESEARCH

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THIS WEEK'S RESEARCH QUESTIONS

405 How effective are different management strategies for urinary tract infection in women in primary care?

406 ...and how cost effective are these strategies?

407 ...and how acceptable are these strategies to women?

408 What is the natural course of these urinary tract infections and what factors are associated with antibiotic resistance?

409 Does moderate hypothermia improve survival and neurological outcome in infants with perinatal hypoxic-ischaemic encephalopathy?

Urinary tract infections in women in primary care

Around half of all women in developed countries will have a urinary tract infection at least once in their lives and, as editorialist Dee Mangin points out, one in 10 a year will be prescribed antibiotics—often empirically (p 373). But many of these infections are resistant to common antibiotics, and about a third of women with symptoms don't even have bacterial infections. Laboratory confirmation is costly and slow, so dipstick testing is widely used instead to target treatment.

In a randomised trial Paul Little and colleagues evaluated these tests, a clinical algorithm, and empirical prescribing of antibiotics—either immediately or after a delay—and found that all the management strategies achieved similar control of symptoms (p 405). They concluded that there is no advantage in routinely sending urine samples for testing, and that antibiotic use could be reduced by targeting treatment according to dipstick tests—with delayed prescription, or empirical delayed prescription, as backup. They also looked at the cost effectiveness (p 406) and, in a qualitative study, at the acceptability to women (p 407) of the strategies tested in the trial.

To complete the package there's an observational study in 800 women, which concludes that antibiotic resistance and not prescribing antibiotics are associated with prolonged and more severe symptoms (p 408). So is a tendency to somatise, but feeling that the doctor communicated positively about diagnosis and prognosis reduced the duration of reported symptoms. To hear Paul Little putting this work in context listen to his podcast interview (http://podcasts.bmj.com/bmj/2010/02/05/urinary-tract-infections).

Ten steps towards improving prognosis research

Patients want to know what's going to happen to them in the long term but, for many common chronic diseases, medicine has few reliable answers. In Research Methods and Reporting, Harry Hemingway and colleagues suggest 10 ways to improve the planning, design, conduct, and reporting of prognosis studies (p 410). They say that, like clinical trials, such studies should have protocols and should be registered

In a Rapid Response, Paul Preziosi from France agrees that "Prognosis studies are often improvised as the 'cherry on the cake' of a work designed for quite another purpose. This is true of marker studies that often use available biological material, literally 'in the freezer', and of multivariate risk prediction models which are often a kind of fishing expedition across all available data items, no matter the nature of their putative relationship with the outcome." (www.bmj.com/cgi/eletters/339/dec30_1/b4184)

The *BMJ* and PLoS Medicine are working with these authors and a wider group of clinicians and epidemiologists to develop better methodologies. Meanwhile, we encourage authors to send us protocols for any observational study and to pursue registration (p 375). Editorialists Henrik Toft Sørensen and Kenneth J Rothman are dubious, however: "How much room would this policy leave for exploration, serendipity, or pursuit of unpopular theories?...researchers might be well advised to write a programme that would register every study idea imaginable within their purview, just to be on the safe side" (p 374).

AJ PHOTO/SPL

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Effect of reduced immunosuppression after kidney transplant failure on risk of cancer: population based retrospective cohort study

This nationwide study of 8173 patients registered on the Australia and New Zealand Dialysis and Transplant Registry looked at cancer specific incidence during periods of transplant function and during dialysis after transplant failure (when immunosuppression had been reduced or stopped). The effect of immunosuppression on cancer risk was rapidly reversible for some cancer types, particularly for those with a confirmed infectious cause. But risk of other cancers, especially those related to end stage kidney disease, remained significantly increased after reduction of immunosuppression.

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bmj.com
Trish Groves talks to Paul Little about these papers on urinary tract infections. http://podcasts.bmj.com/bmj/

Effectiveness of five different approaches in management of urinary tract infection: randomised controlled trial

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EDITORIAL by Mangin

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STUDY QUESTION What is the effectiveness of each of five management approaches to the treatment of women with urinary tract infection?

SUMMARY ANSWER There were no significant differences in duration or severity of symptoms with any of the approaches.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Few trials have compared commonly used management strategies for treating urinary tract infection. Immediate antibiotics targeted with dipstick tests or empirical delayed prescription achieved similar symptom control to immediate empirical antibiotics and helped to reduce antibiotic use.

Design and method

Open parallel randomised controlled trial with five groups: empirical immediate antibiotics, empirical delayed antibiotics (delayed by 48 hours), targeted antibiotics according to symptom score (two or more of cloudy urine, smelly urine, nocturia, dysuria), antibiotics according to result of dipstick tests (nitrite or leucocytes and blood), or antibiotics after positive result of midstream urine analysis. Randomisation was computer generated. Patients were allocated according to instruction sheets in sealed numbered envelopes. The potential to undermine randomisation was minimised by careful attention to maximising equipoise in the presentation of the study to clinicians, and by emphasising that women in all groups had access to antibiotics at their request.

Participants and setting

309 women aged 18-70 presenting to primary care with suspected uncomplicated urinary tract infection.

Primary outcomes

Mean severity of symptoms (at days 2 to 4) and duration; use of antibiotics.

Main results and the role of chance

Women had 3.5 days of moderately bad or worse symptoms if they took antibiotics immediately. There were no significant differences in the severity of frequency symptoms between groups (on a scale of 0 to 6: immediate antibiotics 2.15 (SD 1.18), midstream urine analysis 2.08, dipstick tests 1.74, symptom score 1.77, delayed antibiotics 2.11; likelihood ratio test P=0.177) nor in the duration of symptoms. There were, however, differences in the use of antibiotics (58/60 (97%), 38/47 (81%), 40/50 (80%), 52/58 (90%), 41/53 (77%), respectively; P=0.011). Patients who waited at least 48 hours to start antibiotics reconsulted less (hazard ratio 0.57 (95% confidence interval 0.36 to 0.89), P=0.014) but on average had symptoms for 37% longer than those taking immediate antibiotics (incident rate ratio 1.37 (1.11 to 1.68),; P=0.003), particularly the midstream urine group (73% longer, 22% to 140%); none of the other groups had more than 22% longer duration. The level of significance makes chance unlikely. There was no advantage in routinely sending midstream urine samples for testing, but antibiotics targeted with dipstick test results with a delayed prescription as back up, or empirical delayed prescription, might help to reduce antibiotic use.

Harms

No major adverse events (major illness, admission to hospital, death) were reported for any group, and no significant differences in skin rash or thrush were reported.

Bias, confounding, and other reasons for caution

This was an open trial that used an external generator for the randomisation code. Potential confounders were mostly well distributed between groups, where there were slight differences (such as baseline severity); adjustment for these did not alter the inferences. There was high retention (90%) and an intention to treat analysis was done without imputation. The trial was not powered for potentially important outcomes such as reconsultation rates.

Generalisability

Patients came from a wide range of practice settings and the sample had similar characteristics to observational cohorts from primary care, so the results should be generalisable to primary care settings and even some secondary care populations.

Study funding/potential competing interests

The study was funded by the Heath Technology Assessment NIHR HTA programme. No competing interests declared except JAL who has done consultancy work for Bayer.

Study registration

National Research Register N0484094184 ISRCTN: 03525333.

SUMMARY OF MAIN RESULTS WITH 95% CONFIDENCE INTERVALS

	Immediate antibiotics	Midstream urine	Dipstick testing	Symptom score	Delayed antibiotics	P value
Mean difference in frequency symptoms	—	−0.07 (−0.51 to 0.37)	−0.40 (−0.85 to 0.04)	−0.38 (−0.79 to 0.04)	−0.04 (−0.47 to 0.40)	0.177
Incidence ratio for duration of moderately bad symptoms	1.00	1.21 (0.92 to 1.61)	0.91 (0.68 to 1.22)	1.11 (0.85 to 1.44)	1.12 (0.85 to 1.47)	0.369
Odds ratio for use of antibiotics	1.00	0.15 (0.03 to 0.73)	0.13 (0.03 to 0.63)	0.29 (0.06 to 1.55)	0.12 (0.03 to 0.59)	0.011

All estimates adjusted for self help advice given. Frequency symptoms adjusted for severity of frequency symptoms at baseline.

Cost effectiveness of management strategies for urinary tract infections: results from randomised controlled trial

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EDITORIAL by Mangin

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STUDY QUESTION What are the costs and cost effectiveness of different management strategies for urinary tract infection in women as shown by the results from a randomised controlled trial?

SUMMARY ANSWER Dipstick testing with targeted antibiotics is likely to be cost effective if the value of saving a day of moderately bad symptoms is valued at £10 or more, but caution is required given the uncertainty surrounding the estimates.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS There is limited information on the economic implications of common management strategies for urinary tract infections in primary care. This paper provides estimates of the costs and effectiveness of commonly used strategies.

Design and method

An analysis of cost effectiveness was carried out alongside a randomised controlled trial comparing five management strategies for urinary tract infections in primary care. Patients were randomised to one of five management groups: empirical immediate antibiotics; empirical delayed antibiotics; antibiotic targeted by symptom score; antibiotic according to dipstick algorithm (nitrites or leucocytes and a trace of blood); or midstream urine analysis with symptomatic treatment until culture and sensitivity results were available and then antibiotics targeted accordingly. The differences between the numbers of days of symptoms in the different strategies were used to estimate symptom days avoided.

Estimation of costs

Costs were estimated from an NHS perspective and included the recruitment consultation with the general practitioner and all NHS contacts related to urinary tract infection in a one month follow-up period. Costs for the recruitment visit included the consumable costs for midstream urine analysis and dipstick tests plus laboratory costs for the urine analysis. Practitioners recorded the duration of this visit. We obtained details of use of resources during follow-up directly from the patients' general practice notes. All costs were estimated for the year 2005-6 in pounds (£). No time discounting was required because of the short duration of the study. The results of the cost effectiveness study are based on the 83% (257/309) of participants for whom we had estimates of both effectiveness and follow-up costs.

Participants and setting

Data were obtained from a randomised controlled trial of 309 non-pregnant adult women aged 18-70 in primary care.

Main results and the role of chance

All management strategies for urinary tract infection have similar resource implications. The duration of symptoms was similar between groups, with the dipstick strategy being associated with the shortest duration of symptoms. The midstream urine, immediate antibiotic, and symptoms score groups were all dominated by another strategy that was both more effective and cheaper. The immediate antibiotics and dipstick testing groups were not dominated, and incremental results are given for the dipstick group compared with the immediate antibiotic group. Compared with the group given immediate antibiotics, the dipstick strategy cost £10 per additional day that symptoms were avoided.

Bias, confounding, and other reasons for caution

These results should be interpreted with caution because of the lack of statistically significant differences between the groups for symptom days avoided. In addition, our analysis did not quantify the benefits associated with reducing the use of antibiotics, such as less antibiotic resistance. Strategies that reduce the use of antibiotics are thus undervalued. The highest numbers of individuals receiving antibiotics were in the immediate antibiotics group (96%), while the lowest rates of antibiotic use were in the dipstick (76%) and delayed antibiotics groups (75%). Finally, it was unclear what value should be placed on a day of moderate to severe symptoms avoided. Our analysis suggests that each additional day of symptom can be avoided at a cost of about £10. A judgment would be needed as to whether the value of a symptom day avoided exceeds this.

Study funding/potential competing interests

This study was funded by the National Institute for Health Research Health Technology Assessment Programme.

COST EFFECTIVENESS OF STRATEGIES AT ONE MONTH FOLLOW-UP

Study group	Total cost (including recruitment visit and 1 month follow-up)	Days of moderate/severe symptoms	Incremental cost effectiveness per day of symptoms avoided
Midstream urine analysis	£37	4.17	Dominated
Delayed antibiotics	£32	3.92	Dominated
Symptom score	£32	3.92	Dominated
Immediate antibiotics	£31	3.63	—
Dipstick testing	£35	3.14	£9.70

Women's views about management and cause of urinary tract infection: qualitative interview study

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EDITORIAL by Mangin

RESEARCH, pp 405, 406, 408

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STUDY QUESTION What are the views of women on the acceptability of different management strategies for urinary tract infection, including delayed antibiotics?

SUMMARY ANSWER Women were open to alternative management strategies, but some of those asked to delay taking antibiotics felt a lack of validation or that their general practitioner had not listened to them.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Women with signs/symptoms of urinary tract infection prefer to avoid taking antibiotics. If women are asked to delay taking antibiotics, the clinician needs to address the particular worries that women might have and explain the rationale for not using antibiotics immediately.

Rationale, design, data collection method

Most women presenting in primary care with urinary tract infection are prescribed an antibiotic. In this qualitative study with semistructured one to one interviews conducted with women attending their general practitioner with signs/symptoms of urinary tract infection we elicited views concerning the use of antibiotics, causes of the infection, and management strategies for uncomplicated infection, including the delayed prescribing of antibiotics.

Participants and setting

Twenty women from a randomised controlled trial investigating five different management strategies. The trial was conducted in seven general practices across four counties in southern England. Interviews were conducted in the homes of the participants.

Recruitment/sampling strategy

Eligible participants were taking part in the larger trial, had consented to have a single face to face interview, and had been allocated to a management group in which delayed antibiotics were specified by the protocol (and negotiated with the patient). We explored participants' thoughts on management and their views about and experiences of antibiotic delay.

Data analysis method

We used principles of constant comparison to generate key themes grounded in reported experiences and understandings. Transcribed interviews were organised and systematically analysed to identify key views and experiences regarding urinary tract infection and its management. We checked analysis to safeguard quality (including the validity of themes and consistency of their allocation to the transcribed text).

Main findings

Women indicated a desire to avoid taking antibiotics and were open to alternative management strategies, including delayed antibiotics. They valued the opportunity to avoid unwanted side effects associated with antibiotics. A delayed prescription seemed to reassure them and validate their experience of their symptoms and reason for their visit to their general practitioner. Some women expressed self blame and attributed their signs/symptoms to negligence; these women might be particularly vulnerable to feelings of not being taken seriously when their general practitioner proposes a strategy of no antibiotics or delayed antibiotics. Patients' expectations are likely to focus on being understood and believed and in being helped to understand the rationale for alternative management strategies, such as antibiotic delay.

HOW LONG WOMEN WAITED BEFORE THEY VISITED THEIR GENERAL PRACTITIONER

Time waited before consultation	No of patients
1 night and 1 day	1
2-3 days	6
4 days	1
7 days	5
10 days	1
3 weeks	2
4 weeks	1
Unclear	3

Implications

While women are likely to be open to antibiotic delay as a management strategy for uncomplicated urinary tract infection, satisfaction (and speculatively adherence) is likely to be enhanced if the rationale for the management approach suggested is clearly presented and is contextualised in individual women's understanding of their infection and their attempts to self care before consulting.

Bias, limitations, generalisability

Interviews provide useful perspectives on events or experiences but not a window to events as they occur. Observation of primary care consultations in which the strategy of antibiotic delay is used would improve our understanding of how this strategy is negotiated in practice and help us to understand how this approach might be optimised. The interviewees came from a preselected population who had already consented to randomisation and the average practice population might be less receptive to the concept of delayed treatment. The key findings, however, are similar to those of other studies that looked at patients' views on antibiotics and the strategy of antibiotic delay.

Study funding/potential competing interests

The Health Technology Assessment programme funded the study (grant reference: 97/14/06). The HTA had no involvement in the research process or writing of this article.

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Presentation, pattern, and natural course of severe symptoms, and role of antibiotics and antibiotic resistance among patients presenting with suspected uncomplicated urinary tract infection in primary care: observational study

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STUDY QUESTION What is the natural course of urinary tract infection and what are the important predictors of severe symptoms and the effects of antibiotics and antibiotic resistance?

SUMMARY ANSWER Antibiotic resistance and not prescribing antibiotics are associated with prolonged more severe symptoms.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Antibiotic resistance is associated with delayed complete resolution of symptoms. In this study of women with urinary tract infection, there was a clinically important increase in more severe and prolonged symptoms associated with antibiotic resistance and not prescribing antibiotics. Women with a history of cystitis, frequent somatic symptoms (high somatisation), and severe symptoms at presentation are likely to have severe symptoms for more than three days.

Participants and setting

839 non-pregnant adult women aged 18-70 presenting with suspected urinary tract infection in primary care; 684 women provided some information on symptoms; 511 had both laboratory results and complete symptom diaries.

Design, size, and duration

Observational study relating symptom severity and duration to antibiotic use, antibiotic resistance, and other clinical predictors.

Main results and the role of chance

We had laboratory results and complete information on symptoms for 511. For women with infections sensitive to antibiotics, severe symptoms, rated as a moderately bad problem or worse, lasted 3.32 days on average. After adjustment for other predictors, moderately bad symptoms lasted 56% longer (incidence rate ratio 1.56, 95% confidence interval 1.22 to 1.99, P<0.001) in women with resistant infections; 62% longer (1.62, 1.13 to 2.31, P=0.008) when no antibiotics were prescribed; and 33% longer (1.33, 1.14 to 1.56, P<0.001) in women with urethral syndrome. The duration of symptoms was shorter if the doctor was perceived to be positive about diagnosis and prognosis (continuous 7 point scale: 0.91, 0.84 to 0.99; P=0.021) and longer when the woman had frequent somatic symptoms (1.03, 1.01 to 1.05, P=0.002; for each symptom), a history of cystitis, urinary frequency, and more severe symptoms at baseline. Chance is less likely given the levels of significance, previous research, and group differences all being in the hypothesised direction.

Bias, confounding, and other reasons for caution

Few women received no treatment so negative comparisons here must be treated with caution. A wide range of potential confounders were used (with a 10-30% change in estimates), but uncontrolled confounding is possible. Loss of follow-up diary information was not related to key baseline variables.

Generalisability to other populations

Patients came from a wide range of practice settings and most women approached agreed to participate, so the sample should be generalisable to primary care settings.

Study funding/competing interests

The study was funded by the NIHR Heath Technology Assessment programme. JAL has acted as a consultant for Bayer.

INCIDENCE RATE RATIOS (95% CONFIDENCE INTERVALS) AND P VALUES FOR RELATION BETWEEN ANTIBIOTIC RESISTANCE AND DURATION OF SYMPTOMS RATED MODERATELY BAD OR WORSE

Sensitivity	Univariate analysis		Multivariate analysis	
Sensitive (mean 3.32 days)	1.00	—	1.00	—
Unknown	1.00 (0.79 to 1.27)	0.996	1.03 (0.81 to 1.30)	0.833
Resistant	1.42 (1.12 to 1.81)	0.004	1.56 (1.22 to 1.99)	<0.001
No antibiotic	1.49 (1.06 to 2.10)	0.023	1.62 (1.13 to 2.31)	0.008
Urethral syndrome	1.29 (1.12 to 1.49)	<0.001	1.33 (1.14 to 1.56)	<0.001
Other predictors:				
Positive approach to natural course	0.93 (0.87 to 0.99)	0.020	0.91 (0.84 to 0.99)	0.021
Perceived personal relationship	1.04 (1.00 to 1.07)	0.043	1.05 (1.01 to 1.10)	0.016
Previous cystitis	1.26 (1.09 to 1.46)	0.002	1.25 (1.07 to 1.46)	0.004
Somatic symptom inventory (Number of symptoms)	1.04 (1.03 to 1.06)	<0.001	1.03 (1.01 to 1.05)	0.002
Severity of baseline unwell group of symptoms	1.11 (1.07 to 1.16)	<0.001	1.07 (1.02 to 1.12)	0.006
Daytime frequency (No of times)	1.01 (1.00 to 1.02)	0.008	1.01 (1.00 to 1.02)	0.005

Neurological outcomes at 18 months of age after moderate hypothermia for perinatal hypoxic ischaemic encephalopathy: synthesis and meta-analysis of trial data

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STUDY QUESTION Does moderate hypothermia improve survival and neurological outcome in infants with perinatal hypoxic-ischaemic encephalopathy?

SUMMARY ANSWER Therapeutic hypothermia reduced the combined rate of death and severe disability, and in survivors reduced the rates of severe disability, cerebral palsy, and neurodevelopmental impairment at 18 months of age.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS Three randomised controlled trials have compared moderate hypothermia with normal care for neonates who have hypoxic-ischaemic encephalopathy. All showed a trend to benefit in the primary outcome of death or disability at 18 months of age, but only one reached statistical significance; thus hypothermia was not recommended for general use. Our meta-analysis of these trials and an additional seven trials shows that hypothermia is an effective therapy that significantly improves survival and neurological outcomes in survivors.

Selection criteria for studies

Studies that compared moderate hypothermia with normal care in newborn infants with a diagnosis of perinatal hypoxic-ischaemic encephalopathy were identified from the Cochrane central register of controlled trials, the Oxford database of perinatal trials, PubMed, previous reviews, and abstracts. Meta-analysis was performed using a fixed effect model. Risk ratios (RR), risk difference (RD), and the number needed to treat (NNT), with 95% confidence intervals, were calculated.

Primary outcome

The primary outcome measure was the combined rate of death or major neurodevelopmental disability after at least 18 months' follow-up. Other outcomes included survival without neurological abnormalities, specific neurological impairments, mortality, and the interaction between severity of encephalopathy and treatment effect.

Main results and the role of chance

We found three trials, encompassing 767 infants, that included information on death and major neurodevelopmental disability after at least 18 months' follow-up care in neonates with hypoxic-ischaemic encephalopathy. Therapeutic hypothermia significantly reduced the combined rate of death and severe disability (RR 0.81, 95% confidence interval 0.71 to 0.93, P=0.002; RD 0.11, 95% CI 0.18 to 0.04; NNT 9, 95% CI 5 to 25). Hypothermia increased survival with normal neurological function (RR 1.53, 95% CI 1.22 to 1.93, P<0.001; RD 0.12, 95% CI 0.06 to 0.18, NNT 9, 95% CI 5 to 17), and in infants who survived 18 months or more reduced the rates of severe disability (P=0.006), cerebral palsy (P=0.004), and mental and psychomotor developmental index of less than 70 (P=0.01 and P=0.02, respectively). No significant interaction between severity of encephalopathy and treatment effect was detected. Seven further trials reported survival data, allowing mortality to be assessed in a total of 1320 infants. Mortality was significantly reduced when we assessed all 10 trials (relative risk 0.78, 95% CI 0.66 to 0.93, P=0.005; RD 0.07, 95% CI 0.12 to 0.02; NNT 14 (95% CI 8 to 47).

Bias, confounding, and other reasons for caution

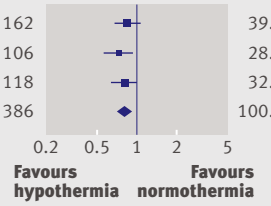
The trials were of high methodological quality, but none was able to mask treatment assignment (although neurodevelopmental assessment was masked), and the method of cooling differed among the studies. No study has yet reported outcomes in later childhood.

Study funding/potential competing interests

AJG was supported by the Health Research Council of New Zealand. Imperial College London (ADE and DA) and University of Oxford (PB, EJ, and BS) are Comprehensive Biomedical Research Centres. Olympic Medical Corp (Seattle, WA) loaned equipment to AJG, MT, and DA for pilot studies preceding the CoolCap trial. The University of Auckland has applied for a related patent that names AJG; however, AJG has no financial interest. DA, ADE, AJG, MT, and AW were members of the CoolCap trial scientific group. DA, PB, ADE, EJ, BS, HH, ML, MT, and AW were members of the TOBY trial scientific group and are members of the TOBY Children study scientific group.

EFFECT OF THERAPEUTIC HYPOTHERMIA COMPARED WITH STANDARD CARE (NORMOTHERMIA) ON DEATH OR DISABILITY ("EVENTS")

Study or subgroup	Hypothermia Events	Hypothermia Total	Normothermia Events	Normothermia Total	Risk ratio (95% CI)	Weight (%)	Risk ratio (95% CI)
TOBY	74	163	86	162		39.0	0.86 (0.68 to 1.07)
NICHD	45	102	64	106		28.3	0.73 (0.56 to 0.95)
CoolCap	59	116	73	118		32.7	0.82 (0.65 to 1.03)
Total (95% CI)		381		386		100.00	0.81 (0.71 to 0.93)
Total events	178		223				



Test for heterogeneity: χ^2=0.82, degrees of freedom=2 (P=0.66); I^2=0%. Test for overall effect: Z=3.03 (P=0.002)