SCIENTIFIC LETTERS

Renin angiotensin system inhibition is associated with reduced free radical concentrations in arteries of patients with coronary heart disease

Angiotensin II, which is also thought to play a key role in atherosclerosis, has recently been shown to have pro-oxidant effects, by increasing superoxide ($\bullet O_2^-$) production in human arteries.[1] Oxidative stress, a state of excessive free radical activity which is associated with reduced bioavailable nitric oxide (NO), may be evident in patients with coronary heart disease (CHD).[2] Lately ACE inhibitors have been shown to reduce cardiovascular morbidity and mortality in patients at high risk of CHD.[3] The aim of the present study was to determine, which, if any, risk factors and drug treatments were associated with altered free radical concentrations in the arteries of CHD patients undergoing coronary artery bypass grafting (CABG).

Seventy nine consecutive patients who were undergoing CABG were prospectively included in this study. Patient characteristics were determined by review of case records. A history of current cigarette smoking, hypertension (defined as either current antihypertensive treatment or a blood pressure > 140/90 mm Hg), diabetes mellitus, and hypercholesterolaemia (plasma cholesterol > 5.5 mmol/l) were considered as risk factors for CHD.

Distal segments of left internal mammary artery which were obtained at the time of CABG were taken to the laboratory in Krebs-Hepes buffer (pH 7.4 ± 0.2), carefully dissected free of loose connective tissue, divided into 4–5 mm segments and weighed. Vascular $\bullet O_2^-$ was measured by lucigenin enhanced chemiluminescence in a liquid scintillation counter (Hewlet Packard Model Tricarb 2100TR).[1] Absolute counts were quantified with a xanthine/xanthine oxidase calibration curve for $\bullet O_2^-$ generation and reported as picomol per milligram per minute of tissue. Statistical analyses of vascular $\bullet O_2^-$ concentrations after log transformation were undertaken using the non-parametric Mann-Whitney Test and a stepwise multiple regression analysis was also performed. A probability value of $p < 0.05$ was considered significant. This study was approved by the hospital's ethics committee.

Table 1 Patient characteristics, including risk factors and treatments

	RAS inhibitor	*No RAS inhibitor*
Number of patients	19	60
Mean (SD) age (years)	61 (9)	62 (8)
Men, n (%)	13 (68)	45 (75)
Women, n (%)	6 (33)	15 (25)
Risk factors, n (%)		
Smoking	3 (16)	10 (17)
Hypertension	9 (47)	21 (35)
Diabetes mellitus	2 (10)	4 (7)
Hypercholesterolaemia	14 (73)	41 (68)
Mean (SD) plasma cholesterol, mmol/l	5.9 (1.2)	5.2 (0.9)
Medication, n (%)		
Aspirin	14 (74)	48 (80)
β Blockers	13 (68)	33 (55)
Calcium channel blockers	11 (58)	34 (57)
HMG-CoA reductase inhibitors	7 (37)	31 (52)
Nitroglycerin	12 (63)	34 (57)

RAS, renin angiotensin system; HMG-CoA, hydroxymethyl-glutaryl-CoA.

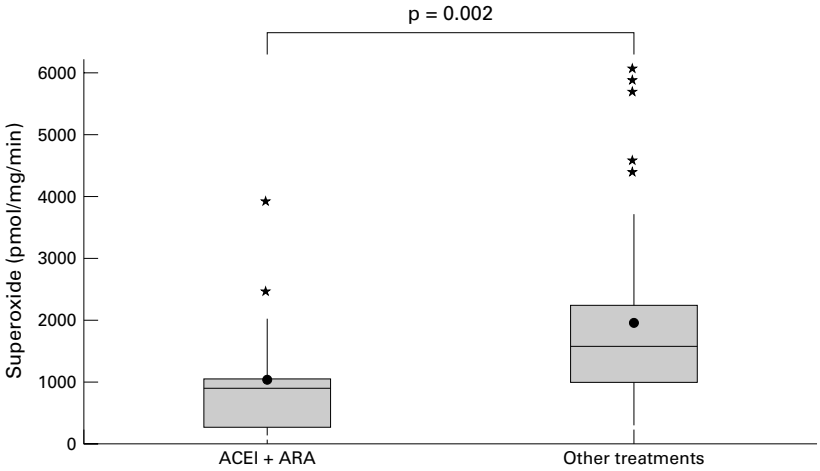

Figure 1 Boxplot graphical representation of superoxide concentrations (pmol/mg/min) in internal mammary arteries from patients undergoing coronary artery bypass surgery who were taking either an angiotensin converting enzyme inhibitor (ACEI) or an angiotensin type 1 receptor antagonist (ARA), compared to those patients not taking these treatments. Means are indicated by solid circles, rectangles represent the lower and upper limits of the interquartile range, and median values are demarcated inside the rectangles. The vertical lines (or "whiskers") represent the spread of the data. The upper line represents the upper, or third quartile, plus 1.5 (interquartile range), and the lower line represents the lower, or first quartile, minus 1.5 (interquartile range). The asterisks (*) represent outlying values which lie between 1.5 and 3 times away from the middle 50% of the data.

Data on age, sex, risk factors, and drug treatment are given in table 1. The profiles of risk factors and different classes of drug treatments were similar between patients who were taking an angiotensin converting enzyme (ACE) inhibitor or an angiotensin type 1 receptor antagonist (ARA), compared to those who were not taking these treatments.

An ACE inhibitor or ARA was prescribed in 16 and three patients, respectively. The median rate of production of $\bullet O_2^-$ in internal mammary arteries was 1137 (interquartile range (IQR) 1290) pmol/mg/min. Superoxide concentrations were lower in those patients taking either an ACE inhibitor or an ARA (857 (IQR 670) pmol/mg/min; n = 19) compared to those who were not (1600 (IQR 1511) pmol/mg/min; n = 60; p = 0.002; 95% confidence interval for median difference 487 to 1228 pmol/mg/min (fig 1)). No other associations between age, sex, risk factors or drug treatments and superoxide concentrations were identified.

We have shown, for the first time in human arteries, that $\bullet O_2^-$ concentrations were lower in patients treated with either an ACE inhibitor or an ARA, compared to those who were not. The clinical characteristics of both of these groups were similar such that the observed differences in vascular $\bullet O_2^-$ concentrations were unlikely to be explained by any other patient characteristic or treatment. It is of interest that despite the fact that a large proportion of these patients were taking drugs with putative antioxidant properties, such as aspirin, β blockers and HMG-CoA reductase inhibitors, vascular free radical concentrations were detected at physiologically important concentrations. The absence of any important antioxidant effect of these other treatments suggests that the sample size may not be sufficiently large to detect what may be a lesser antioxidant effect of these drugs. The variation in basal vascular $\bullet O_2^-$ concentrations observed in this and other investigations in humans,[4 5] and the lack of correlation of $\bullet O_2^-$ production with some atherosclerotic risk factors, may be caused by the heterogeneous clinical characteristics of patients with CAD.

Our observations raise two questions. The first is how does such treatment exert this effect? Though some ACE inhibitors may have direct free radical scavenging properties, this effect has been difficult to show at therapeutic concentrations in humans.[6] A more likely explanation is that the antioxidant effect of this treatment is caused by inhibition of the effects of angiotensin II.[1] The second question is what, if any, might be the therapeutic significance of this effect of RAS inhibitors? A reduction in vascular free radical production associated with RAS inhibition, as is the case in the current study, may lead to enhanced bioavailable nitric oxide in vivo.

Taken together, these observations suggest that RAS inhibition leads to a reduction in oxidative stress in patients with CHD. Given the damaging effects of increased free radical activity in the vasculature, the antioxidative effects of these treatment may be one further mechanism which may contribute to their beneficial effects in patients with CHD.

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Strong prognostic value of combining N-terminal atrial natriuretic peptide and ECG to predict death in heart patients from general practice

The exact role of natriuretic peptides in general practice remains to be defined.[1] While raised plasma concentrations of N-terminal atrial natriuretic peptide (N-ANP) or brain natriuretic peptide (BNP) are associated with left ventricular systolic dysfunction and heart failure,[2–4] the prognostic value of these peptides outside hospital populations remains uninvestigated. We recently showed that the risk of left ventricular systolic dysfunction in heart patients from general practice can be assessed from abnormal N-ANP concentrations, abnormal ECG, and a heart rate > diastolic blood pressure.[3] The importance of these prespecified variables, in particular a raised N-ANP, would be confirmed if they also predicted mortality. The present follow up study from general practice examines this question.

All subjects ⩾ 40 years of age from one general practice and all subjects ⩾ 50 years of age from two general practices in Copenhagen were screened from 1994 to 1996 by a procedure based on a questionnaire and review of general practice records. Of 2158 subjects, 357 had past or present signs or symptoms of heart disease; of these, 105 were excluded (and not invited for examination), 126 withdrew, and 126 subjects were examined. Reasons for exclusion by priority were: 38 living in nursing homes, 36 questionnaire non-responders, 21 patients without definite heart disease for administrative reasons in an early study phase, and 10 patients with advanced heart failure. Half the remaining subjects withdrew: 32 declined the invitation, 1 died, 37 were disabled because of various medical and psychosocial conditions, and 56 patients, after various degrees of contact, did not show up.[3 5] Those withdrawing were older than examined subjects (47% were ⩾ 80 years of age) but they did not have more recognised ischaemic heart disease, hypertension or diabetes as inferred from general practice case notes. As no self perceived deterioration of health was involved non-participation is understandable.

We thus examined 126 patients who were willing to, and fit for, attending an outpatient cardiological examination. Their mean age was 70 years (range 49–93 years), 55 were men, 30 had a previous myocardial infarction, 11 had atrial fibrillation, 69 had hypertension, 12 had diabetes, 31 had chronic obstructive pulmonary disease, and 43 had received treatment for suspected heart failure. On examination 15 had an echocardiographic left ventricular ejection fraction ⩽ 0.45, and 22 were normal according to a full cardiac assessment. The median plasma concentration of N-ANP in these 22 patients was 0.41 nmol/l (range 0.17–0.76 nmol/l; reagents OY NT-pro-ANP ^{125}I RIA kit, Biotop OY, Finland). A significantly raised plasma concentration of N-ANP was subsequently defined as > 0.8 nmol/l. Seventeen subjects had raised N-ANP, and 60 had an ECG showing QRS or ST changes, or both. The Danish Central Populations Register provided information on all deaths from the day of examination up to 2 May 2000. We used total death as the end point while waiting for a search on causes of death, the registration of which lags two years behind.

The approval of the hospital ethics committee was obtained, as was informed consent from those patients examined.

We observed 34 deaths during a median follow up period of 4.3 years (range 3.9–6.1 years). The three prespecified binary markers were examined in the multivariate Cox regression model along with sex and age (< or ⩾ 70 years). Significant predictors of mortality were raised N-ANP (hazard ratio 5.6, 95% confidence interval (CI) 2.7 to 11.3), abnormal ECG (hazard ratio 2.2, 95% CI 1.1 to 4.4), and age ⩾ 70 years (hazard ratio 2.9, 95% CI 1.3 to 6.4), while sex and "heart rate > diastolic blood pressure" were not significant predictors (z score < 1.96). A critical question is whether the relation between N-ANP and mortality is distorted by treatment with angiotensin converting enzyme inhibitor or loop diuretic, or both (n = 26). When treatment was entered into the final model the predictive power of all four variables remained strong and significant. We also tested the independent prognostic value of N-ANP in addition to recognised prognostic factors: N-ANP (nmol/l), age, ejection fraction, New York Heart Association (NYHA) (Ia, Ib, IIa, IIb, IIIb), and heart rate minus diastolic blood pressure (bpm − mm Hg) treated as continuous variables, and sex and abnormal ECG as dichotomised variables. The significant variables in this model were N-ANP (z = 4.1), NYHA (z = 2.5), age (z = 2.4), and male sex (z = 2.4).

Table 1 outlines survival in various groups formed by combining the three significant predictors from the prespecified Cox model. The effect of N-ANP and ECG was dependent on age. The table is therefore split at the mean age of 70 years. Data at 3 years and 6.1 years illustrate trends in survival (all subjects were followed for > 3 years). The younger reference group, with two normal test results, had a significantly better survival than the older reference group (96% *v* 71%, p = 0.0086). Raised N-ANP was seen in 10% of those with a normal ECG (6/[26 + 1 + 28 + 5]), and in 18% of those with an abnormal ECG (11/60). Compared with the age matched reference groups mortality was not significantly higher with a single abnormality of either a raised N-ANP or an abnormal ECG. Having two abnormal tests, however, was a strong predictor of death in both age groups.

The main finding of this study, along with its predecessor,[2] is that when N-ANP is measured in patients with an abnormal ECG it is a powerful predictor of early deaths and a moderate predictor of left ventricular systolic dysfunction in heart patients from primary care.

This study is the first to provide prognostic data about natriuretic peptide in heart patients from general practice. It supports the idea of using natriuretic peptide measurement in selected patients rather than advocating it for an unrestricted use. The strength of this study lies in its validation of prespecified variables, and that N-ANP remained the strongest predictor of death after considering recognised prognostic factors. A larger study is required to show the prognostic value of N-ANP in subjects with a normal ECG. BNP measurements were not available for this

Table 1 Survival of patients according to having an ECG with QRS or ST changes and N-terminal atrial natriuretic peptide (N-ANP) > 0.8 nmol/l or not

		3 year follow up		6.1 year follow up		Median survival (years)	Log rank test p value
	Total (n)	Deaths (n)	Survival actual (%)	Deaths (n)	Survival K-M (%)		
Patients < 70 years of age (n=53)							
Normal ECG, normal N-ANP	26	1	96	1	96	> 6.1	Reference
Abnormal ECG, normal N-ANP	22	2	91	4	82	> 6.1	0.052
Normal ECG, raised N-ANP	1	0	100	0	100	> 6.1	1.0
Abnormal ECG, raised N-ANP	4	3	25	3	25	1.6	< 0.0001
Patients ⩾ 70 years of age (n=67)							
Normal ECG, normal N-ANP	28	4	86	8	71	> 6.1	Reference
Abnormal ECG, normal N-ANP	27	4	85	8	70	> 6.1	0.46
Normal ECG, raised N-ANP	5	0	100	3	40	5.2	0.17
Abnormal ECG, raised N-ANP	7	6	14	7	0	1.1	0.0003

The p values test the hypothesis that 6.1 year survival in a group equals survival in the age matched reference group with a normal ECG and N-ANP. Survival is shown as actual percentages at 3 years and as Kaplan-Meier (K-M) estimates at 6.1 years.

study. Nor have we evaluated these variables in acute patients, which is a different situation.[4]

Just half the target group accepted our invitation for a full cardiac assessment. Those who withdrew were old, they were probably more disabled, and their prognosis may have been worse than for subjects who were examined. In view of the understandable withdrawal pattern, we believe our results are applicable to a scenario in general practice where a physician wants to make a risk assessment for a presumed heart patient without overt congestive heart failure. A normal ECG will convince the physician and patient of a favourable prognosis and a low likelihood of left ventricular systolic dysfunction. Our study suggests that measurement of natriuretic peptide is particularly useful in subjects with an abnormal ECG. If both N-ANP and the ECG are abnormal, further cardiac assessment seems sensible to determine whether treatable conditions exist, although we have no data on whether cardiac assessment will indeed change the outcome.

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Olav Wendelboe Nielsen formed the primary study hypothesis and core ideas, designed the protocol, made the data analysis and wrote the paper. Jørgen Fischer Hansen discussed core ideas and participated in the writing of the paper. Jørgen Hilden participated in statistical analysis and the writing of the paper. OWN will act as guarantor of the paper. The study was supported by the Danish Heart Foundation.

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Docetaxel induced cardiotoxicity

Docetaxel is a new taxoid antineoplastic agent.[1 2] Its mechanism of action is primarily related to its ability to enhance microtubule assembly and to stabilise microtubules by preventing their depolymerisation, thus disrupting normal cell division.[2] Since docetaxel has significant cytotoxic activity against human breast cancer in vitro and in vivo, it is widely used to treat patients with breast cancer, especially those with metastatic breast cancer. It has been shown that increased microtubule density, for which microtubule stabilisation is one potential mechanism, causes contractile dysfunction in cardiac hypertrophy.[3] Since docetaxel exerts its actions by stabilising microtubules, it is reasonable to consider that docetaxel may induce contractile dysfunction as a cardiotoxic agent. Thus, we examined the effect of docetaxel on cardiac function and the serum concentration of cardiac neurohormones one day before, one day after, and three weeks after docetaxel administration.

Table 1 Serial changes in biochemical and echocardiographic parameters

	1 day before chemotherapy	*1 day after chemotherapy*	*3 weeks after chemotherapy*	*Reference values*
Circulating concentrations				
BNP (pg/ml)	13.7 (1.9)	53.8 (3.5)*	12.6 (2.4)	< 20
ANP (pg/ml)	24.9 (4.5)	30.3 (4.6)	27.4 (3.9)	< 40
Noradrenaline (pg/ml)	277.1 (35.3)	277.1 (33.8)	257.9 (51.9)	100–450
Adrenaline (pg/ml)	33.0 (6.0)	32.4 (5.7)	39.0 (12.8)	< 100
Renin (resting supine) (ng/ml/h)	1.37 (0.27)	1.30 (0.23)	1.09 (0.68)	0.2–2.7
Aldosterone (pm/ml)	70.6 (8.2)	69.2 (7.0)	74.6 (16.0)	45–105.5
Echocardiographic parameters				
Fractional shortening (%)	36.4 (1.0)	36.0 (1.2)	37.5 (0.9)	> 28
Ejection fraction (%)	72.9 (5.2)	73.2 (6.3)	72.4 (7.4)	> 56
Mitral inflow E:A ratio	1.45 (0.16)	0.71 (0.24)*	1.29 (0.12)	> 1.0
Deceleration time (ms)	192.1 (9.9)	271.3 (16.3)*	209.2 (13.6)	199 (32)
Maximum diameter of IVC (mm)	12.5 (1.8)	12.9 (1.6)	12.0 (2.0)	< 23

All data are expressed as mean (SEM).
Two way analysis of variance (ANOVA) and Fisher's exact test for post hoc analysis were carried out for multiple comparisons among groups. *$p < 0.05$ versus a day before chemotherapy.
ANP, atrial natriuretic peptide; BNP, brain natriuretic peptide; IVC, inferior vena cava.

Ten consecutive patients with breast cancer having skin metastasis who received docetaxel were investigated. All patients were women and their mean (SEM) age was 51.8 (2.5) years. Docetaxel dissolved into 500 ml of 0.9% saline solution was administered with an intravenous drip injection for three hours. The mean dosage of docetaxel was 52.36 (6.35) mg/m^2. Although the serum concentration of brain natriuretic peptide (BNP) was within normal range before treatment, it was significantly raised on the day after docetaxel administration (table 1). In contrast, concentrations of other circulating cardiac neurohormones (atrial natriuretic peptide, renin, aldosterone, noradrenaline (norepinephrine), and adrenaline (epinephrine)) were within the normal range at both determinative points (table 1). Additionally, blood pressure was not affected by this treatment (one day before chemotherapy 126 (7)/74 (6) mm Hg; one day after chemotherapy 123 (8)/76 (8) mm Hg; three weeks after chemotherapy 127 (5)/69 (9) mm Hg; NS). To assess left ventricular systolic and diastolic functions, we measured fractional shortening, ejection fraction, mitral inflow E:A ratio, and deceleration time by echocardiography. While fractional shortening and ejection fraction were not affected by docetaxel, the E:A ratio was significantly decreased and deceleration time was significantly increased (table 1). Additionally, the maximum diameter of inferior vena cava was not affected by this treatment. These results suggest that docetaxel induced left ventricular diastolic dysfunction and an increase in serum BNP concentration without increasing preload or afterload.

BNP is a useful biochemical marker of left ventricular dysfunction, having diagnostic, therapeutic, and prognostic implications.[4] In addition, diastolic dysfunction is well known as a cause of congestive heart failure.[5] In this study, the increase in BNP concentration, the decrease in E:A ratio, and the increase in deceleration time were transient and returned to baseline within three weeks in all patients (table 1). However, since docetaxel induced the transient abnormalities of the serum BNP concentration, E:A ratio, and deceleration time, even in patients with normal cardiac function, it is possible that this agent may induce heart failure in patients with left ventricular dysfunction. Consequently, it is advisable to check the cardiac function of patients to be treated with docetaxel by echocardiography. In addition, serum BNP can be a useful marker by which to evaluate docetaxel induced cardiotoxicity.

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Implementation of the NICE guidelines for the primary prevention of mortality from ventricular tachyarrhythmias: implications for UK electrophysiology centres; activity modelling from the UK-HEART study

It is now well established that the implantable cardioverter-defibrillator (ICD) is the most effective treatment for the primary prevention of life threatening ventricular arrhythmia.[1 2] Despite this, its widespread use in the UK for this indication has been minimal, at least in part because of perceived resource implications. In September 2000, the National Institute for Clinical Excellence (NICE) recommended electrophysiological testing (EPS) for all patients with a history of myocardial infarction who have an ejection fraction of less than 35% and three or more beats of non-sustained ventricular tachycardia (NSVT) on a 24 hour Holter monitor. NICE further recommended that all patients in whom a significant ventricular arrhythmia is induced at EPS should have an ICD

implanted. The potential effect of the NICE guidelines on workload in UK electrophysiology centres has not been evaluated.

UK-HEART examined the utility of heart rate variability as a predictor of mortality in heart failure patients.[3] Ambulant patients with stable heart failure were enrolled in four UK cardiac centres over a 17 month period (1 December 1993 to 30 April 1995). Patients with diabetes and atrial fibrillation were excluded; otherwise allcomers to cardiology clinics were eligible. All patients underwent echocardiographic estimation of ejection fraction and screening for arrhythmia, including NSVT, using 24 hour ambulatory electrocardiography. The baseline demographic and clinical characteristics of these patients were similar to those in MADIT[1] and MUSTT,[2] the two primary prevention trials on which the NICE guidelines are based.

A total of 555 patients were entered into UK-HEART, of whom 551 had interpretable 24 hour ECGs. Of these, 57 fulfilled the NICE criteria for EPS. If diabetics and patients with atrial fibrillation had been included this figure would increase to 88 as approximately 35% of heart failure populations suffer from either of these conditions.[4] Recent data[5] have demonstrated that a second 24 hour tape will identify a further 38% of patients with NSVT, increasing numbers to 142. In MUSTT, sustained ventricular arrhythmia was induced at EPS in 35% of patients. Other smaller studies in similar populations have found equivalent positivity rates.[6] If our cohort reacted in the same way there would be 50 positive studies and hence 50 ICD implants.

During the period of recruitment 68 electrophysiological studies for ventricular arrhythmia were performed on patients within the four centres. During an equivalent, contemporary period (1998-2000), 72 studies were performed. Application of NICE guidelines would lead to a further 142 studies, equivalent to three extra per month in each of the three centres performing this procedure. During 1993-95 there were 11 ICDs implanted. Between 1998-2000 there were 79 implanted. The NICE guidelines would mean a further increase of 50, representing one extra ICD per implanting centre per month.

The UK-HEART study was primarily designed to investigate the prognostic utility of measures of heart rate variability in a heart failure population and therefore has some limitations in its application to NSVT. Diabetics and patients with atrial fibrillation were excluded from UK-HEART because of the heart rate variability analysis. Diabetics make up 20% and patients with atrial fibrillation 15% of major heart failure studies. We have assumed that if these patients had been included, our population eligible for further investigation would increase by 35%. Clearly there will be some crossover between the groups and they may have different rates of NSVT. The patients in the study were allcomers to cardiology clinics. Numbers would increase if all primary and secondary care physicians had enrolled patients.

The numbers of investigations and ICDs estimated apply to the first year of guideline implementation. The numbers requiring investigation and treatment the following year, including new diagnoses and those whose disease had progressed, would differ; theoretically fewer than in the first year. The numbers would also fall as some patients eligible for investigation or treatment would be unsuitable for non-cardiological reasons.

Overall, these data provide evidence that implementation of the NICE guidelines for the use of ICDs in primary prevention is unlikely to lead to an unmanageable increase in EPS or ICD implantation in UK electrophysiology centres.

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Trial acronyms
UK-HEART United Kingdom Heart Failure Evaluation and Assessment of Risk Trial
MADIT Multicenter Automatic Defibrillator Implantation Trial
MUSST Multicenter Unsustained Tachycardia Trial

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