RESEARCH

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LIFE IN VIEW/SPL

WHAT OUR READERS ARE SAYING

Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism

According to this meta-analysis of nine studies, including 16 701 patients, published on 13 November, the new oral anticoagulants have a similar risk of recurrence of acute venous thromboembolism and all cause mortality as vitamin K antagonists, although rivaroxaban is associated with a reduced risk of bleeding. Large randomised controlled trials are needed, powered to directly compare new oral anticoagulants and assess the superiority of any one of these drugs over another, say the authors.

Here's what haematologist Jecko Thachil said in a rapid response:

"The bigger safety issue with these agents is likely to be related to the lack of compliance . . . Unlike the other routine drugs, the short half life of these newer drugs would mean rebound thrombotic risk even after missing a day's tablet. This 'adverse effect' is seen much less commonly with warfarin, whose half life is much longer, and missing one or two doses does not lead to complete washout of the drug from the circulation. Also, visits to the anticoagulation department provide an additional checkpoint to ensure the compliance of vitamin K antagonists and a place for regular advice about the importance of anticoagulant therapy. Regular visits are required to educate patients and ensure compliance."

Effect of intensive structured care on individual blood pressure targets in primary care

In this randomised controlled trial of 2185 patients from 119 general practices in Australia, intensive structured care resulted in higher levels of blood pressure control in a primary care setting, with clinically lower blood pressure and absolute risk of future cardiovascular events overall and with more people achieving their target blood pressure.

Medical student Simon Pybus responded:

"The impact of initial blood pressure may be a further confounding factor not considered for response to antihypertensive therapy. Intervention groups had slightly higher mean systolic blood pressure, possibly generating a greater response to therapy. Although this effect has been disputed, an artificially greater reduction in blood pressure may still be present. The significance of this variable for response to treatment deserves further exploration."

Comprehensive self management and routine monitoring in chronic obstructive pulmonary disease patients in general practice: randomised controlled trial

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STUDY QUESTION What are the effects of comprehensive self management and routine monitoring on quality of life, frequency and patients' management of exacerbations, and self efficacy compared with usual care in primary care patients with chronic obstructive pulmonary disease (COPD)?

SUMMARY ANSWER Comprehensive self management or routine monitoring did not show long term benefits over usual care alone on quality of life or self efficacy, although patients in the self management group seemed more capable of appropriately managing exacerbations compared with the usual care group.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Well studied and effective management strategies are needed to face the burden of COPD, particularly in general practice. Although self management did not improve quality of life or self efficacy, it did improve management of exacerbations among COPD patients in primary care.

Design

This was a 24 month, multicentre, investigator blinded, three arm, parallel group, randomised controlled trial using a computer generated two block randomisation procedure with stratification on severity of COPD, smoking status, and past exacerbation frequency. Patients were allocated to the self management programme "Living well with COPD" provided by practice nurses who acted as case managers, routine monitoring through scheduled periodic monitoring visits provided by practice nurses, or usual care (that is, care at the initiative of the patient).

Participants and setting

Fifteen Dutch general practices recruited patients ≥35 with a spirometry confirmed diagnosis of COPD (post-bronchodilator ratio of forced expiratory volume in one second to forced vital capacity (FEV_1/FVC) <0.70).

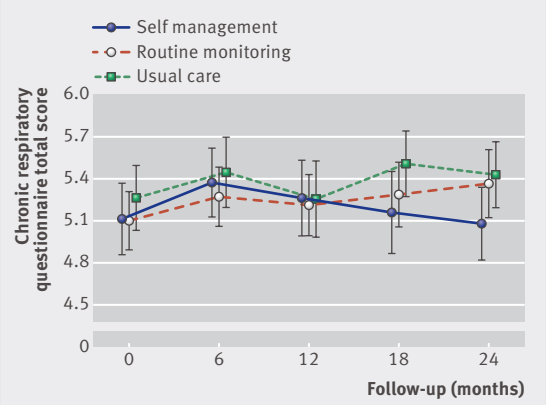
Outcome(s)

The primary outcome was change from baseline in health related quality of life at 24 months (self administered chronic respiratory questionnaire). Secondary outcomes were frequency and management of exacerbations as recorded with an automated call system and self efficacy scores (COPD self-efficacy scale).

Main results and the role of chance

We randomly allocated 165 patients with COPD to the three groups. At 24 months, we found no statistically significant treatment differences between the groups in mean chronic respiratory questionnaire total score. Changes in self efficacy score and exacerbation frequency did not differ between the three groups. In the second year of follow-up, more exacerbations in the self management group compared with the usual care group were managed by an increase of bronchodilator use (odds ratio 2.81, 95% confidence interval 1.16 to 6.82) and by starting prednisolone, antibiotics, or both (3.98, 1.10 to 15.58).

Changes in unadjusted means (95% CI) of chronic respiratory questionnaire total score over 24 months



Harms No participants died during the study period.

Bias, confounding, and other reasons for caution

We used strict protocols and registration forms to prevent potential treatment contamination caused by randomising patients instead of practices. We checked practices' compliance during and after the study.

Generalisability to other populations

More than 60% of the patients who had COPD according to their general practitioner were excluded, mostly because of a post-bronchodilator FEV_1/FVC of 0.70 or above. Of the 285 eligible patients, less than 60% were willing to participate. These patients were comparable to patients who declined participation in terms of sex, age, and disease severity (FEV_1). Almost 16% dropped out during follow-up, but baseline characteristics did not differ between dropouts and those who finished follow-up; in addition, we anticipated a 25% dropout rate in our sample size calculation.

Study funding/potential competing interests

This study was funded by the Netherlands Organisation for Health Research and Development (ZonMw) and Partners in Care Solutions for COPD (PICASSO).

Trial registration number

Clinical trials NCT00128765.

bmj.com

- Research: Glasgow supported self-management trial (GSuST) for patients with moderate to severe COPD (*BMJ* 2012;344:e1060)
- Research: Community based integrated intervention for prevention and management of chronic obstructive pulmonary disease (COPD) in Guangdong, China (*BMJ* 2010;341:c6387)
- News: Improving COPD and asthma outcomes to EU average would save 2000 lives a year in the UK (*BMJ* 2011;343:d4651)
- Editorial: Improving the management of COPD (*BMJ* 2011;342:d1674)

The spectrum of thyroid disease and risk of new onset atrial fibrillation: a large population cohort study

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- Bad Medicine: Thyroid disease (*BMJ* 2012;345:e7596)
- Clinical Review: Diagnosis and management of primary hyperparathyroidism (*BMJ* 2012;344:e1013)
- Research: Influence of experience on performance of individual surgeons in thyroid surgery (*BMJ* 2012;344:d8041)

STUDY QUESTION What is the risk of atrial fibrillation in relation to the whole spectrum of thyroid function?

SUMMARY ANSWER Thyroid function is closely associated with the risk of atrial fibrillation, with even high normal euthyroidism and subclinical hyperthyroidism associated with increased risk, whereas subclinical and overt hypothyroidism are associated with lowered risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Patients with overt hyperthyroidism are known to have increased risk of atrial fibrillation. In this study, the risk of atrial fibrillation was closely associated to thyroid activity, with a low risk in overt hypothyroidism, high risk in hyperthyroidism, and a TSH level dependent association with risk of atrial fibrillation across the spectrum of subclinical thyroid disease.

Participants and setting

Participants in our study were citizens of Copenhagen, Denmark, aged 18 years or more who underwent thyroid screening at the Copenhagen General Practitioners Laboratory between 1 January 2000 and 22 January 2010.

Design, size, and duration

We included 586 460 individuals in the study population with a mean (SD) age of 50 (17) years: 562 461 were euthyroid, 1670 overt hypothyroid, 12 087 subclinical hypothyroid, 3966 overt hyperthyroid, and 6276 subclinical hyperthyroid. During a follow-up of 3 215 807 person years, a total of 17 154 patients had a hospital diagnosis of first time atrial fibrillation.

Main results and the role of chance

Overall, adjusted incidence rates for atrial fibrillation were lower in patients with overt hypothyroidism and higher in patients with overt hyperthyroidism compared with the euthyroid state. Patients with subclinical hypothyroidism had incidence rates slightly lower than euthyroid individuals, whereas the subclinical hyperthyroid patients had markedly higher rates of atrial fibrillation. Patients with overt hyperthyroidism had higher rates of atrial fibrillation than those with subclinical hyperthyroidism (see table). An almost linear relation was seen between thyroid function and risk of atrial fibrillation—that is, from a decreased risk in overt and subclinical hypothyroidism, to an increased risk in subclinical and overt hyperthyroidism compared with the euthyroid state. A similar almost linear relation was seen with levels of thyroid stimulating hormone (TSH) in mild hyperthyroid states and risk of atrial fibrillation: compared with the normal euthyroid individuals (TSH levels 0.4–5.0 mIU/L), the risk increased with decreasing TSH from high normal euthyroidism (TSH 0.2–0.4 mIU/L) with an incidence rate ratio of 1.12 (95% CI 1.03 to 1.21) to subclinical hyperthyroidism with reduced TSH (0.1–0.2 mIU/L) and incidence rate ratio 1.16 (0.99 to 1.36) and subclinical hyperthyroidism with suppressed TSH (<0.1 mIU/L) and incidence rate ratio 1.41 (1.25 to 1.59).

Bias, confounding, and other reasons for caution

As this was an observational study, we were not able to draw direct conclusions on causal relations of the findings. Specifically, it is impossible with our available data to explore the reasons for each individual subject undergoing thyroid screening. Furthermore, the study was based on administrative registers that did not include clinical parameters correlated with outcome such as body mass index, smoking status, serum lipid levels, thyroid autoantibody levels, and echocardiographic or electrocardiographic findings.

Generalisability to other populations

The Danish population comprises mainly white people, and so extrapolation of these results to other ethnic groups should be done with care.

Study funding/potential competing interests

The study was part funded by unrestricted grants from the Danish Heart Foundation, Danish Thyroid Association, Agnes and Knut Mørk Foundation, and the FUKAP and START Foundations, Gentofte University Hospital. The authors have no conflicts of interest to declare.

Rates and incidence rate ratios (IRR) of atrial fibrillation in study cohort by thyroid function

	Thyroid function				
	Overt hypothyroid	Subclinical hypothyroid	Euthyroid	Subclinical hyperthyroid	Overt hyperthyroid
No of events	42	402	16 275	435	183
Time at risk (1000 person years)	9.7	67.5	3100.0	34.9	23.7
Incidence rate (No/1000 person years):					
Crude	4.3	6.0	5.2	12.5	7.7
Age and sex adjusted	4.4	5.7	6.4	8.4	9.1
Incidence rate ratio (95% CI)*	0.67 (0.50 to 0.92)	0.88 (0.79 to 0.97)	1.00 (reference)	1.30 (1.18 to 1.43)	1.41 (1.22 to 1.63)
Attributable risk percent†	NA	NA	—	23%	30%

*Risk estimates are adjusted for sex, age, calendar year, Charlson comorbidity index, and socioeconomic status.
†Attributable risk percent = (IRR−1)/IRR×100.

Cardiovascular medicine updates from BMJ Group http://www.bmj.com/specialties/cardiovascular-medicine

Cardiovascular mortality after pre-eclampsia in one child mothers: prospective, population based cohort study

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Practice: Pre-eclampsia (*BMJ* 2012;345:e4437)
Research: Cancer after pre-eclampsia (*BMJ* 2004;328:919)

STUDY QUESTION

Is pre-eclampsia in the first pregnancy associated with an increased risk of cardiovascular mortality in all affected mothers?

SUMMARY ANSWER

For women who have pre-eclampsia in first pregnancy, excess risk of cardiovascular death is concentrated primarily among those with no additional children; women who go on to have more children are at relatively modest risk.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Women with pre-eclampsia in their first pregnancy (especially preterm pre-eclampsia) have an increased risk of cardiovascular death. This result depends strongly on whether the women have more pregnancies after the pre-eclamptic pregnancy.

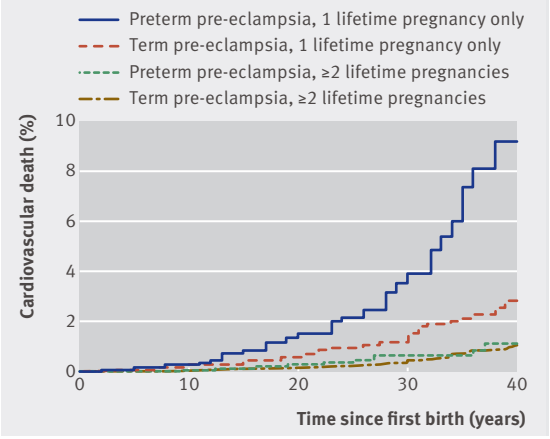
Participants and setting

Our study was based on the Medical Birth Registry of Norway, which includes all 2.5 million births in Norway in 1967-2009. We followed 836 147 Norwegian women with a first singleton birth between 1967 and 2002. Data were internally linked to identify each woman's later pregnancies, up to 2009.

Design, size, and duration

Maternal deaths were identified through linkage to the national Cause of Death Registry. More than 23 000 women had died by 2009, of whom 3891 died of cardiovascular causes. We assessed associations between pre-eclampsia and cardiovascular death by using hazard ratios, as estimated by Cox regression analyses. Hazard ratios were adjusted for maternal education (three categories), maternal age at first birth, and year of first birth.

Cumulative rate of cardiovascular death in women with pre-eclampsia during first pregnancy



Main results and the role of chance

The figure shows cumulative rates of cardiovascular death in the study cohort. The rate of cardiovascular mortality among women with preterm pre-eclampsia was 9.2% after having only one child, falling to 1.1% for those with two or more children. With term pre-eclampsia, the rates were 2.8% and 1.1%, respectively. Risk of cardiovascular death overall nearly doubled in women with pre-eclampsia in the first pregnancy, compared with those who did not have pre-eclampsia (adjusted hazard ratio 1.9, 95% confidence interval 1.6 to 2.2). The risk increase in cardiovascular death was higher after preterm pre-eclampsia than after term pre-eclampsia (3.7 (2.7 to 4.8) *v* 1.6 (1.4 to 2.0)). Women with only one child in their lifetime had a particularly high increase in risk of cardiovascular death (9.4 (6.5 to 13.7) after preterm pre-eclampsia; 3.4 (2.6 to 4.6) after term pre-eclampsia). These hazard ratios fell to 2.4 (1.5 to 3.9) and 1.5 (1.2 to 2.0), respectively, among women with pre-eclampsia who went on to have more births. There was little evidence of additional risk after recurrent pre-eclampsia. Death in men was unaffected by their partner's pre-eclampsia.

Bias, confounding, and other reasons for caution

Weaknesses of this study included a lack of detailed data for underlying cardiovascular risk factors before and after pregnancy, lack of information on important covariates such as body mass index and smoking, and an absence of information on why women might have had only one child. Low social class and education are unlikely to be confounders, since they were associated with cardiovascular risk but with a larger family size. The analysis of fathers provided further evidence that social factors might not be the underlying explanation. The results suggest that the health problems leading to pre-eclampsia and cardiovascular disease could themselves discourage or prevent further pregnancies. These data do not support a causal relation between pre-eclampsia and cardiovascular death.

Generalisablity to other populations

We expect similar results in other populations in which relatively few women stop their reproduction after one child (15% in Norway), thus allowing the possibility of strong selection in one child families.

Study funding/potential competing interests

All researchers were independent of the study funders, the Norwegian Research Council and the National Institute of Environmental Health Sciences.

Oncology updates from BMJ Group http://www.bmj.com/specialties/oncology

Prognosis in women with interval breast cancer: population based observational cohort study

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STUDY QUESTION

What is the prognosis for women with breast cancer detected after a normal screening mammogram (interval cancers) compared with breast cancer detected among women not invited to mammography screening?

SUMMARY ANSWER

Tumours associated with interval breast cancers are more likely to be larger than those diagnosed in the absence of mammography screening, although the survival outcomes were strikingly similar between the groups.

WHAT IS KNOWN AND WHAT THIS PAPER ADDS

Previous randomised trials on mammography screening found that interval breast cancers were associated with similar, better, or poorer survival compared with non-screened breast cancers. Our study provides no compelling support for more aggressive primary treatment of interval breast cancers than non-screen detected cancers with similar prognostic features.

Participants and setting

We analysed data from the population based Norwegian breast cancer screening programme, successively implemented in different counties from 1996 to 2005. Participants were women with breast cancer diagnosed at age 50 to 72 years.

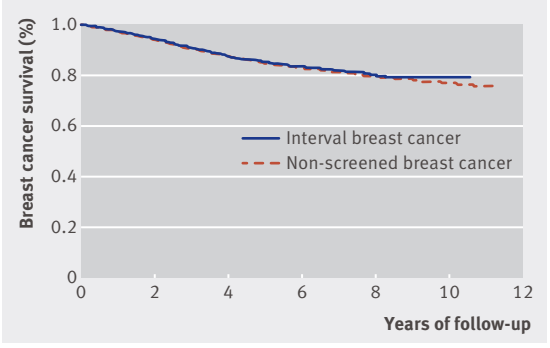
Design, size, and duration

This was a prospective observational study. We compared the prognosis of 1816 women with interval breast cancer diagnosed after a normal mammogram with 5300 women with breast cancer diagnosed within the same time period among women not yet invited to screening. Interval cancers are defined as breast cancers detected after a normal mammogram but before the next scheduled mammography.

Main results and the role of chance

Although interval cancers on average were slightly larger than tumours in women not invited to screening, histological type and axilliary lymph node status did not differ between the two groups. After 10 years of follow-up, the survival rates were 79.1% (95% confidence interval 75.4% to 82.3%) among women with interval cancer and 76.8% (75.3% to 78.2%) among women in the non-screened cancer group (hazard ratio 0.98, 95% confidence interval 0.84 to 1.15; P=0.53).

Cumulative survival plot for women with breast cancer by group



Bias, confounding, and other reasons for caution

In each Norwegian county, introduction of the breast cancer screening programme was preceded by the establishment of specialised multidisciplinary teams. These teams provide the best possible management of all newly diagnosed breast cancers in the county, regardless of whether they are diagnosed by mammography screening. Owing to the design of this study, only women with interval cancers were managed by multidisciplinary teams. The possible influence of such confounding cannot be tested in our study because it would require more detailed individual data on prognostic factors, treatment, and overall management. However, the similar proportion of women in each group who received adjuvant tamoxifen provides some reassurance against a major confounding.

Generalisability to other populations

These data are generalisable to other populations of women aged 50-72 years.

Study funding/potential competing interests

This study was funded by research grants from the Norwegian Research Council and Frontier Science. We have no competing interests.