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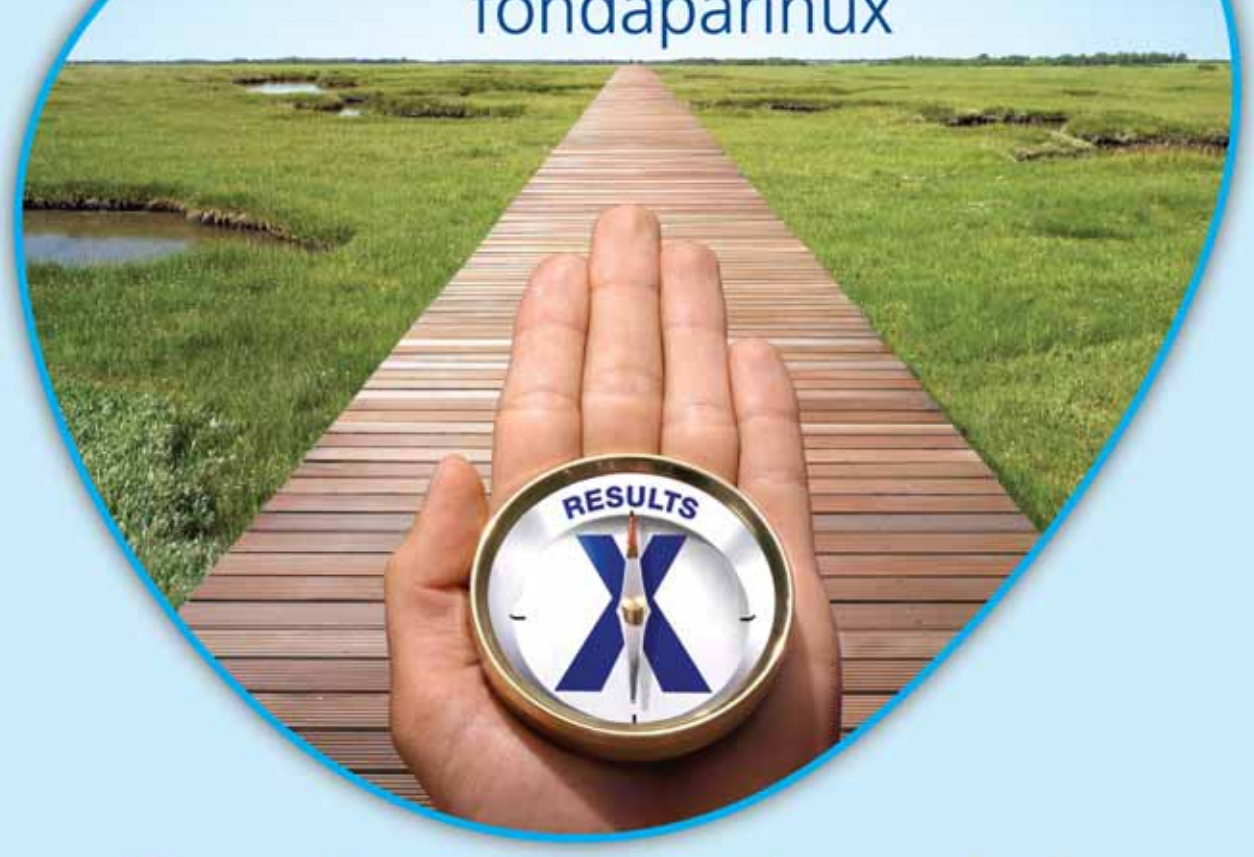

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QJM EXCERPTS

SOUTH AFRICAN EDITION

Editorial Comment

This issue contains four original articles, a review article, a commentary, and a case report. It has a bias to cardiology, but also has articles concerning diabetes and endocrinology, neurology, respiratory medicine and therapeutics.

The first article is a case report by B.E. Stahli, *et al.* on *"Acute myocardial infarction after botlinum toxin injection"*. It describes a 56-year old patient with a history of Friedreich ataxia who was referred to the cardiac catheterization laboratory after electromechanical rescusitation for ventricular fibrillation. Two hours before , trans-urethral botulinum toxin A injection had been performed for neurogenic bladder dysfunction. The temporal coincidence of injection and the onset of myocardial infarction suggests a causal relationship.

The commentary is by Vaz Perez, *et al.* on *"Digoxin in chronic heart failure; possibility of a second chance?"* Digoxin is one of the oldest and probably the least expensive drugs for the treatment of chronic heart failure (CHF), but its role still remains controversial. It is a potent inhibitor of the cellular sodium pump activity in cardiac and non-cardiac tissue, also involving the vagal afferent fibres and the kidneys. The authors state that the dosage of 0.25 mg daily has shown no benefit in CHF. They suggest that the dosage should be reduced to achieve a blood level of 0.6-0.8 ng/ml. They feel that only a prospective randomized study of low dosage digoxin could settle the issue so that it could regain its status as a first line drug in CHF.

The first original article is by P. Mandal, *et al.* on "*Vascular complications are associated with poor outcome in community-acquired pneumonia"*. There is recent evidence that lower respiratory tract infections are linked to the development of acute myocardial infarction. The aim of this study was to determine the frequency of cardiovascular and cerebrovascular events during hospitalization for community-acquired pneumonia (CAP) and their clinical outcomes . It was a retrospective study of 4408 patients with CAP presenting to five hospitals over a period of 2 years in Scotland. Using multivariate analysis 2.2% developed stroke, 5% acute coronary syndrome or myocardial infarction and 9.3% new onset atrial fibrillation. These factors were associated with increased 90-day mortality. Vascular events were independently associated with increased length of hospital (median 12 days) stay. Recognition of cardiovascular risk factors are important for primary and secondary prevention strategies.

The second original article is on *"The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study"* by N. Yu, et al. This study provides an update of the natural history of treated and untreated primary hyperparathyroidism (PHPT) in patients who were followed in a well defined cohort from 1997 to 2006 in Tayside, Scotland. Cohorts of "mild untreated" patients (n=904) and surgically treated patients (n=200) were identified for this study. Baseline age and parathyroid hormone concentration were the only significant risk factors for disease progression. However, most untreated patients with mild PHPT had no progression of serum calcium, but approximately 15% did show some evidence of progression. Serum calcium normalized in the 200 "surgically treated" patients.

The third original article is by G. Modi, *et al.* on "*Non-traumatic myelopathy at the Chris Hani Baragwanath Hospital, South Africa - the influence of HIV."* This is a prospective study of 100 consecutive in-patients admitted with myelopathy. Myelopathy aetiologies were established by collateral information obtained from magnetic resonance imaging (MRI), CSF and blood studies, CXR findings, non-neurological illness and response to treatment. About 50% of the patients presenting and admitted to the hospital were HIV-positive. The HIV-positive myelopathy patients were younger (20-40 years) and had infectious aetiologies. Tuberculosis was the most frequently identified cause of myelopathy. The majority of HIV-positive patients had advanced HIV infection. Anti-retroviral treatment did not influence myelopathy aetiologies. The HIV-negative patients were older and neoplasms followed by degenerative spondylosis were the main causes of myelopathy. The authors feel that in HIV-related myelopathy patients, where resources are limited, treatment with anti-tuberculous therapy is justified.

The last original article is on *"Long-term glycaemic outcome of structured nurse-led diabetes in rural Africa"* by C. Price, et al. The study was done in Hlabisa, Zululand and was a single-centre observational cohort study. It was a nurse led intervention programme for type 2 diabetes mellitus and eighty patients had data available at all time collection points. Hlabisa is a rural area with poor resources and inadequate medication and medical resources. The programme included lifestyle measures, education in self-care, and provision of only two drugs which were available, viz. metformin and glibenclamide. Over a period of 18 months the body mass index (BMI) decreased and the HbA1c decreased significantly. However, at the end of four years the BMI rose to its original level and the HbA1c increased, although it was lower than the baseline level. One could speculate on the reasons for the rise in HbA1c - it could be due to "education fatigue", which may occur in any intervention programme, or resistance to the two available drugs. Unfortunately there were no other anti-diabetic drugs available. This programme is interesting and it could apply to other chronic diseases in developing countries.

The last article is a review on *"Ischaemic and bleeding complications with new compared to standard ADP antagonists in acute coronary syndromes: a meta-analysis of randomized trials"* by E.P. Navarese, et al. The authors did a meta-analysis of seven randomized trials enrolling patients with acute coronary syndromes (ACS) evaluating new ADP receptor antagonists compared to standard-dose clopidogrel (loading dose 300 mg followed by 75 mg daily). Compared to clopidogrel, there was a significant reduction in mortality, recurrent myocardial infarction and definite in-stent thrombosis with the comparator drugs, pasugrel and ticagrelor. There was no overall increase in bleeding.

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EXCERPTS

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A beautiful autumn photograph of The Promenade, Clifton, Bristol, UK.

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Reference 1.: Kjeldsen SE, Lyle PA, Kizer JR, et al. Fixed combination of losartan and hydrochlorothiazide and reduction of risk of stroke. Vascular Health and Risk Management 2007; 3(3): 299-305.

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Case report

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Acute myocardial infarction after botulinum toxin injection

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Case presentation

A 56-year-old male patient with a history of Friedreich ataxia was referred to the cardiac catheterization laboratory after electromechanical resuscitation due to ventricular fibrillation. Two hours before, trans-urethral intra-vesical botulinum toxin A injection (300 U) had been performed because of neurogenic bladder dysfunction. His past medical history was positive for hypertension and smoking, but negative for any cardiovascular event.

On admission, laboratory analysis had been unremarkable and baseline ECG showed incomplete right bundle branch block and T-wave inversions in leads V1–V2. Postrescuscitation, new preterminal T-wave inversions were noted in the inferior leads and in leads I, and V3–6, along with troponin T elevation (0.72 μg/l). In the course, dynamic discrete ST segment elevations developed in leads V1–V3. Unfractionated heparin, acetylsalicylic acid and clopidogrel were administered for suspected acute coronary syndrome. Coronary angiography revealed thrombotic occlusion of the right coronary artery with a large thrombus extending from the proximal to the mid segment (Figure 1A). Of note, there were no coronary artery spasms observed; in particular, vascular tone was unchanged after intracoronary nitroglycerine administration. Immediate percutaneous coronary intervention was performed and the vessel reopened by means of thrombus aspiration using a diver catheter and the utilization of two drug-eluting stents (Biomatrix). Final angiographic documentation revealed complete restoration of flow and normal left ventricular wall motions with preserved left ventricular systolic function (Figure 1B). The post-interventional course on the intensive care unit (ICU) was unremarkable and the patient was transferred to the regular ward 1 day after admission.

Discussion

We describe a case of acute myocardial infarction in a patient with Friedreich ataxia following intravesical botulinum toxin A injection.

Cardiac involvement is frequently observed in Friedreich ataxia. However, acute coronary syndromes have rarely been described in these patients. Typically, hypertrophic cardiomyopathy, which was excluded in our patient using echocardiography, and an abnormal repolarization phase and arrhythmias are detected.[1]

Botulinum toxin A impedes neuromuscular transmission causing muscle weakening. It blocks acetylcholine release in nerve terminals by cleaving SNARE proteins, thereby preventing fusion of acetylcholine vesicles with the cell membrane. Botulinum toxin A is widely used for cosmetic applications, and in the treatment of muscle spasms, chronic pain syndroms or bladder dysfunction.[2]

Botulinum toxin A is assumed to have mainly local effects. However, systemic side effects have been described. Hence, botulinum toxin A might also affect vasoreactivity or interact with the

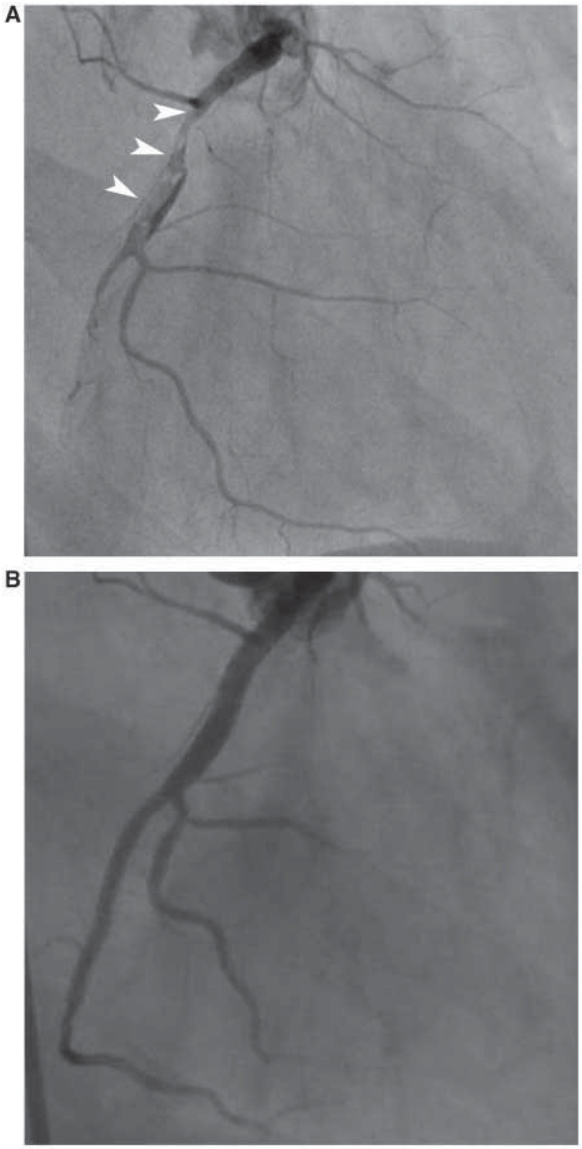

Figure 1. (**A**) Coronary angiography revealing thrombotic occlusion of proximal and mid segments of the right coronary artery with collateral flow from the left anterior descending artery. (**B**) Coronary angiography of the right coronary artery following percutaneous coronary intervention.

coagulation cascade, endothelial cells or platelets and in turn promote thrombus formation. Indeed, single cases of myocardial infarction, pulmonary embolism, and even death have been reported after botulinum toxin A injection.[3] The effect of botulinum toxin A on vasoreactivity is not fully understood. In rat, aortic rings suspended in organ chambers, contractions to potassium chloride (KCl) and norepinephrine were completely inhibited after incubation with botulinum toxin.[4] Furthermore, in Sprague Dawley rats, femoral vessel diameter was increased after subcutaneous botulinum toxin injection.[5] Hence, and in line with the coronary angiogram, vasospasms as the primary cause of the acute myocardial infarction appear unlikely in this patient. Rather, the extensive thrombus burden suggests a pro-thrombotic state. As we did not exclude a patent foramen ovale in our patient, paradoxical embolism cannot be ruled out completely. However, such events are rare and typically present with abrupt distal coronary occlusion suggestive of embolism on angiogram. In any case, pro-thrombotic effects of botulinum toxin A have not been described so far, both, *in vitro* and *in vivo*, and may be assumed.

The temporal coincidence of botulinum toxin injection and the onset of myocardial infarction in our patient suggest a causal relationship. Importantly, as botulinum toxin injections are widely performed, also in elderly patients with cardiovascular disease, and as acute coronary syndromes are serious complications, clinicians should be cautious using botulinum toxin A because of the risk of serious side effects and patients have to be monitored carefully after botulinum toxin injections.

Conflict of interest: None declared.

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Commentary

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Digoxin in chronic heart failure: possibility of a second chance?

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The cardiac glycoside digoxin is one of the oldest and probably the least expensive drug for the treatment of chronic heart failure (CHF). But still treatment with this drug in patients with CHF and sinus rhythm remains highly controversial. Despite the fact that the use of digoxin in CHF is considered to be effective and safe, its use has significantly declined due to the belief that digoxin is not able to favourably affect the natural history of CHF.[1] Another important fact is the occurrence of its well-known toxic side effects, although the incidence of digoxin toxicity seems to have diminished in the first years of the 21st century.[2]

The European Society of Cardiology guidelines for the diagnosis and treatment of acute and CHF recommend the administration of digoxin in symptomatic patients with impaired left ventricular ejection fraction (LVEF) and sinus rhythm despite its lack of effect on survival.[3] This recommendation is based on level B of evidence in view of the fact that only one meta-analysis of a single randomized controlled trial, the Digoxin Investigation Group (DIG) trial, could demonstrate a reduction in CHF-associated hospital admissions.[3] The DIG trial is the most relevant study investigating the long-term effects of a median daily dose of 0.25 mg of digoxin in CHF and showed no evidence of decreased mortality but a reduced rate of hospitalizations both overall and for worsening CHF.[4] Nevertheless, in more recent studies the use of digoxin has been associated with increased mortality not only in advanced CHF[5] but also after hospitalization due to acute decompensated heart failure.[6] On the other hand, *post hoc* and propensity-matched analyses of the DIG trial have delivered some evidences of a potentially beneficial effect in patients with CHF also on mortality.[7–10] In a *post hoc* re-analysis of the DIG data, differences in outcome have been demonstrated for diverse ranges of serum concentrations of the drug. While serum digoxin concentrations (SDCs) between 0.5 and 0.9 ng/ml were related to lower mortality, all-cause hospitalization and CHF-specific hospitalization, a SDC above 1 ng/ml was associated with lower CHF hospitalizations but did not affect mortality, the latter regardless of LVEF.[7] Moreover, a further *post hoc* analysis of the DIG trial has found analogous results in geriatric CHF patients aged $\geq$65 years.[8] In a more recent retrospective propensity-matched study of the DIG trial, low concentrations of digoxin reduced major endpoints including mortality and hospitalization in ambulatory, systolic and diastolic patients with CHF.[9] In these studies, a low digoxin dose ($\leq$0.125 mg/day) was the strongest predictor of a low serum concentration of the drug, which is thought to be the most important predictor of beneficial clinical outcome.[8,9] Furthermore, a retrospective analysis of two digoxin withdrawal studies, the Prospective Randomized Study of Ventricular Failure and Efficacy of Digoxin (PROVED) and the Randomized Assessment of

Digoxin on Inhibitors of the Angiotensin-Converting Enzyme (RADIANCE), found a lower risk of worsening CHF in patients taking digoxin (independent of the dosage) and, in particular, patients with low SDC (0.5–0.9 ng/ml) were less likely to experience worsening of CHF.[11]

Digoxin is a potent inhibitor of the cellular sodium pump activity in cardiac and non-cardiac tissues, also involving vagal afferent fibers and the kidneys. By inhibiting the sodium–potassium adenosine triphosphatase, digoxin suppresses both the renin–angiotensin–aldosterone and the sympathetic nervous system,[9,12] what may explain the favourable effects of this drug also in CHF patients with preserved LVEF.[12,13] Of interest, improvements in the neurohormonal profile have been achieved with low doses and low SDC.[14]

Close monitoring of electrocardiographic changes, SDC, and in particular calculation of the target dosage are important observations concerning this point, since the safety window of digoxin is relatively narrow. With this objective, numerous equations and nomograms to calculate digoxin dosages have been developed.[15–17] Importantly, most of these equations were employed to target higher SDC than the ones recommended now due to safety concerns.[18] Against this background, Bauman and colleagues[15] developed in 2006 a method to accurately calculate the initial dose of digoxin corresponding to a low SDC in CHF patients. Similarly, Konishi *et al.*[19] had formulated a simple equation to determine the daily dose of digoxin based only on creatinine clearance and SDC. Muzzarelli *et al.*[20] in their manuscript published in the current issue of this journal, have tested the Konishi equation, which had only been validated in Asian subjects before, and have also compared it with several equations for determining digoxin dosages including the one from Bauman. Digoxin doses were first calculated using the Konishi equation for a target SDC of 0.6–0.8 ng/ml. Digoxin compliance was then assessed in 40 CHF patients by means of a validated questionnaire and SDC was measured after 1 and 6 months. The relationship between the predicted SDC using the different equations and the measured SDC was assessed by linear regression analysis. The authors obtained the best correlation with the Konishi equation.

Thus, given the intriguing retrospective evidence and the low costs of digoxin, the most important question arises of whether digoxin given in adequately small dosages on top of standard therapy, allowing to achieve and maintain low serum concentrations, may become first-line therapy in patients with CHF and, thereby, resembles a second chance of digoxin to enter mainstream heart failure drug therapy. Considering the lack of prospective trials showing a positive effect on mortality and hospitalization by using low doses of digoxin in CHF with sinus rhythm and left ventricular systolic dysfunction, the clinical use and optimization of equations and nomograms to determine the most appropriate administration of digoxin based on safety and efficacy aspects should be continued and tested prospectively in real-world CHF patients. Therefore, we certainly hope that a prospective randomized trial exploring the potential beneficial effects of low dose digoxin will be performed in the near future. By saying this, we speculate about the second chance of digoxin to enter first-line therapy in CHF—providing evidence-based benefit for our patients with the oldest known drug to treat heart failure.

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Original papers

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Long-term glycaemic outcome of structured nurse-led diabetes care in rural Africa

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Summary

Background: Diabetes care delivery in rural Africa is difficult. Problems include lack of dedicated personnel, monitoring systems, laboratory support and drugs. Few structured intervention projects have been undertaken, none with long-term follow-up.
Aim: To determine the long-term (4 years) glycaemic outcome of a structured nurse-led intervention programme for type 2 diabetic patients in rural Africa.
Design: Single-centre, observational cohort study.
Methods: The programme was delivered in the scattered primary health clinics of Hlabisa District, in northern Kwazulu Natal, South Africa. Monthly diabetic clinics were held at which empowerment-based education was delivered and regularly reinforced. Oral hypoglycaemic agents (OHAs) were titrated according to a previously validated clinical algorithm. Outcome was measured by glycated haemoglobin (HbA_1c), as well as body mass index (BMI). Data were collected at baseline, and then 6, 18, 24 and 48 month's post-intervention.
Results: Eighty patients had data available at all time collection points. They were of mean ± SD, age 56 ± 11 years, 70% were female, BMI 31.5 ± 7.2 kg/m^2 and HbA_1c 10.8 ± 4.2%. HbA_1c fell significantly to 8.1 ± 2.2% at 6 months and 7.5 ± 2.0% at 18 months. By 24 months, it had risen (8.4 ± 2.3%), and at 4 years post-intervention it was 9.7 ± 4.0% (still significantly lower than baseline, $P = 0.015$). BMI rose significantly at 6 and 18 months, but by 48 months was not significantly different from baseline.
Conclusions: We conclude that the intervention led to marked HbA_1c improvements up to 18 months follow-up, but thereafter there was 'glycaemic slippage'. This may be not only due to educational 'wear-off', noted in other education-intervention programmes, but also to the expected glycaemic deterioration with time known to occur in type 2 diabetes. Nevertheless, 4-year HbA_1c levels were still significantly lower than at baseline. The programme was also well received by staff and patients, and we believe is an appropriate and effective diabetes intervention system in rural Africa.

Introduction

Diabetes mellitus, particularly the predominant type 2 variant, is globally increasing in prevalence, and rises over the next 20 years will be most marked in resource-limited developing countries.[1] Delivering care to these growing numbers is already problematic, and is particularly difficult in the rural tropics where drugs, equipment and staff are in short supply. The current and future burden of diabetes in such areas requires that systems of health-care delivery are appropriate to local resources and geography; and sensitive to indigenous cultural, socio-economic and educational factors.[2]

Attempting to respond to these problems, we initiated in 2001 the 'Hlabisa Diabetes Project' in a remote, rural area of KwaZulu Natal in South Africa to deliver diabetes care to the scattered population by nurses in primary health clinic (PHC) situations.[3] Using clinical algorithms for oral hypoglycaemic agent (OHA) titration, and structured education programmes, we have demonstrated highly beneficial falls in glycated haemoglobin (HbA_1c) over an 18-month period since the programme was introduced (mean HbA_1c at baseline $11.6 \pm 4.5\%$ and 18 months later $7.7 \pm 2.0\%$).[3]

In this article, we report longer term outcome (4 years since initiation) from the Hlabisa Diabetes Project, to examine whether such improved control could be maintained.

Patients and methods

Details of the location of the project, the study population and the management intervention delivered have been published in full elsewhere.[3] Briefly, Hlabisa District is a rural area of northern Kwazulu Natal in South Africa. The area has a central hospital with 14 peripheral PHCs, many of which are very remote. A previous study in the area had demonstrated a relatively large diabetic population with high rates of complications (e.g. retinopathy 40% and microalbuminuria 46%) and also poor glycaemic control—mean HbA_1c 11.3%.[4]

The intervention study involved a local diabetes-trained nurse visiting each PHC every month to see diabetic patients. OHAs—glibenclamide and metformin—were initiated and titrated according to a clinical algorithm,[3] which had been previously validated.[5] These two OHAs were the only ones available. The algorithm included confirmation of diagnosis, trial of lifestyle modification and education. OHAs were then added if necessary—glibenclamide if the body mass index (BMI) was <27.0 and metformin if >27.0. Patients attended monthly and doses were titrated upwards as necessary. The algorithm later allowed combination OHAs, and if these failed, patients were referred to medical staff at the central hospital for insulin initiation. The target for 'control' was largely clinical. Neither self-blood glucose monitoring nor HbA_1c assay was available (though the latter was used in the study as a research end point). Even random blood glucose could not be always measured. Control of osmotic symptoms (nocturia less than once) and absence of OHA-related hypoglycaemic side effects were therefore the key targets.[3]

In addition to drug titration, structured empowerment-based diabetes education was delivered in groups and regularly reinforced. This was adapted from the 'Zahke Programme'—a simple pictorial based flip-chart system that had been previously successfully field tested.[6] The education was sensitive and appropriate to the low literacy rates in the community. It was delivered to groups in the clinic at the start of the project and was reinforced at each clinic visit. The educational programme was also delivered via community support workers, and a handbook was developed for PHC nurses when the diabetes nurse team was not available. As the research element of the programme was carried out in remote areas, and in the context of a busy clinical service, data collection was kept to a minimum. Outcome was, therefore, measured only by HbA_1c and BMI. Data were collected prior to initiation of intervention, and then at 6 months, 18 months, 2 years and 4 years afterwards. HbA_1c was measured by high-performance liquid chromatography and was aligned to the Diabetes Control and Complications Trial[7] (reference range 4.5–5.7%). Samples were transported to Durban (240 km away) for assay, and the results were not available for routine control purposes.

Statistical analysis was by paired *t*-tests, using Statistical Package for Social Sciences computer package version 15.0. Local ethical committee approval was obtained.

Results

We originally recruited 320 diabetic patients to the programme. As with all diabetes services, intermittent missed appointments were common, and we therefore identified a core of 80 patients who had attended at all the five data collection points (0, 6 and 18 months, 2 and 4 years), thus allowing paired *t*-test comparisons at these follow-up times. All the 80 patients had type 2 diabetes, age (mean ± SD) was 56 ± 11 years, diabetes duration 7 ± 6 years, 70% were female, BMI was $31.5 \pm$

Table 1 Changes in HbA_1c and BMI during 4 years of follow-up of the Hlabisa diabetes intervention programme ($n = 80$)

Time (months)	HbA_1c (%)	BMI (kg/m^2)
0	10.8 ± 4.0	31.5 ± 7.2
6	8.1 ± 2.2	32.0 ± 7.1
18	7.5 ± 2.0	32.0 ± 6.5
24	8.4 ± 2.3	–
48	9.7 ± 4.0	32.2 ± 6.3

There was incomplete BMI data collection at 24 months. BMI at 6 and 18 months was significantly higher than at baseline (both $P < 0.01$), but the 48-month value was not significantly different from 0 months. Compared with baseline, HbA_1c falls were all significant ($P < 0.001$ for 6, 18 and 24 months and $P = 0.015$ for 48 months).

7.2 kg/m^2 and initial HbA_1c 10.8 ± 4.0%. To check for 'self-selection' bias, we compared all these parameters with the other 240 patients, and there were no significant differences.

Changes in HbA_1c and BMI over the 4 years of follow-up are shown in Table 1. BMI showed a small but significant rise from baseline to the 6- and 18-month testings (31.5 ± 7.2 to 32.0 ± 7.1 to 32.0 ± 6.5, $P < 0.01$ for both 6 and 18 months). However, the 4-year value of 32.2 ± 6.3 was not significantly different from baseline. HbA_1c fell significantly ($P < 0.001$) from baseline to 6 and 18 months (10.8 ± 4.0% to 8.1 ± 2.2% to 7.5 ± 2.0%). There was a small rise to 8.4 ± 2.3% at 2 years, and a larger rise to 9.7 ± 4.0% at 4 years. The 4-year level, however, still remained significantly lower than at baseline ($P = 0.015$).

Of the 80 patients followed, 26 (33%) were 'non-obese' (BMI < 27.0) and 54 (67%) 'obese' (BMI > 27.0). The non-obese group showed a consistently greater change in HbA_1c—baseline was 13.1 ± 5.2% and 24-month level 6.7 ± 0.2%. Similar figures for the obese group were 11.8 ± 4.3% and 9.3 ± 1.7% ($P < 0.001$).

Discussion

In our report on 18 months of follow-up of this intervention programme, we demonstrated that HbA_1c falls were related to both OHA introduction and titration, and also the associated education programme.[3] Thus, in a subgroup analysis of a cohort of patients who had no drug manipulations (only education), HbA_1c also fell significantly. Education programmes for type 2 patients in Europe have shown variable effects on glycaemic control[8–11], and when improvement occurs, there is some evidence that this may be short term, with a later 'wear-off' effect.[11] The fall in HbA_1c we noted in the first 18 months was dramatic and far greater than noted in European education programmes;[8,9,11] this may be related to the initial very poor control of our patients (baseline mean HbA_1c 10.8%) as well as the fact that they had never had any significant previous diabetes education.

As well as 'education fatigue' being a possible cause of the post-18 months glycaemic slippage, a further problem is likely to be the natural history of type 2 diabetes to deteriorate, a factor only detectable in long-term studies. Steady deterioration in HbA_1c with time in type 2 diabetes was clearly demonstrated in the United Kingdom Prospective Diabetes Study, and was found in both the intensively treated and control goups.[12] Data from this study would predict a 0.7% deterioration in HbA_1c for type 2 patients of mean diabetes duration 7 years (as in our study) over the subsequent 4 years of follow-up (again, the same follow-up period of our cohort).[12] Our cohort improved mean HbA_1c by 1.1% over the same time period.

Our protocol used only glibenclamide and metformin—other oral agents such as glitazones were not available. Though we do not have quantitative data, sulphonylurea use and dosages clearly increased with time, and it is known that these drugs may accelerate beta cell failure, and be less 'glycaemically durable' in the long term. This could be a factor in the later glycaemic deterioration which we noted.[13] However, most (67%) of our patients were overweight or obese (BMI > 27.0) and would therefore have been treated with metformin, at least initially. Those with BMI levels <27.0 (33%) also appear to improve glycaemically more than the overweight group (see 'Results' section).

We believe ours is the only long-term outcome study of structured diabetes management in rural Africa using objective glycaemic outcomes. Positive hospital-based initiatives have been reported from Soweto (South Africa),[14] Ghana[15] and Eritrea.[16] A system of devolved care of non-communicable disease, including diabetes, to rural health centres has been described from the Jimma area of Ethiopia,[17] but was not evaluated by HbA_1c measurement.

Glycaemic improvements are especially important for diabetic patients in resource-poor areas, as complication occurrence and progression will be reduced in the long term.[12] The management of complications such as significant retinopathy, nephropathy or foot ulceration is difficult or impossible in remote primary care areas of Africa.

A final implication of our work is that the model of care we used, based on patient education and

treatment algorithms, could be adapted to other chronic diseases such as hypertension, asthma and epilepsy. We have some short-term experience of such initiatives in Hlabisa District,[5] but more structured and long-term trials would be well worthwhile.

In conclusion, our study has shown that structured nurse-led diabetes intervention in rural Africa can be associated with dramatic improvement in HbA_1c. Though there is certainly longer term glycaemic escape at 4 years of follow-up, our patients still had a mean HbA_1c significantly better than at baseline. We also noted that the programme of care was very warmly and positively received by both staff and patients. 'You are our saviour', one man with previously neglected diabetes said to the project diabetes nurse.

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Vascular complications are associated with poor outcome in community-acquired pneumonia

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Summary

Background: Recognition of cardiovascular risk factors is important for primary and secondary prevention strategies. Recent evidence has linked lower respiratory tract infections with the development of acute myocardial infarction.
Aim: The aim of this study was to determine the frequency of cardiovascular and cerebrovascular events and the clinical outcomes, during hospitalization for community-acquired pneumonia (CAP).
Design: We performed a retrospective study of 4408 patients with CAP presenting to five hospitals over a 2-year period. Clinical information, co-morbidities, cardiovascular events and 90-day mortality were collected from review of medical case notes. The relationship between cardiovascular events and outcomes were analysed using multivariable logistic regression.
Results: From a total of 4408 patients, 2.2% developed stroke, 5% acute coronary syndrome or myocardial infarction and 9.3% new onset atrial fibrillation. These were associated with increased 90-day mortality [odds ratio (OR), 1.49 95% CI 1.18–1.87, $P = 0.0006$].
Vascular events were independently associated with increased length of hospital stay—median 12 days (IQR 5–22), compared to patients with no vascular events 8 days (IQR 3–17 days, $P < 0.0001$).
Conclusions: Cardiovascular and cerebrovascular events are common during hospitalization for CAP and are associated with increased 90-day mortality.

Introduction

Community-acquired pneumonia (CAP) is the most common infectious disease requiring hospitalization in western countries and a major cause of morbidity and mortality worldwide.[1] It is known that 50% of all deaths in patients with pneumonia, and more than a quarter of deaths within 30 days are related to co-morbidities such as vascular disease (including acute coronary syndrome, decompensated cardiac failure and stroke).[2]

There is an established link between vascular events following acute infection and this is particularly augmented in the first few days but persisting for several weeks following an acute infection.[3–5] To date, there have been no studies of arrhythmias, transient ischaemic attack (TIA) and stroke in CAP and limited small retrospective studies of acute coronary syndrome in patients with CAP.[6,7]

The aim of our study was to describe the frequency of cardiovascular and cerebrovascular events in patients admitted with CAP and to assess whether these events are independently associated with poor outcome.

Methods

We conducted a retrospective study of patients admitted to five hospitals in South East Scotland

over a 2-year period from 2005 to 2007. Lothian Research Ethics Committee approved the study.

Identification of cases of CAP

Patients aged ≥18 years were identified from an administrative database of hospital admissions to five National Health Service hospitals in the East of Scotland. ICD-10 codes were used to identify all adult patients with a primary diagnosis of pneumonia (ICD-10 codes J12–J18). Patients were excluded if they did not have clinical or radiological features consistent with CAP or had any of the following exclusion criteria: hospital-acquired pneumonia; admission or transfer from a health-care facility; post-operative pneumonia; HIV; age <18 years. The use of International classification of diseases (ICD) codes in combination with medical chart review has been shown to have good accuracy for identifying cases of CAP.[8] ICD codes, including the ICD-10 codes used in this study are widely used in epidemiological and prognostic studies of CAP.[1]

Medical records of those identified by ICD-10 to have a vascular event were reviewed retrospectively to obtain details of clinical and demographical characteristics in addition to confirmation of the vascular events.

Identifying cardiovascular complications

From review of medical case notes and laboratory results, the incidences of four vascular complications—ST elevation myocardial infarction (STEMI), acute coronary syndrome, new onset atrial fibrillation (AF) and cerebrovascular events were recorded. We have defined vascular events to include any of the four vascular complications. STEMI diagnosis was based on reported ST elevation on ECG along with positive cardiac troponin result and a clinical diagnosis of STEMI.[9] Acute coronary syndrome was defined as acute non-ST elevation myocardial infarction [compatible ECG changes along with positive Troponin I and a clinical diagnosis of non-STEMI or unstable angina (clinical diagnosis of non-myocardial infarction acute coronary syndrome comprising chest pain with one of the ECG abnormalities, positive cardiac specific troponin or a clinical diagnosis of cardiac ischaemia)].[9] In the absence of the above, chest pain occurring during hospitalization was not regarded as constituting acute coronary syndrome. An elevated cardiac specific troponin may occur in CAP in the absence of an acute coronary syndrome and hence an elevated troponin in the absence of a compatible clinical history was not regarded as an acute cardiovascular event.[10]

New onset atrial fibrillation was diagnosed in a patient without a prior history of AF in whom the attending physician made a diagnosis of AF based on ECG findings. Stroke was defined as a new onset neurological deficit lasting >24 h with a confirmatory CT or MRI.[11]

Outcomes

The primary outcome was 90-day mortality. The secondary outcome measured was length of hospital stay.

Statistical analysis

All data were analysed using Graphpad prism (Graphpad software, San Diego, CA, USA). For demographic and clinical variables, data are presented as median (interquartile range) for continuous variables and *n* (%) for categorical variables unless otherwise stated. Survival curves were constructed by Kaplain–Meier analysis and curves compared using the Log-rank test. Adjustment for potential confounders was achieved using multivariable logistic regression. Multivariable regression models were constructed by including demographic (age, gender, co-morbidities, smoking history—as listed in Table 1) and clinical characteristics (site of care, including admission to intensive care unit) with cardiovascular or cerebrovascular events as

Table 1 Demographics of the study population

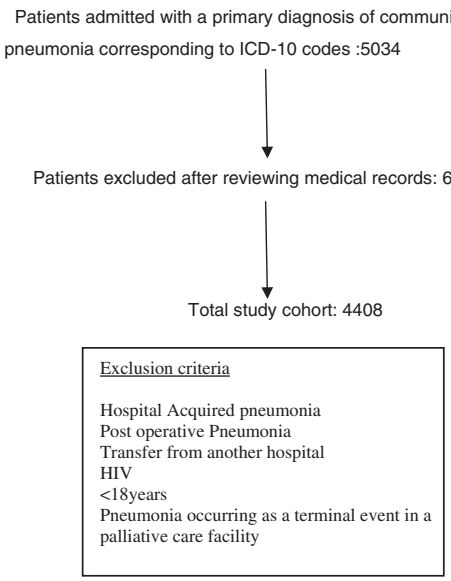
Baseline characteristics	Study population *N* = 4408
Age (years)	73 (52–82)
Gender: male (%)	48%
Previous myocardial infarction (%)	8.3%
Previous diagnosis of heart failure (%)	18.9
Previous cerebrovascular disease (%)	10.8
Peripheral vascular disease (%)	2.9
Dementia (%)	3.7
COPD (%)	19.8
Asthma (%)	4.8
Connective tissue disease (%)	2.5
Liver disease (%)	2.9
Diabetes (%)	7.9
Chronic renal disease (%)	11.7
Malignancy (%)	12.6
Peptic ulcer disease (%)	0.5
Charlson co-morbidity index (%)	
0	34.9
1	32.4
2	20.1
≥3	12.6

independent variables. As this was a retrospective study, full data to calculate severity scores such as CURB65 and PSI were not available for all patients. Therefore these were not included in the logistic regression analysis. Model fit was assessed using the Hosmer–Lemeshow goodness-of-fit test ($P > 0.05$ indicates adequate model fit). To analyse factors associated with length of stay, multiple linear regression was performed using the above co-variates in addition to cardiovascular events as independent variables.

Results are presented as adjusted odds ratio (AOR) with 95% CIs. A *P*-value of <0.05 was considered statistically significant for each analysis.

Results

After removing patients with a diagnostic code corresponding to an exclusion criterion, 5034 patients were identified. After reviewing medical records for these patients a further 626 patients were excluded, leaving a study cohort of 4408 patients.



In this cohort, median age was 73 years (interquartile range 58–82 years). About 65.6% of the patients were aged ≥65 years (age range 18–105 years). About 52.0% of the patients were female and 48.0% were male. Median duration of admission was 8 days (IQR 3–17 days)—range 0–272 days. Ninety-day mortality was 13.9%.

ICU admission was required for 172 patients (3.9%) of the study population.

Baseline characteristics of the study population are shown in Table 1.

Frequency of cardiovascular and cerebrovascular events in patients with CAP

Acute myocardial infarction associated with ST elevation occurred in 1.8% patients during hospitalization. Acute coronary syndrome incorporating non-ST elevation myocardial infarction and unstable angina occurred in 3.2% patients. Cerebrovascular events occurred in 2.2% of the patients (0.5% developed haemorrhagic stroke and 1.7% developed ischaemic stroke) and new onset atrial fibrillation occurred in 9.3% of patients during hospitalization.

The frequency of myocardial infarction ($P < 0.0001$), NSTEMI and acute coronary syndrome ($P < 0.0001$), atrial fibrillation ($P < 0.0001$) and cerebrovascular events ($P < 0.0001$) were all increased in patients aged ≥65 years.

In a multivariable logistic regression model, factors significantly associated with acute myocardial infarction were age, previous acute myocardial infarction, COPD and chronic renal disease. Only age was independently associated with acute coronary syndrome diagnosis (Table 2).

Age, diabetes mellitus and prior myocardial infarction were associated with increased risk of atrial fibrillation.

Finally, cerebrovascular events were associated with increasing age and a prior history of cerebrovascular disease but having prior COPD was protective.

Outcomes of patients with cardiovascular and cerebrovascular events

Ninety-day mortality

Ninety-day mortality was 13.9%. Figure 1 shows the outcome of patients with each cardiovascular complication and cerebrovascular event compared with outcome in patients with no history of these events.

Kaplain–Meier survival analysis showed increase in 90-day mortality in patients with vascular events during hospitalization (Figure 1E) (log-rank test χ^2 19.1, df = 1, $P < 0.0001$). Acute myocardial infarction (log-rank test χ^2 6.4, df = 1, $P = 0.01$), acute coronary syndrome (log-rank test χ^2 4.37, df = 1, $P = 0.04$), stroke (log-rank test χ^2 15.8, df = 1, $P < 0.0001$) and new onset atrial fibrillation (log-rank test χ^2 4.46, df = 1, $P = 0.03$) were all associated with increased 90-day mortality.

In multivariable analysis, stroke during hospitalization (AOR 1.79, 95% CI 1.51–2.12, $P < 0.0001$), acute myocardial infarction during hospitalization

Table 2 Clinical predictors of cardiovascular and cerebrovascular events—multivariable model

Outcome	Independent predictors	AOR (95% CI)	*P*-value	Hosmer–Lemeshow Goodness-of-fit test *P*-value
Cardiovascular events				
Acute myocardial infarction	Age ≥ 65 years	14.0 (4.39–44.8)	<0.0001	0.82
	Previous acute MI	1.62 (1.26–2.07)	0.0001	
	Renal failure	1.90 (1.01–3.55)	0.04	
	COPD	2.01 (1.12–3.60)	0.02	
Acute coronary syndrome	Age ≥ 65 years	4.73 (2.50–8.95)	<0.0001	0.99
	Previous acute MI	1.47 (1.01–2.17)	0.05	
New onset atrial fibrillation	Age ≥ 65 years	5.70 (4.21–7.71)	<0.0001	0.34
	Previous acute MI	1.53 (1.28–1.84)	<0.0001	
	Diabetes mellitus	1.37 (1.01–1.87)	0.04	
Stroke	Age ≥ 65 years	3.37 (1.90–5.97)	<0.0001	0.86
	Prior history of cerebrovascular disease	1.72 (1.11–2.75)	0.01	
	COPD	0.34 (0.18–0.67)	0.002	

(AOR 1.93, 95% CI 1.60–2.33, $P < 0.0001$) and new onset atrial fibrillation during hospitalization (AOR 2.39, 95% CI 1.65–2.19, $P < 0.0001$) were all associated with increased 90-day mortality. Acute coronary syndrome (AOR 1.46, 95% CI 0.82–2.76, $P = 0.2$) was not significant in this model.

Length of stay

Median duration of admission for the population as a whole was 8 days (IQR 3–17 days).

The duration of stay for acute myocardial infarction was 12 days (interquartile range 8–23 days, $P < 0.0001$), new onset atrial fibrillation was 12 days (6–23, $P = 0.008$) and stroke 14 days (6–33, $P < 0.0001$), were all associated with increased length of stay. Patients with acute coronary syndrome did not have significantly prolonged length of stay (median 10 days, 4–18, $P = 0.07$).

Overall, patients with one or more vascular events had a higher median length of stay of 12 days (IQR 5–22), compared to patients with no vascular events 8 days (IQR 3–17 days, $P < 0.0001$).

In a linear regression analysis, stroke (coefficient 7.58 SE 2.91, $P = 0.0009$), atrial fibrillation (coefficient 3.91 SE 1.45, $P = 0.007$) and myocardial infarction during hospitalization (coefficient 7.16 SE 2.46, $P = 0.004$) were associated with increased length of stay, independent of confounders. Acute coronary syndrome was not independently associated with increased length of stay (coefficient 0.08 SE 3.41, $P = 0.9$).

Discussion

This large study involving 4408 patients has shown that vascular events are common in patients admitted with CAP. About 16.5% patients developed STEMI, acute coronary syndrome, new onset atrial fibrillation and/ or cerebrovascular event. Among these events, the most frequent was new onset atrial fibrillation. Vascular events were associated with increased 90-day mortality.

The association between respiratory infections and cardiovascular events has been the subject of extensive recent study. Although some studies in hospitalized patients have shown an association between acute infections and increased cardiovascular events and stroke,[4,12,13] there is a paucity of data in patients admitted with CAP. It is known that cardiovascular events peak during the winter when respiratory infections are also most frequent.[14,15] There have been three major primary care studies comprising a total of 33 563 patients with first acute myocardial infarction and 28 271 with first stroke[3,5,16] following respiratory tract infection. The risk of a vascular event persists for up to 90 days after infection. In our study, we have shown a similar association in patients admitted with CAP.

In a retrospective study conducted in the USA, Ramirez *et al.*[6] showed that a combined diagnosis of CAP and acute myocardial infarction is common among hospitalized patients with severe CAP (15% of 86 patients), and in cases in which the clinical course of a hospitalized patient with CAP is

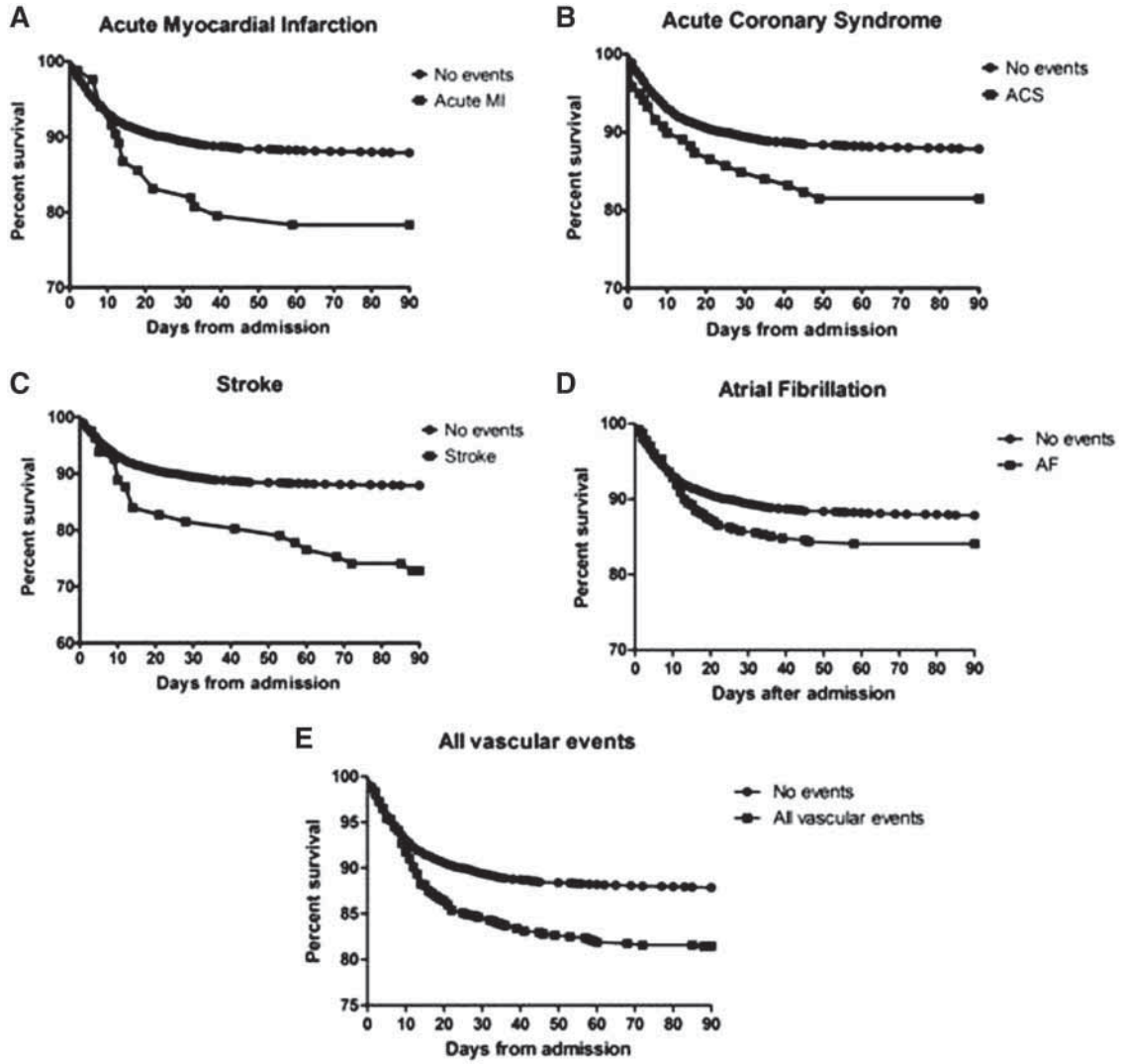


Figure 1. Ninety-day mortality rates and the development of cardiovascular complications. (**A**) Acute myocardial infarction, (**B**) Acute coronary syndrome, (**C**) Stroke, (**D**) New onset atrial fibrillation and (**E**) all vascular events.

complicated by clinical failure (development of respiratory failure or shock), acute myocardial infarction should be considered as a possible aetiology. Another retrospective study, by Musher *et al.*[7] also conducted in the USA found in 170 patients admitted with pneumococcal pneumonia, 19.4% had one or more cardiac events (myocardial infarction, atrial fibrillation or ventricular tachycardia, or new onset or worsening congestive heart failure) which was associated with higher mortality.

The present study confirms the findings of these smaller studies that vascular events are common in patients with CAP and are associated with prolonged length of hospital stay and increased risk of 90-day mortality.

Potential mechanisms that result in increased 90-day mortality in patients admitted with CAP include the degree of hypoxia, pyrexia, systemic inflammation, acidosis, coagulopathy and metabolic disturbance. Both pneumonia and acute coronary syndromes are associated with major systemic inflammation and activation of coagulation pathways.[17] CAP leads to elevation in pro-inflammatory cytokines such as C-reactive protein, Interleukin 6, Tumour Necrosis Factor-α and Interleukin 8 and also induces a marked pro-thrombotic state associated with elevation of thrombotic markers such as fibrinogen, factor IX, thrombin–anti-thrombin complex and D-dimer.[18] In a recent study, Milbrandt *et al.*[19] identified significant pro-thrombotic effects and elevation of coagulation markers during hospital admission with CAP. The combination of systemic inflammation and thrombosis are highly conducive to plaque rupture and clot formation.

It is known that acute respiratory infections are associated with reduced myocardial contractility, increased myocardial oxygen demand and reduced myocardial oxygen delivery.[20] Cytokines (Interleukin 1, Tumour Necrosis Factor-α, Interleukin 6), prostanoids, endothelin-1 and nitric oxide produced in sepsis are all known to depress myocardial contractility.[20] Several clinical and scientific studies have shown that decreased systolic and diastolic ventricular contractility in septic patients results in reduced coronary perfusion pressure.[20–22] Associated arrhythmias may also be a risk factor for the development of a TIA or ischaemic stroke. The coagulopathy associated with severe pneumonia may also be a potential risk factor for cerebral haemorrhage.[23]

Limitation

This study has limitations. First, it is a retrospective study using ICD-10 codes to identify cases of CAP and vascular events. These codes have modest sensitivity and specificity and it is likely that some cases of pneumonia admitted during the study period were missed. In addition, we did not have the data to calculate severity scores such as CURB65/PSI or data on prior secondary prevention treatment, which would ideally have been added to the multivariable model. Although, we reviewed clinical data, ECG, troponin testing and brain imaging to diagnose vascular events, a prospective study would be desirable to better characterize the patients in terms of both cardiovascular events and severity of CAP.

Conclusion

Cardiovascular events and stroke are common during hospitalization for CAP and are associated with increased length of hospital stay and 90-day mortality. Further prospective studies are needed to define the pathogenesis of this association and possible therapeutic modalities to prevent these vascular events.

Conflict of interest: None declared.

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The natural history of treated and untreated primary hyperparathyroidism: the Parathyroid Epidemiology and Audit Research Study

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Summary

Background: Primary hyperparathyroidism (PHPT) is a common endocrine disorder with the majority of cases being mild and untreated.
Aim: To provide an update on the natural history of treated and untreated PHPT.
Design: Retrospective population-based observational study.
Methods: From 1997 to 2006, a well-defined cohort of PHPT patients was established in Tayside, Scotland. Subsequent cohorts of 'mild untreated' and 'surgically treated' PHPT patients were selected for the present study. Their serum calcium (S-Ca) and PTH concentrations were followed until September 2009. Surgical outcomes were evaluated using hospital admission data.
Results: A total of 904 'mild untreated' patients were identified (median follow-up = 4.7 years), with a baseline median S-Ca of 2.62 mmol/l. A general decreased trend was observed in the S-Ca concentration for up to 12 years but an increasing trend in PTH ($P < 0.001$ in both instances). Disease progression, defined as an increase in S-Ca concentration, was observed in 121 patients (13.4%). Twenty-six (2.9%) patients had undergone surgery during the subsequent follow-up period. Baseline age and PTH concentration were the only significant risk factors for disease progression. In comparison, there were 200 'surgically treated' patients (median follow-up = 5.8 years). S-Ca was normalised after surgery, in 196 patients (98%). Hospital admissions for renal complications were reduced after surgery. In conclusion, most untreated patients with mild PHPT had no progression of S-Ca but approximately 15% did show some evidence of progression. Parathyroidectomy, with a high success rate, normalized the S-Ca in patients with PHPT.

Introduction

Primary hyperparathyroidism (PHPT) is characterized by an elevated serum calcium (S-Ca) and plasma parathyroid hormone (PTH) concentrations, usually as a result of a single over-active parathyroid gland. With automated biochemical screenings becoming more routinely available, diagnosis is earlier and the majority of patients (>85%) are now asymptomatic. Although parathyroidectomy (PTX) is the only definite cure for the disease, conservative management has been favoured, as few complications have been observed among asymptomatic PHPT.[1–8] Studies of the natural history of

asymptomatic PHPT have continued since the 1980s but the generalizability is limited, often due to small patient numbers.[2,6–12] In light of the shift to a further subclinical profile of PHPT with absence of any traditional symptoms, the third international workshop was held in May 2008, with a focus on reviewing and updating the diagnosis and management of asymptomatic PHPT.[13–17] In order to answer the question of whether or not asymptomatic PHPT patients could be left safely under surveillance without surgery, it was recommended that issues on disease progression, involvement of other complications and possible predictors of complications among mild asymptomatic PHPT patients, should be addressed.

Previously, in our region of Scotland, UK, a well-defined cohort of PHPT patients was established during the decade of 1997 to 2006.[18] In a previous study, we have shown that this is a common disease with possibly 1% of the total population affected, and that there are increased risks of mortality and morbidity for CVD, cerebrovascular disease, cancer and other poor outcomes, in patients with mild PHPT.[19] This present article is aimed at providing an update of the natural history, with a focus on S-Ca progression, of untreated PHPT patients with raised, but milder hypercalcaemia (S-Ca < 2.90 mmol/l at the baseline). Complete observational data at population level, including biochemical records and hospital admissions, were linked to observe the long-term results in these patients and to compare the outcomes with those who had undergone PTX. We also proposed to look at the surgical cure rate and possible predictors of S-Ca progression in unoperated patients.

Patients and methods

Study population

During the period from January 1997 to December 2006, a pre-defined biochemical algorithm, in addition to other hospital data, was used to establish a data set of all patients with PHPT in Tayside, Scotland.[18] Briefly, a positive biochemical diagnosis was made if a patient met either of the following criteria: (i) albumin-corrected S-Ca > 2.55 mmol/l (reference range 2.10–2.55 mmol/l) on at least two occasions, with plasma PTH concentration >3 pmol/l (reference range 1.0–6.9 pmol/l) or (ii) albumin-correct S-Ca >2.55 mmol/l on one occasion, with plasma PTH concentration >6.9 pmol/l. Definite biochemical diagnoses were then confirmed using urine calcium excretion data (available in 30%), hospital data, including hospital admission data on PHPT, hospital operation and procedure data on PTX, nuclear medicine scans, renal function databases and hospital letters indicating positive PHPT and any additional PHPT cases were also added to the cohort.[18] Further linkage to patient demographic information, inpatient hospital admissions, biochemical test results and community prescription from the Health Informatics Centre, was made possible via a unique anonymous patient identifier, the Community Health Index (CHI), in accordance with the Data Protection Act, to establish a complete and linked data set for all diagnosed PHPT patients.[20,21]

By scrutinizing the linked data set, subsequent cohorts of 'mild untreated' and 'surgically treated' PHPT patients were selected to form the basis of the present study (Figure 1). The 'mild untreated' group were defined as untreated PHPT patients whose S-Ca concentrations were <2.9 mmol/l within the first 6 months after a positive diagnosis with absence of previous (prior to PHPT diagnosis) fracture fragility,[17] renal stones and renal failure and not treated with cinacalcet; the 'surgically treated' group were patients who had undergone PTX by the end of 2006. Further exclusion criteria were applied to the 'mild untreated' group. These were: (i) S-Ca was followed up for <6 months; (ii) less than two S-Ca measurements within the first 6 months. For those who were biochemically identified PHPT patients, the date of first raised S-Ca ($\geqslant$2.55 mmol/l) was treated as the date of PHPT diagnosis and the corresponding S-Ca was treated as the baseline value; for those who were identified solely from the hospital records, the result of S-Ca concentration tested on the date of admission was treated as the baseline value.

The study was approved by the Tayside Research Ethics Committee and the Tayside Caldicott Guardians.

Definition of disease progression

For the selected patients, all S-Ca test records after a positive PHPT diagnosis were compared to the baseline. If S-Ca increased by 0.2 mmol/l, or S-Ca reached 2.9 mmol/l during the study period, a marker was made indicating a biochemical progression of the disease.

Statistical methods

Descriptive statistics were used to summarize baseline characteristics of the patients. Differences in biochemical indices and follow-up times between sub-groups were tested using non-parametric methods because their distributions were non-Normal. Other differences were examined using independent-samples *t*-test or chi-squared test as

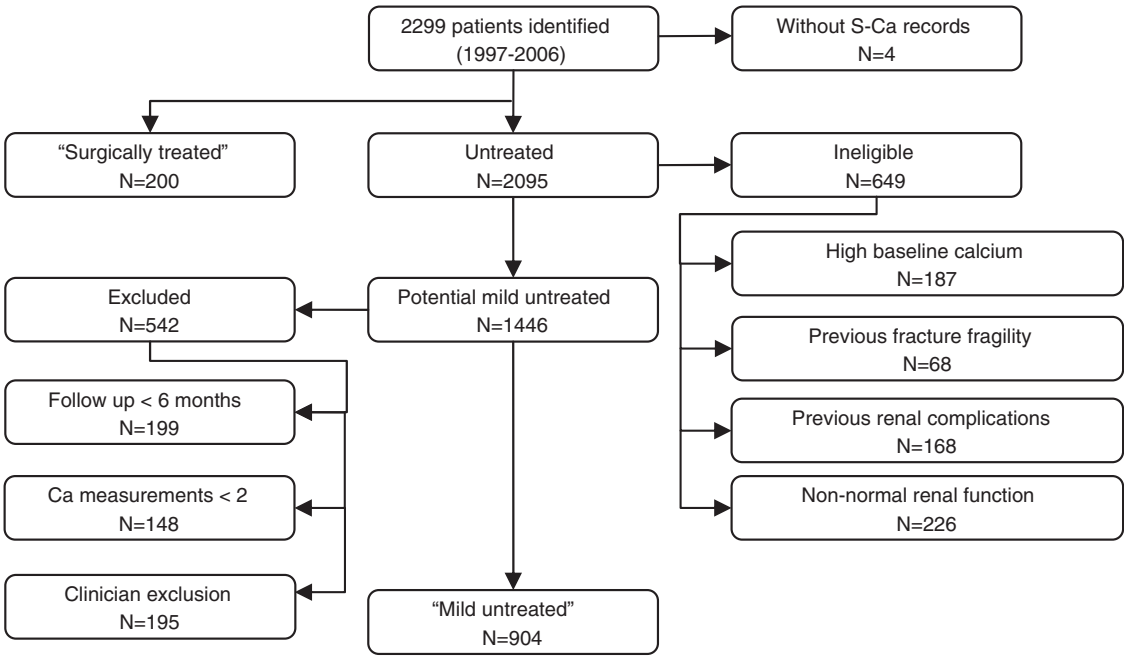

Figure 1. Flow diagram of patient selection process. Previous fracture fragility was defined as previous admissions on osteoporotic fractures, i.e. fractures at the sites of spine, wrist, humerus and femur, suggested from the hospital records; previous renal complications were any previous hospital admissions on renal failure and/or renal stones; non-normal renal functions were indicated if the baseline serum creatinine level were above 150 mmol/l.

appropriate. Changes in pooled biochemical indices were assessed using curve estimation. Within-subject changes in S-Ca and PTH concentrations during the follow-up period, in the 'mild untreated' group, were further estimated using linear mixed models, allowing repeated but unequal number of measurements within subjects.[22] The Akaike's information criterion (AIC) was used to select the best model in describing the trend.[23] In addition, the Cox proportional hazards model was used to examine possible predictors of S-Ca progression. Predictor variables considered were baseline age, gender, baseline biochemical values and other pre-existing clinical complications. Each factor was tested individually, initially, to identify the most important predictors. In the 'surgically treated' group, the rates of developing other co-morbidities, or complications, denoted as number of events per five person years, before and after surgery were computed and compared using the Poisson Exact test. Co-morbidity information was obtained from the hospital admission records indicating an inpatient admission. Before surgery events included any admission from a positive PHPT diagnosis being made to the time of surgery; and post surgery events were any post-operative admission that occurred till the end of study. Rates of event were calculated as the number of event in each observed period divided by the total corresponding person time. Postoperative biochemical indices at 2, 6 and 12 months after surgery, were compared with the baseline. All statistical analyses were carried out using the SPSS (version 17) and SAS (Version 9.1) software, and statistical significance was demonstrated with $P < 0.05$.

Results

Baseline characteristics

During the decade of 1997 to 2006, we identified 1099 'mild untreated' PHPT patients and 200 'surgically treated' patients who were potentially eligible for this study (Figure 1). By examination of the biochemical records (consultant endocrinologist GL) of all the 1099 untreated patients, 195 patients were further excluded. These exclusions were made because of the following reasons: suppressed PTH concentration (<3 pmol/l) 6 months after a positive diagnosis ($n = 9$); presence of low S-Ca concentration (<2.1 mmol/l) 6 months after a positive diagnosis ($n = 89$) and PTH mediated hypercalcaemia was unclear in the remaining 97 patients. Thus, the final study cohort comprised 904 'mild untreated' PHPT patients and 200 'surgically treated' patients. The baseline characteristics of these patients are tabulated in Table 1. S-Ca was followed up from

Table 1 Baseline characteristics of patients with mild untreated PHPT and PHPT treated with surgery

Variables	Mild untreated	Surgically treated	*P*-value	Normal range
Number of patients	904	200	–	–
Age, mean (SD) (years)	67.3 (13.5)	58.2 (13.9)	<0.001	–
Female *n* (%)	674 (74.6%)	151 (75.5%)	NS	–
S-Ca follow-up, median months (range)	56 (6.2–152.1)	70 (7.5–154.7)	<0.001	–
Baseline biochemical indices[a]				–
Serum calcium (mmol/l)	2.62 (2.55–2.89)	2.80 (2.56–5.49)	<0.001	(2.1–2.55)
PTH (pmol/l)	6.5 (3.0–29.9)	12.7 (3.9–274.0)	<0.001	(1.0–6.9)
Alkaline phosphatase (μ/l)	94 (28–1187)	91 (43–516)	NS	F (20–190) M (30–150)
Serum creatinine (μmol/l)	96 (56–150)	92 (48–1266)	NS	F(50–160) M (60–190)
Total cholesterol (mmol/l)	5.10 (1.69–14.08)	5.23 (2.4–9.4)	NS	(ideal $\leqslant$ 5)

[a]Biochemical values and follow-up time are shown as median (range), as the natural of non-normal distribution, Serum calcium was corrected for albumin.

Table 2 Rates (event per 100 person years) of developing other co-morbidities before and after parathyroidectomy in the 200 surgically treated PHPT patients

Other complications	Before surgery	After surgery	*P*-value
Cardiovascular disease	2.48	1.66	NS
Renal stones	3.10	0.38	0.01
Renal failure	4.96	0.90	<0.001
Osteoporosis fractures	1.56	0.76	NS
Cancer	1.86	2.30	NS
Psychiatric disease	0.32	0.12	NS

the date of PHPT diagnosis and was continued until the end of September 2009 or death or migration whichever was earlier, giving a median follow-up of 4.7 years for the 'mild untreated' and 5.8 years for the 'surgically treated' group, respectively. 'Surgically treated' patients were younger and with higher baseline S-Ca and PTH concentrations than the 'mild untreated' patients ($P<0.001$ in all instances; Table 1).

By the end of September 2009, there were 299 (33.1%) who had died in the 'mild untreated' group and 28 (14.0%), in the 'surgically treated' group (chi-square = 28.56, $P<0.001$).

Surgical cure rate

S-Ca concentration was normalized after surgery with median postoperative S-Ca concentration at 2 months being 2.44 mmol/l, significantly lower than the baseline measurement ($P<0.001$), and remained stable within the normal range at 6 and 12 months check-up (2.42 and 2.36 mmol/l, respectively). Four patients showed evidence of S-Ca progression 6 months after the surgery, indicating a surgical failure rate of 2%. There was no homogeneity among these four patients in terms of baseline characteristics. PTH was reduced from a median value of 12.5 pmol/l at the baseline to a postoperative value of 6.4 pmol/l at 2 months but there was no trend observed over time. There was no significant change in other biochemical indices, such as postoperative alkaline phosphatase and serum creatinine concentrations, when compared to the baseline. Surgery also significantly reduced risks of developing renal complications, among in PHPT patients (Table 2).

Disease progression among mild, untreated PHPT patients

Of the 904 mild untreated patients, biochemical indices were followed up over a maximum of 12-year period. A total of 15 741 post-diagnosis measurements of S-Ca were made. According to the AIC, the linear mixed model adjusted for age as a time dependent variable and gender provided the best fit for both S-Ca and PTH concentrations, which showed a decreasing trend in S-Ca by time and an increasing trend in PTH ($P<0.001$ in both instances). Figure 2 illustrates changes in pooled S-Ca and PTH concentrations by follow-up time. The pooled median S-Ca concentration regressed to normal range within the first year and remained stable, with a significant decreasing trend ($P<0.001$) over a 10-year period of observation. The pooled median PTH concentration, on the contrary, was persistently above the upper limit of normal range (6.9 pmol/l), with an increasing trend ($P<0.001$). Serum creatinine and alkaline phosphatase fluctuated around the normal ranges, with no clear patterns identified.

Over one tenth of the 'mild untreated' patients ($n=121$, 13.4%) developed evidence of progression, with a mean time to progression of 3.2 years

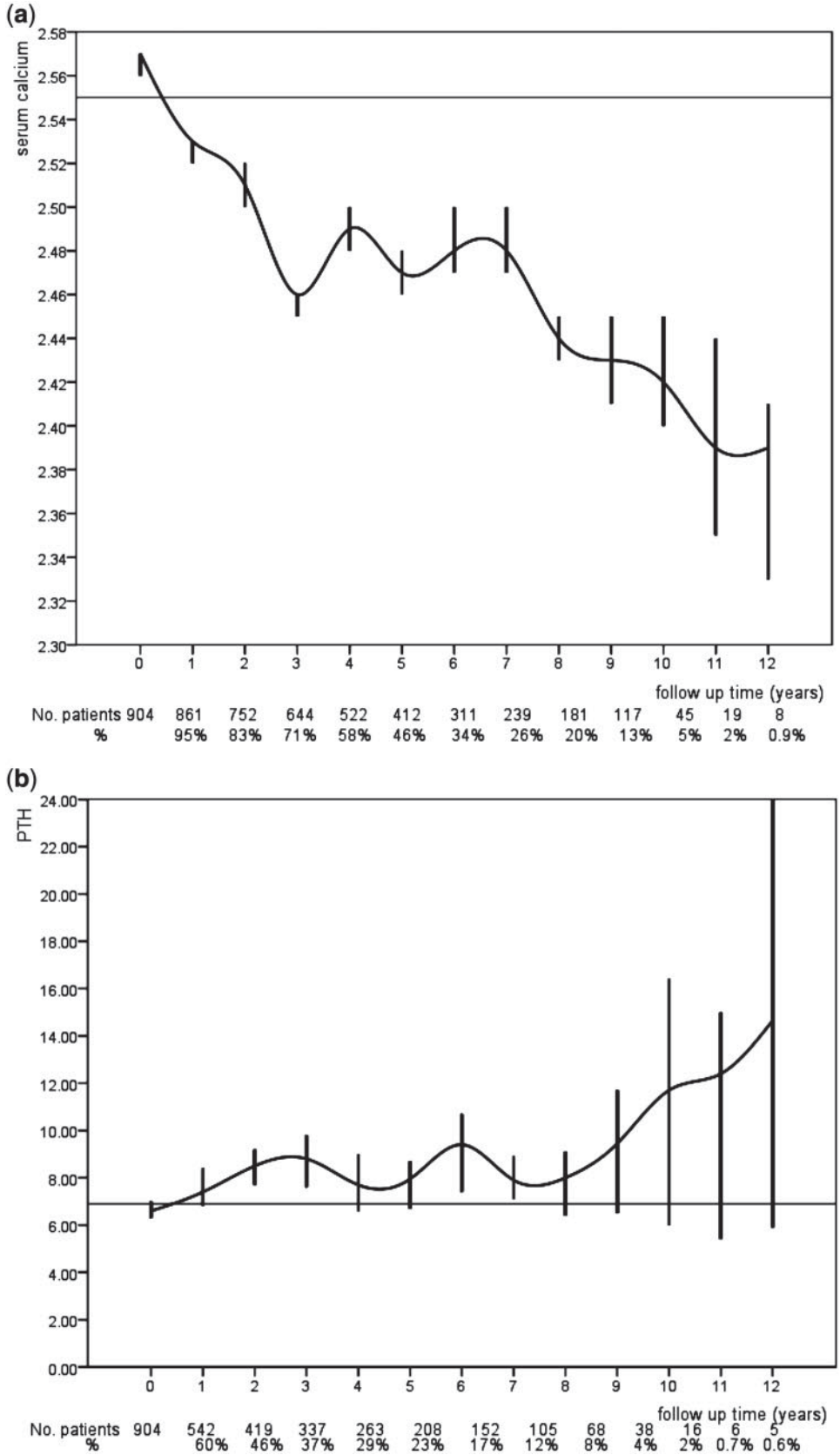

Figure 2. Changes in biochemical indices (pooled median values) among mild untreated PHPT patients with error bar (vertical segments on the curve) representing 95% confidence intervals. The reference line indicating the upper limit of the normal reference. (**a**) Serum calcium concentration (upper limit of normal range = 2.55 mmol/l). (**b**) Plasma PTH concentration (upper limit of normal range = 6.9 pmol/l).

Table 3 Comparison of baseline characteristics between progressed and un-progressed mild untreated PHPT patients

Variables	No progression	Progression	*P*-value
Number, *n* (%)	783 (86.6)	121 (13.4)	–
Age, mean (SD), years	66.9 (13.4)	69.7 (13.7)	0.032
Female, *n* (%)	587 (75)	87 (71.9)	NS
Follow-up time, median months (range)	55 (6.2–151.9)	64 (7.4–152.1)	0.018
Progression time, median months (range)	–	39 (6.8–114.0)	–
Baseline biochemical indices[a]			
Serum calcium (mmol/l)	2.61 (2.55–2.88)	2.63 (2.55–2.89)	0.036
PTH (pmol/l)	6.4 (3.0–29.9)	8.5 (3.0–25.6)	0.006
Alkaline phosphatize (μ/l)	93 (28–1187)	94 (36–258)	NS
Serum creatinine (μmol/l)	96 (56–150)	96 (60–150)	NS
Cholesterol (mmol/l)	5.1 (1.7–14.1)	5.4 (2.2–8.7)	NS

[a]Biochemical values are shown as median (range), as the natural of non-normal distribution, serum calcium was corrected for albumin. Any difference between progressed and un-progressed subgroups was compared using either the Independent Samples *t*-test or Mann–Whitney test as appropriate.

(Table 3). Patients who progressed were older, with longer follow-up and higher baseline S-Ca and PTH concentration than the un-progressed patients. According to the changes in individual's S-Ca concentrations, two types of progression were observed, these being 'unsustained progression' and 'persistent progression'. Nine patients (1.0% of the total 'mild untreated' patients) had 'persistent progression', i.e. their S-Ca remained at a progressed level for more than a 6-month interval, with the last S-Ca concentration being progressed compared to the baseline. In the majority of patients ($n = 102$, 84% of all progressed patients) who progressed, S-Ca concentration later decreased, defined as 'unsustained progression'. Ten patients of the original 121 patients who progressed could not be grouped by progression type, due to insufficient follow-up time.

Twenty-six (2.9%) patients from the 'mild' initially 'untreated' group were eventually surgically treated during the follow-up period of 2007 to September 2009. Of these, nine had shown progression in S-Ca prior to surgery and the others had developed other surgical indications. These patients had higher baseline S-Ca and PTH concentrations compared to the remaining 'mild untreated' patients ($P < 0.001$ and $P = 0.07$, respectively). Both S-Ca and PTH concentrations were normalized after surgery.

Predictors of disease progression

Age at diagnosis and baseline PTH were shown to be significant risk factors of S-Ca progression with HR of 1.18 and 1.35, respectively (Table 4). The risk of progression increased by 35% for each 5 pmol/l increase in the baseline PTH concentration ($P = 0.017$) and the risk increased by 18% for each 5 years increase in age at diagnosis ($P = 0.020$). Figure 3 illustrates the increased rate of S-Ca progression in the 'mild untreated' patients by the range (in quintile) of their baseline PTH concentration. In each PTH quintile, there was no difference in the baseline S-Ca concentration.

Discussion

This study provided up-to-date information on the natural history of asymptomatic 'mild' PHPT patients with a long follow-up period, in terms of the biochemical progression of the disease; our data is based on a larger patient cohort when compared to previous studies.[2,7,11,24–26] Our patient cohort was based on an unselected stable population from all residents in the region. It represents the Scottish population structure and is similar to the UK population, although with slightly fewer ethnic minorities. As the diagnosis of cases was based on electronic records and subject to biochemical measurements, undiagnosed cases were not detected in this study. However, because the diagnosis was based on biochemical features rather than clinical referral patterns, we identified a large number of patients with borderline raised serum calcium concentrations, from a population base. In addition, due to the nature of retrospective observational study design, a substantial proportion of patients were lost-to-follow-up or had incomplete biochemical measurements (Figure 2). Despite this, the numbers, as shown in Figure 2, were fairly robust for 3–4 years during which time there were significant trends, which continued later even when the data was less complete. Nevertheless, since we have access

Table 4 The results from the unadjusted and adjusted Cox proportional hazards models looking at possible predictors of progression of S-Ca in the mild untreated PHPT patients

Variables	Unadjusted		Adjusted	
	HR 95% CI	*P*-value	HR 95% CI	*P*-value
Age (+5 year)	1.16 (1.07–1.25)	<0.001	1.18 (1.03–1.35)	0.020
Female (vs. Male)	0.93 (0.63–1.39)	NS	–	–
Baseline biochemical indices				
PTH (+5 pmol/l)	1.49 (1.19–1.87)	0.001	1.35 (1.06–1.73)	0.017
Creatinine (+5 μmol/l)	0.98 (0.94–1.02)	NS	–	–
Alkaline phosphatase (+5 μ/l)	0.99 (0.98–1.01)	NS	–	–
Cholesterol (+1 mmo/l)	0.95 (0.78–1.14)	NS	–	–
Pre-existing conditions (yes vs. no)			–	–
Cardiovascular disease	0.92 (0.57–1.51)	NS	–	–
Cerebrovascular disease	0.87 (0.38–1.98)	NS	–	–
Hypertension	0.49 (0.18–1.33)	NS	–	–
Cancer	0.78 (0.38–1.60)	NS	–	–
Diabetes	1.09 (0.62–1.94)	NS	–	–

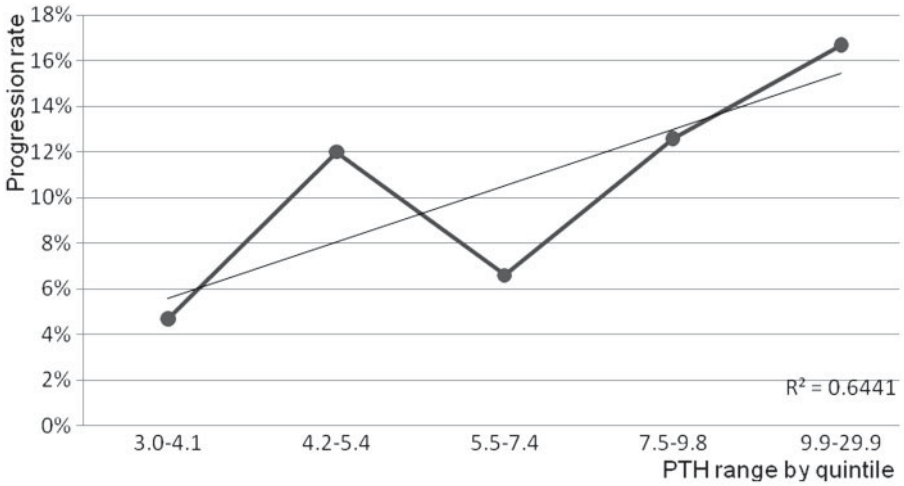

Figure 3. The progression rate of serum calcium (dotted line) among mild untreated PHPT patients arranged by the baseline PTH values with fitted trend line (straight line). The baseline PTH concentration was divided into five quintiles; the rate was calculated as the number of patients who had shown progression of S-Ca divided by the total number of patients in each quintile. R^2 indicates the closeness of the regression line vs. the actual rates.

to an exhaustive population database of all laboratory records, the reason for non-follow-up was more likely linked to cases with normalized test results. As a result, the interpretation of our results on disease progression, i.e. abnormal biochemical values, was robust, thus overcoming the limitations of study design.

The 'mild untreated' group were largely identified biochemically, who had mild hypercalcaemia with normal renal function and absence of previous fracture fragility at the time of diagnosis supplemented with clinical examination of case notes for further exclusions, therefore they reflected the contemporary asymptomatic PHPT patients who were without any overt symptoms. The definition of S-Ca progression (increase in serum calcium of >0.2 mmol/l or reached 2.9 mmol/l), broadly followed the NIH guidelines, and represented a clinically important change in S-Ca and indicated a worsening of the disease.[17,27–30] By our definition, we found three patterns of S-Ca development, these being (i) no progression, (ii) unsustained progression and (iii) persistent progression. In support of previous studies on the natural history of asymptomatic PHPT, the majority of our mild patients (86.6%) had stable or decreased S-Ca over the 10-years of follow up from initial diagnosis.[7,11] However, 3% of 'mild untreated' patients developed surgical indications and had undergone

PTX by the end of September 2009. We found the rates of S-Ca progression did not differ by the baseline S-Ca concentration, but was positively correlated with the baseline PTH concentration. PTH as a genuine predictor of progression was also demonstrated in the multiple regression when we took both baseline biochemical indices and pre-existing co-morbidities into consideration.

In many patients the S-Ca reverted to the normal range but continued with a raised serum PTH concentration. Many patients will have been diagnosed with PHPT when they were unwell with other conditions. It is likely that the serum calcium improved when the condition unmasking the PHPT was treated. It is also possible that some of these may have had vitamin D insufficiency but it seems unlikely that vitamin D insufficiency would have been the reason for a raised S-Ca or S-Ca within upper reference range at baseline. There was no seasonal bias in serum calcium measurements, which may have been expected if vitamin D insufficiency had contributed in a major way to S-Ca concentrations. We found that the number of measurements was roughly equally spread through the year with similar pooled median calcium concentrations. In addition, as all patients presented with raised calcium at diagnosis, we have also examined the number of diagnoses made in each calendar month and found the numbers were similar (data not shown). Therefore, our data suggested that the influence of vitamin D insufficiency on our biochemical results was minimal. However, it is interesting that vitamin D insufficiency may contribute to the increased morbidity observed in so called 'mild' PHPT.[19]

In the 200 'surgically treated' PHPT patients, we have detected a high surgical success rate (98%), comparable to other series.[24,31–33] In agreement with existing evidence, we have shown that both S-Ca and PTH concentrations were normalized postoperatively.[11,33–38] In a recent randomized study, Bollerslev *et al.*[34] found that successful PTX normalized S-Ca and PTH concentrations but had no observable benefit on cardiovascular morbidity. We used hospital admission data to evaluate the impact of successful PTX on cardiovascular involvement, renal complications and neuropsychological complaints and found no significant improvement in cardiovascular risk, although we may not be powered to detect such a difference, since there was a non-statistical trend. Moreover, we were unable to detect any surgical benefits on psychiatric symptoms; this was possibly due to the fact that neuropsychological complications in mild PHPT patients were too subtle to result in hospital admission. Existing evidence showing neurocognitive improvements were often detected retrospectively, when asking patients to compare particular symptoms before and after the surgery.[2,24,25,39–41] We found, however, the risks of developing renal stones and renal failure were significantly reduced after successful surgery (Table 2).

In summary, in most patients with mild asymptomatic PHPT serum calcium did not progress if left untreated but around one tenth of them did show some evidence of progression. High baseline PTH concentration was and increasing age were important predictors of progression.

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Non-traumatic myelopathy at the Chris Hani Baragwanath Hospital, South Africa—the influence of HIV

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Summary

Background: Non-traumatic myelopathy from developing regions has been described widely. In these regions infections, mainly tuberculosis, followed by acute transverse myelitis and neoplasms, dominate. These are also regions of high HIV prevalence. In developed regions, the most prominent reported spinal cord disease in HIV/AIDS is vacuolar myelopathy (VM). Other myelopathy causes in HIV/AIDS include opportunistic infections, neoplasms, vascular lesions and metabolic disease. In developing regions, opportunistic infections are more commonly encountered with VM occurring less frequently.
Aim: To determine the influence of HIV on the myelopathy spectrum in an HIV endemic region.
Design: Prospective case series.
Methods: Hundred unselected consecutive in-patients admitted with myelopathy were studied. Myelopathy aetiologies were established by collating information obtained from magnetic resonance imaging (MRI) scans, CSF and blood studies, CXR findings, non-neurological illness and response to treatment. Data were analysed in terms of two cohorts, HIV positive and HIV negative.
Results: Approximately 50% of the patients presenting and admitted to our hospital with non-traumatic myelopathy are HIV positive. The HIV positive myelopathy patients were younger (20–40 years) and had infectious aetiologies. Tuberculosis was the most frequently identified cause of myelopathy. The majority of HIV-positive patients had advanced HIV infection. Anti-retroviral treatment did not influence myelopathy aetiologies. The HIV-negative patients were older and had neoplasms, followed by degenerative spondylosis as the main myelopathy causes.
Conclusions: HIV influences the non-traumatic myelopathy spectrum in regions with high HIV prevalence. Empiric treatment of HIV-myelopathy patients with anti-tuberculous medications where resources are severely limited has merit.

Introduction

Non-traumatic myelopathy in the developing regions of sub-Saharan Africa and Asia is caused mainly by infectious and para- or post-infectious immune aetiologies.[1–3] Tuberculosis, viral myelitis and parasitic infestations are the commonly encountered aetiologies.[1–3] These are also regions of high HIV prevalence. Data from the Joint United Nations Programme on HIV/AIDS (UNAIDS) in 2009 showed that sub-Saharan Africa bears the brunt of the HIV epidemic with 22 million infected individuals (66% of the 33.4 million HIV-infected people worldwide).[4] In South Africa, an estimated 5.7 million people are HIV infected (11% of the population) making it the country with the highest number of HIV-infected people.[5]

Myelopathy in HIV has been widely described. It is a less common neurological manifestation of

HIV/AIDS with frequencies between 5% and 10% compared with HIV-associated dementia frequencies of 15% and distal sensory polyneuropathy frequencies of 30%.[6] In developed regions, the most prominent reported spinal cord disease in HIV/AIDS is vacuolar myelopathy (VM).[7,8] Other myelopathy causes in HIV/AIDS include opportunistic infections, neoplasms, vascular lesions and metabolic disease. In developing regions, opportunistic infections are more commonly encountered with VM being infrequently reported.[9,10]

The influence of HIV on non-traumatic myelopathy spectrum in developing regions is, however, not clearly documented. In these regions, where resources are limited, this becomes an important consideration as it may impact on efficient and cost-effective diagnosis and management. We therefore studied 100 consecutive and unselected (in terms of HIV status) adult in-patients with non-traumatic myelopathy at the Chris Hani Baragwanath Hospital, Soweto, South Africa, an HIV endemic region, to address this question.

Study design

Prospective consecutive case series.

Patients and methods

We studied 100 consecutive patients with non-traumatic myelopathy who presented to the medical wards at the Chris Hani Baragwanath Hospital (CHBH) in Soweto, South Africa over a period of 8 months. The CHBH is a 3300-bed public university hospital that serves a predominantly black urban population of ~3 million people.

The patients were in-patients who presented with myelopathy defined as a disorder of the spinal cord resulting in motor (paraplegia, triplegia or quadriplegia with upper motor neuron signs or features consistent with spinal shock), sensory (sensory level for pin prick and light touch and/or loss of proprioception and vibration) and autonomic dysfunction (impaired sphincter control). HIV testing in those with unknown status was done after patients were counselled by an experienced HIV counsellor and with written and informed consent. Ethics approval was obtained from the university ethics committee and review board.

The following data were recorded:

(i) Demographics: age and sex.
(ii) Blood: full blood count, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), glucose, urea and electrolytes, serum calcium, phosphate and magnesium, liver function tests, HIV enzyme-linked immunosorbent assay (ELISA), T cell subsets, serological tests for syphilis, toxoplasma gondii, HTLV-1, antinuclear factor (ANF), angiotensin converting enzyme (ACE), Vitamin B12, red cell folate, cytomegalovirus (CMV) serology and pp65 CMV antigen were done.
(iii) Cerebrospinal fluid (CSF): Chemistry, cell counts, cytology, CMV serology with pp65 CMV antigen, HTLV-1 serology, adenosine deaminase (ADA) level, syphilis serology, India ink staining, cryptococcal antigen, bacterial and fungal cultures, polymerase chain reaction (PCR) for HSV-1, HSV-2, HHV-6, VZV, CMV, EBV, enteroviruses and TB.
(iv) Radiology: Chest X-rays (CXR), magnetic resonance imaging (MRI) scans of the entire spine and brain.
(v) Histology: Biopsies were performed in selected patients and
(vi) Presumed Aetiologies: Diagnoses of myelopathy were based on collating clinical examination findings with information obtained from the MRI scans, CSF and blood studies, CXR findings, associated neurological and non-neurological illness/es, histology, where available, and response to treatment (e.g. tuberculostatics).

Results

Patient profiles

Of the 100 patients assessed, HIV testing was not done in three patients (two demised prior to testing, one refused consent) (Tables 1–3). Fifty patients were HIV positive and 47 patients were HIV negative. In the HIV-positive group, the mean age was 35 years (range: 16–59 years, SD: 8.6 years), and there were equal numbers of male and female patients. In the HIV-negative group, the mean age was 53 years (range: 15–87 years, SD: 15.2 years). There was a male predominance in this group (female:male ratio 1:2).

Clinical presentation and clinical manifestations

The patients' temporal presentation, symptoms and signs are presented in Table 1. Sixty-eight percent of the patients in the HIV-positive group presented acutely. Fifty-three percent of the HIV-negative group presented acutely. In both groups, the majority had back pain, autonomic dysfunction, sensory symptoms and paraplegia. Sixty percent of HIV positive and 58% of HIV-negative patients presented with complete transverse myelopathy (paraplegia/quadriplegia with a sensory level involving all modalities of sensation). Quadriplegia was uncommon (4% of HIV positive and 13% of HIV-negative patients).

Table 1 Clinical presentation and manifestations in 97 patients with myelopathy

Presentation/Manifestations	HIV positive *n* (%)	HIV negative *n* (%)
Acute (<6 weeks)	34 (68)	25 (53)
Chronic	16 (32)	22 (47)
Paraplegia	47 (94)	39 (83)
Quadriplegia	2 (4)	6 (13)
Triplegia	1 (2)	2 (4)
Sensory symptoms	48 (96)	42 (89)
Autonomic symptoms	46 (92)	38 (81)
Back pain	30 (60)	34 (72)
Transverse myelopathy (TM)	30 (60)	27 (58)
Partial transverse myelopathy (PTM)	20 (40)	20 (42)

n = number of patients; % = percentage.

Aetiologies

The aetiologies of the two groups of patients are shown in Table 2. In the HIV-positive group, 36 patients (72%) had infection as a cause. Twenty-five of these cases had tuberculosis. The diagnosis of TB, albeit difficult in the absence of histology and culture, was made in our patients where these were not available by collating information as described in the 'Materials and methods' section. Other aetiologies identified include HIV-VM in eight patients (all had normal MRI brain), CMV (one patient) and varicella zoster (two patients). Acute disseminated encephalomyelitis (ADEM) was diagnosed in four and neuromyelitis optica (NMO) in two HIV-positive patients. Neoplasms in this group occurred in six patients. These included two patients with lymphoma, one with plasmacytoma and three with spinal metastases (one of unknown origin, one patient from renal cell carcinoma and one from breast carcinoma). Vitamin B12 deficiency was identified in one patient and another patient was diagnosed as a malingerer.

In the HIV-negative group, neoplasms (primary or secondary) constituted the largest number of patients (20 patients or 43%). These were widely spread in terms of types. More than half of the neoplasms were spinal metastases (14 patients) with metastatic prostate carcinoma being the commonest (four patients). The next category in order of frequency was cervical spondylosis occurring in 15 patients (32%). Infections were identified in six patients (13%). Of these, five patients had TB and one patient was diagnosed with HTLV-1-associated myelopathy. Four patients (8%) had idiopathic acute transverse myelitis (ATM). Other causes of myelopathy in the HIV-negative group included SLE in one patient and spinal cord infarction in one patient.

Table 2 Aetiologies

Category	Diagnosis	HIV positive *n* (%)	HIV negative *n* (%)
Infectious		**36 (72)**	**6 (13)**
	TB	25 (50)	5 (11)
	HTLV1		1 (2)
	VM	8 (16)	
	CMV	1 (2)	
	VZV	2 (4)	
ATM	Idiopathic		**4 (8)**
Immune	Lupus myelitis		**1 (2)**
Demyelinating		**6 (12)**	
	ADEM	4 (8)	
	NMO	2 (4)	
Vascular	Cord infarction		**1 (2)**
Degenerative	Cervical spondylosis		**15 (32)**
Neoplasms	Total	**6 (12)**	**20 (43)**
	Primary	**3 (6)**	**6 (13)**
	Neurofibromatosis		1 (2)
	Meningioma		1 (2)
	Astrocytoma		1 (2)
	Multiple myeloma		2 (5)
	Lymphoma	2 (4)	1 (2)
	Plasmacytoma	1 (2)	
	Metastases	**3 (6)**	**14 (30)**
	Undetermined	1 (2)	3 (7)
	Bronchial		2 (4)
	Renal cell	1 (2)	
	Prostate		4 (9)
	Vulval		1 (2)
	Thyroid		1 (2)
	Basal cell		1 (2)
	Haematomyeloid		1 (2)
	Cervix		1 (2)
	Breast	1 (2)	
Nutritional	B12 deficiency	**1 (2)**	
Malingerer		**1 (2)**	

Bold values reflect only total number of 'big' categories of causes.

HIV-positive cohort profiles

Number of patients: 50.

Latency to presentation

Thirty-one patients were already known HIV positive at presentation. The latency from diagnosis of positive HIV status to presentation with myelopathy in these patients was 1 month to 6 years. Nineteen patients were newly diagnosed HIV positive at presentation with myelopathy. We did not repeat

Table 3 CD4 counts vs. aetiologies in ARV-naïve patients

Category	CD4 (cells/ml)	CDC 1			CDC2	CDC3	Total
		<50	50–100	100–200	200–500	>500	
Infectious							
	TB	3	1	9	6		19
	VM	2	2	1			5
	CMV	1					1
	Zoster	1		1			2
Demyelinating							
	ADEM	1		2	1		4
	NMO	1					1
Neoplasms							
	Primary	2			1		3
	Plasmacytoma	1					
	Lymphoma	1			1		
	Metastases	1			2		3
	Undetermined				1		
	Renal Cell CA				1		
	Breast CA	1					
Nutritional							
	B12 deficiency					1	1
Other							
	Malingerer			1			1

HIV testing and therefore some of these patients, especially those with very high CD4 counts could have been in a seroconverting phase. None of the patients in the study improved spontaneously, a feature that is often seen in seroconverting illnesses associated with HIV.

CD4 counts and staging

Staging was determined using the Centers for Disease Control (CDC) 1993 revised classification system for HIV infection and AIDS-defining illnesses.[11]

The patients had CD4 T lymphocyte counts ranging from 3 to 942 cells/ml (mean: 154 cells/ml, SD: 168 cells/ml, median 108 cells/ml). One patient (2%) had a CD4 count of >500 cells/ml; 10 patients (20%) had CD4 counts between 200 and 500 cells/ml; 38 patients (76%) had CD4 counts of <200 cells/ml.

In one patient, the CD4 count was not done. The blood viral load range in 44 of the 50 patients (not done in 6 patients) was <25–1 700 000 copies/ml (median: 89 000 cells/ml).

ARV medication

Nine patients were on ARVs, whereas 41 patients were not on ARVs (subsequently referred for ARV treatment).

CD4 counts versus aetiologies in ARV-naïve patients

In this subgroup of HIV-positive patients, infections were dominant (Table 3). Of the total of 40 patients, 27 (68%) had an infectious aetiology for the myelopathy. TB was the commonest of these (19 patients). Correlations with CD4 counts showed that most infectious myelopathies occurred in patients with CD4 counts below 200 cells/ml (21 patients). With respect to TB, 6 of the 19 patients had CD4 counts between 200 and 500 cells/ml. All six patients with VM had CD4 counts of <200 cells/ml (4 had CD4 counts of <100 cells/ml). The patient with CMV myelopathy had a count of <50 cells/ml. The two patients with herpes zoster myelopathy had CD4 counts of <200 cells/ml. Three of the four ADEM patients had counts of <200 cells/ml. The NMO patient had a CD4 count of <50 cells/ml.

CD4 counts versus aetiologies in patients treated with ARV

In this group of nine patients, eight had CD4 counts <200 cell/ml, (four with TB, three with VM and one with NMO). All three VM patients had CD4 counts <100 cells/ml (two of whom had counts <50 cells/ml). The patient with NMO had a CD4 count of between 50 and 100 cells/ml.

Discussion

Our study reported here is unique in that we looked at an unselected group (from an HIV point of view) of hospital-based non-traumatic myelopathy patients from a developing region with high HIV prevalence. This allowed us to determine the influence HIV has on the myelopathy profiles in our population and thereby in other comparable regions.

Approximately, 50% of patients presenting and admitted to our hospital with non-traumatic myelopathy are HIV positive. This is in accordance with the high HIV prevalence in our hospital with admissions to the general medical ward being commonly HIV-related (estimated to be 50%—but unpublished as data).

The majority of patients in this study regardless of HIV status presented with an acute myelopathy and complete paralysis (paraplegia), a reflection of our hospital-based selection bias that largely excludes ambulatory myelopathy patients.

By analysing the data in terms of the two cohorts, HIV positive and HIV negative, we immediately noted the striking difference that emerged in terms of patient 'ages and aetiologies'. The HIV-positive patients had a mean age of 35 years compared to the patients who were HIV negative where the mean age was 52.7 years ($P < 0.0001$, Student's *t*-test).

In the HIV-positive group, almost three-quarters of patients had an infectious aetiology with TB being the most prominent. TB occurred with a frequency of 50% in the HIV-positive cohort (95% CI: 36–64%). Only 6 of the 19 ARV-naive patients diagnosed with TB in this cohort had CD4 counts between 200 and 500 cells/ml. TB is a granulomatous disorder and requires a certain degree of immune competence for granulomatous disease formation. In HIV patients, however, we often find ourselves diagnosing TB even with very low CD4 counts. The mechanisms underlying this are not fully understood. We previously proposed that the pathological spectrum in HIV-positive patients is largely determined by the infectious pathologies that are prevalent in the region being studied.[9] TB has an incidence of 940/100 000/year and a prevalence of 998/100 000 in South Africa which ranks among the highest in the world.[12] Not surprisingly, it featured as the dominant myelopathy cause in our HIV-positive cohort and was also the most common infectious aetiology in the HIV-negative cohort.

In the HIV-negative group, neoplasms accounted for >40% of patients followed by spondylotic myelopathy (32%). This concurs reasonably well with findings from other populations with low HIV prevalence. In a cohort of myelopathies from Liverpool, UK, cervical spondylosis accounted for 23.8% and neoplasms accounted for 16.4% of myelopathies.[13] Infections in this study occurred in 2.1% compared to 12.7% (10.6% TB) in our HIV-negative group.[13] Interestingly, multiple sclerosis (MS) occurred relatively frequently at 17.8% in the Liverpool study.[13] In our patients who were mainly Black, regardless of HIV status none was diagnosed with MS. This reflects on the prevalence of MS in our study population. MS is described rarely in Black South Africans.[14] However, we previously documented a different, yet similar type of central nervous system demyelinating disease that occurs in our Black population. This disorder bears resemblance clinically to NMO and radiologically to MS with ADEM and NMO features.[14] In our HIV cohort, we found six patients with demyelination as a cause of which four patients were diagnosed as ADEM and two patients with NMO (anti-aquaporin antibody testing not available at time of study). None of these patients had features of the demyelinating disease described by us previously.[14] In a study from KwaZulu Natal, South Africa, ADEM was described in six HIV-positive patients during early infection.[15] In a myelopathy study on HIV-positive patients from the same group of investigators from this region, ADEM and NMO were excluded from the study and were thus not listed as causes of myelopathy.[10]

In contrast to the HIV-negative group, there were no HIV-positive patients with spondylotic myelopathy in our study. This presumably relates to the younger age of the HIV cohort (mean of 35 years vs. 52.7 years of the HIV-negative cohort). With respect to neoplasms, in Johannesburg, South Africa, HIV infection was found to be associated with significant increased risks of Kaposi's sarcoma, non-Hodgkins lymphoma and cancers of the cervix and vulva.[16] In our series, there was no specific type of neoplasm associated with HIV myelopathy.

Analysis of the HIV cohort showed that myelopathy was the presenting manifestation of HIV/AIDS in 19 patients (38%). The remainder of patients were known HIV positive at presentation with latencies varying from 1 month to 6 years. The mean CD4 count in the newly diagnosed HIV patients was 199 cells/ml compared to 124 cells/ml in the known HIV patients (not statistically significant). The majority of our HIV patients regardless of HIV status at presentation with myelopathy were in CDC Stage 3 or advanced HIV infection. This included nine patients who were on anti-retroviral medication. The low CD4 counts in these patients on ARV treatment may be related to the duration of treatment and/or the co-infection. In the ARV-naïve patients, 66% had an infectious aetiology. TB was the commonest cause and also occurred in patients with CDC Stage 2 disease. In the ARV-treated group,

the majority of patients were also diagnosed with TB. This once again presumably relates to the high prevalence of TB in our region.

In our study, VM occurred in eight patients (five ARV-naïve and three ARV treated) accounting for 16% of the HIV myelopathy cohort. In varying series described in the literature from predominantly clade B regions, VM at autopsy is found in 20–55% of HIV/AIDS patients with only 5–10% of patients being clinically symptomatic.[6,17,18] In an audit conducted by us (in a clade C dominated HIV population), VM occurred in 2% of 500 hospitalized HIV-positive patients.[9] VM is described less frequently in clade C regions where opportunistic infections are the main myelopathy causes.[10] The reasons for this are not clear, but have been postulated to be related to different risk factors (heterosexual vs. homosexual or intravenous drug use), nutritional status (accompanying malnutrition), genetic susceptibilities, viral or clade differences and the general lack of ARV use in developing regions compared with developed regions.[19] In a study of 33 HIV-positive patients with myelopathy from KwaZulu Natal in South Africa, only one patient was considered to have VM.[10] Interestingly, in this study, 12 patients (36%) had co-infection with HTLV-1. In our HIV patients described here, none had HTLV-1 infection (only one patient was diagnosed with HTLV-1 myelopathy and was HIV negative). This probably relates to the regional differences in HTLV-1 seroprevalence. Other than this observation, our findings were similar in that infections, notably TB were the dominant causes of myelopathy in HIV-positive patients. The low frequency of VM in this present study and as reported previously from Ethiopia and KwaZulu Natal, South Africa, may reflect (in particular in our study) on patient selection and study bias (inpatients only).[10,20,21] The majority of our patients had total paralysis at presentation. VM does not commonly present in this way. We may thus have selected out by restricting our study to hospital inpatients a large proportion of VM patients. Thus the low reported occurrence of VM in sub-Saharan African countries may be the result of under-reporting. Community or population-based and/or HIV out-patient clinic studies could address this issue.

Non-traumatic myelopathy from regions such as ours has been described widely. In studies from sub-Saharan Africa, including Ethiopia, Tanzania, Zimbabwe, Ghana and Nigeria, the common myelopathy causes were similar to our study with infections, mainly TB and neoplasms dominating.[3,10,20–24] These studies were largely retrospective and conducted in both the pre-HIV and HIV era but did not specifically address the issue of the influence of HIV on myelopathy spectrum. In recent studies from India and Bangladesh, TB, ATM and neoplasms were the common non-traumatic myelopathy causes.[1,2,25] Similar findings were reported from Fiji and Papua New Guinea.[26,27] On the contrary, non-traumatic myelopathies from the developed regions of Europe and North America show a distinctly non-infection-dominated spectrum. In these regions, common myelopathy causes include spondylosis, neoplasms, MS and ATM.[13]

The most important observation of our study is that in developing regions 50% of hospital based myelopathy patients will be HIV positive is endemic and thereby influences the type of admission, 50% of myelopathy patients will be HIV positive and regardless of ARV treatment, 50% of HIV-positive patients will have TB as the cause of the myelopathy. In our study, we undertook extensive investigations from a research perspective to identify in detail the exact myelopathy aetiologies and thereby strengthened this observation. The implication of our finding is that in resource-limited settings with high TB prevalence, treating HIV-positive myelopathy patients for TB empirically would be appropriate. Hypothetically, since almost three-quarters of our HIV-positive patients had an infection, with TB in 50%, we could have treated empirically these patients with anti-TB treatment and steroids without any investigations. This would have produced a successful result in 62% of our HIV patients (50% infection and 12% demyelinating). The failed response patients could then be referred to a tertiary facility.

Conclusion

HIV influences the non-traumatic myelopathy spectrum in regions with high HIV prevalence in hospitalized patients. In such regions, myelopathy in the young patient is likely to be HIV associated and caused by TB. These observations could justify empiric TB treatment of such patients when resources are severely limited, but more data and studies are needed.

Conflict of interest: None declared.

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Review

QJM

Ischaemic and bleeding complications with new, compared to standard, ADP-antagonist regimens in acute coronary syndromes: a meta-analysis of randomized trials

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Summary

Background: Platelets play a pivotal role in the pathogenesis of acute coronary syndromes (ACS) and their inhibition remains a mainstay therapy in this setting. We aimed to perform a meta-analysis of randomized trials to evaluate the benefits of new oral antiplatelet regimens to block platelet ADP-receptors compared to standard-dose clopidogrel (300 mg loading dose followed by 75 mg/daily).

Methods: We obtained results from all randomized trials enrolling patients with ACS. Primary endpoint was mortality. Secondary endpoints were myocardial infarction and definite in-stent thrombosis. Safety endpoint was the risk of major bleeding complications. We prespecified subanalyses according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel (600 mg) and patients undergoing percutaneous coronary intervention.

Results: A total of seven randomized trials were finally included in the meta-analysis ($n = 58\,591$). We observed a significant reduction in mortality (2.9% vs. 3.4%, OR = 0.87, 95% CI 0.79–0.95, $P = 0.002$), recurrent myocardial infarction (4.2% vs. 5.2%, OR = 0.80, 95% CI 0.74–0.87, $P < 0.0001$), definite in-stent thrombosis (0.9% vs. 1.7%, OR = 0.52, 95% CI 0.43–0.63, $P < 0.0001$). The benefits in mortality and reinfarction were driven by the treatment with prasugrel or ticagrelor, without a significant difference in terms of major bleeding complications as compared to standard-dose clopidogrel (5% vs. 4.7%, OR = 1.06 95% CI 0.96–1.17, $P = 0.25$).

Conclusions: This meta-analysis showed that new oral antiplatelet regimens are associated with a significant reduction in mortality, reinfarction and in-stent thrombosis in ACS patients without an overall increase of major bleeding when treated with new antiplatelet drugs.

Introduction

Platelets play a pivotal role in the pathogenesis of acute coronary syndromes (ACS). The combination of aspirin and clopidogrel (300 mg loading dose followed by 75 mg/daily) has represented for years the oral antiplatelet therapy of choice.[1] Large interests have been focused on new therapeutic strategies to block ADP receptors in order to overcome several limitations of clopidogrel, such as large interindividual variability, delay in onset of action and irreversibility.[2–4] However, it must be recognized that an improvement in platelet aggregation inhibition may be counterbalanced by a higher risk of bleeding complications.[5] Thus, the aim of the current study was to perform a meta-analysis of randomized trials to evaluate the benefits in terms of ischemic and bleeding complications of new oral antiplatelet regimens to block platelet ADP receptors as compared to standard dose of clopidogrel.

Methods

Eligibility and search strategy

We obtained results from all randomized controlled trials (RCTs) on adjunctive ADP receptor antagonists among patients with ACS. The literature was scanned by formal searches of electronic databases (MEDLINE and CENTRAL) from January 1990 to January 2010, the scientific session abstracts in Circulation, Journal of the American College of Cardiology, European Heart Journal and American Journal of Cardiology from January 1990 to January 2011. Furthermore, oral presentations and/or expert slide presentations were included (searched on the TCT (www.tctmd.com), EuroPCR (www.europcr.com), ACC (www.acc.org), AHA (www.aha.org) and ESC (www.escardio.org) websites from January 2002 to January 2011. The following key words were used: randomized trial, ACS, unstable angina, coronary angiography, coronary angioplasty, antiplatelet therapy, thienopyridine, ADP antagonist, clopidogrel, high-dose clopidogrel, prasugrel, ticagrelor, AZD-6140. Inclusion criteria were: (i) randomized treatment allocation and (ii) availability of complete clinical data. Exclusion criteria consisted of: (i) follow-up data in <90% of the patients; (ii) ongoing studies or irretrievable data and (iii) intravenous therapy with periprocedural but not chronic administration. No language restrictions were enforced.

Data extraction and validity assessment

Data were independently abstracted by two investigators. In case of incomplete or unclear data, authors, where possible, were contacted. Disagreements were resolved by consensus. Data were managed according to the intention-to-treat principle.

Outcome measures and prespecified subanalyses

Clinical endpoints assessed were mortality as primary endpoint (all-cause mortality was preffered when reported, or cardiovascular mortality), myocardial infarction and definite in-stent thrombosis (secondary endpoints) at follow-up, whereas major bleeding complications (according TIMI major bleeding definition when available, or according to study definition) were assessed as safety endpoint.

We performed prespecified subanalyses according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel (600 mg) and patients undergoing percutaneous coronary intervention (PCI).

Data analysis

Statistical analysis was performed using the Review Manager 4.27 freeware package, SPSS 11.5 statistical package. Odds ratio (OR) and 95% confidence intervals (95% CIs) were used as summary statistics. The pooled OR was calculated by using a fixed effect model (the Mantel-Haenszel method) and the random effect model between study heterogeneity was analyzed by means of $I^2 = [(Q-df)/Q] \times 100\%$, where Q is the χ^2 statistic, and df is its degrees of freedom. This describes the percentage of the variability in effect estimates that is due to heterogeneity rather than sampling error (chance). A value >50% may be considered substantial heterogeneity. The potential publication bias was examined by constructing a 'funnel plot', in which the standard error (SE) of the ln OR was plotted against the OR (mortality). Prespecified subanalyses were conducted according to new antiplatelet drugs (prasugrel/ticagrelor), high-dose clopidogrel and patients undergoing PCI. The study was performed in compliance with the Quality of Reporting of Meta-Analyses (QUOROM) guidelines.[6]

Results

A total of 10 RCTs were initially identified (Figure 1).[7–19] Two trials[17,18] were excluded because of a temporary (periprocedural) intravenous

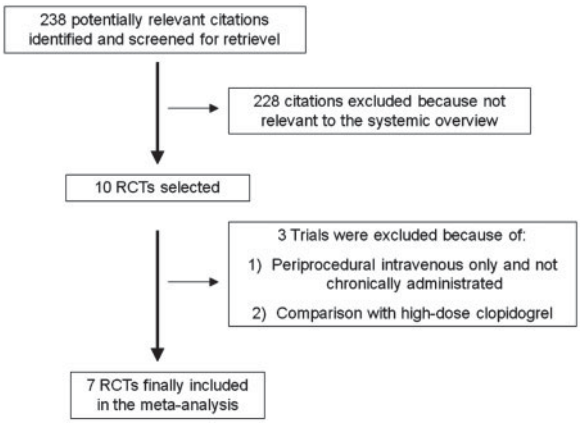

Figure 1. Flow diagram of the systematic overview process.

ADP-blocker administration but not chronic therapy. One trial was excluded because of comparison between prasugrel and high-dose clopidogrel.[19] Therefore, a total of seven randomized trials were finally included in the meta-analysis (Table 1), with 58 591 patients randomized to 300 mg clopidogrel ($n = 29\,284$) or new antiplatelet drugs (prasugrel or ticagrelor) or dosages (high-dose clopidogrel) ($n = 29\,307$). A total of 43 807 patients underwent PCI.

The TRITON-TIMI 38[7,8] included only patients undergoing coronary angioplasty, with randomization occurring just before the procedure. In the PLATO trial,[9,10] the decision to administrate a bolus of 300 or 600 mg was left to the discretion of local investigator. Finally, in the clopidogrel arm 59.5% of participants were treated with a loading dose of 300 mg. In this study, 15 170 of 18 624 enrolled patients (81.4%) underwent coronary angiography.

The DISPERSE-2 study[16] was a second phase clinical trial in which patients were randomly assigned in a 1:1:1 double-blind fashion to receive either twice daily ticagrelor 90 mg, ticagrelor 180 mg or clopidogrel 300 mg loading dose plus 75 mg once daily for up to 12 weeks. In our meta-analysis, we included only patients receiving the dose of ticagrelor used in the PLATO trial.

In the CURRENT OASIS-7 trial,[14] patients referred to invasive management were assigned to high-dose clopidogrel [600 mg bolus and a daily double dose of clopidogrel (150 mg) up to 7 days after enrolment] or to a standard clopidogrel regimen. In this trial, patients were additionally randomized to low (75–100 mg) or high-dose (300–325 mg) aspirin. In the ALBION trial,[11] patients were randomized to 300, 600 and 900 mg clopidogrel.

Primary endpoint

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)[7–10] follow-up. A total of 1886 patients died (3.2%). We observed a significant reduction in mortality with new regimens (2.9% vs. 3.4%, OR = 0.87, 95% CI 0.79–0.95, $P = 0.002$, $P_{heter} = 0.32$) (Figure 2: total), that was confined to new molecules (3.6% vs. 4.3%, OR = 0.83, 95% CI 0.74–0.92, $P = 0.0002$, $P_{heter} = 0.21$), especially to ticagrelor, as observed in the PLATO trial (Figure 2A: novel antiplatelet drugs). Similar results were observed in patients undergoing PCI ($n = 43\,807$) (2.4% vs. 2.7%, OR = 0.88 (95% CI 0.78–0.99, $P = 0.03$, $P_{heter} = 0.13$) (Figure 2B: PCI subgroup). As shown in Figure 3, no publication bias was observed.

Secondary endpoints

Myocardial infarction

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)[7–10] follow-up. Recurrent myocardial infarction was observed in 2740 (4.7%) patients. A significant reduction was observed with new regimens as compared to standard-dose clopidogrel (4.2% vs. 5.2%, OR = 0.80, 95% CI 0.74–0.87, $P < 0.0001$, $P_{heter} = 0.15$) (Figure 4: total). The benefits were mostly evident with new agents (6.0% vs. 7.5%, OR = 0.79, 95% CI 0.72–0.86, $P < 0.0001$, $P_{heter} = 0.11$) (Figure 4A: novel antiplatelet drugs) but not with high-dose clopidogrel (2% vs. 2.2%, OR = 0.88, 95% CI 0.75–1.05, $P = 0.16$, $P_{heter} = 0.3$) (Figure 4B: 600 mg clopidogrel). Similar benefits were observed when restricted to patients undergoing coronary angioplasty (4.5% vs. 6%, OR = 0.73, 95% CI 0.67–0.80, $P < 0.0001$, $P_{heter} = 0.24$) (Figure 4C: PCI subgroup).

In-stent thrombosis

Follow-up data were collected at 30 days or up to 12–15 months (PLATO and TRITON-TIMI 38)[7–10] follow-up. Definite in-stent thrombosis was observed in a total of 517 out of 40 276 patients (1.3%). Therapy with ADP-antagonist regimens when compared to standard-dose clopidogrel was associated with a significant reduction in definite in-stent thrombosis (0.9% vs. 1.7%, OR = 0.52, 95% CI 0.43–0.63, $P < 0.0001$, $P_{heter} = 0.40$) (Figure 5).

Safety endpoint

A total of 1973 patients (3.4%) had a major bleeding complication. High-dose (600 mg) clopidogrel as compared with 300 mg clopidogrel was associated

Table 1 Study characteristics

References	Study name	Journal	Year	ACS type	Overall pts[a]	PCI group pts	Study drug design		Survival endpoint	Follow-up time (months)	Definition of major bleeding
							Loading dose	Maintenance dose			
Cuisset *et al.*[12]	–	*JACC*	2006	NSTE-ACS	387	387	300 vs. 600 mg clopidogrel	75 mg/daily	CV mortality	1	TIMI classification
Montalescot *et al.*[11]	ALBION	*JACC*	2006	NSTE-ACS	69	–	300 vs. 600 vs. 900 mg clopidogrel	75 mg/daily	All-cause mortality	1	GUSTO classification
Cannon *et al.*[16]	DISPERSE-2	*JACC*	2007	NSTE-ACS	650	–	300 mg clopidogrel vs. 90 mg ticagrelor vs. 180 mg ticagrelor	75 mg/daily clopidogrel vs. twice daily 90 mg ticagrelor vs. twice daily 180 mg ticagrelor	All-cause mortality	0.9	Modified TIMI classification
Wiviott *et al*,[7,8]	TRITON TIMI -38	*NEJM, Lancet*	2007	STEMI and NSTE-ACS	13 608	12 844	300 vs. 60 mg prasugrel	75 mg/daily clopidogrel vs. 10 mg/daily prasugrel	All-cause mortality	15	TIMI classification
Wallentin *et al.*[9]/ Cannon *et al.*[10]	PLATO	*NEJM, Lancet*	2009	STEMI and NSTE-ACS	18 624	13 408	300/600 mg clopidogrel vs. 180 mg ticagrelor	75 mg/daily clopidogrel vs. twice daily 90 mg ticagrelor	All-cause mortality	12	TIMI classification
Yong *et al.*[13]	PRACTICAL	*Am. Heart J.*	2009	NSTE-ACS	256	140	300 vs. 600 mg clopidogrel	at the discretion of the treating physician	All-cause mortality death	6	TIMI classification
Mehta *et al.*[14,15]	CURRENT OASIS-7	*NEJM*	2010	STEMI and NSTE-ACS	25 086	17 263	300 vs. 600 mg clopidogrel	75 mg/daily clopidogrel vs. 150 mg/daily clopidogrel up to 7 days, and later 75 mg/daily clopidogrel	All-cause mortality	1	TIMI classification

[a]The total of patients allocated in the included studies to novel drugs or 600 vs. 300 mg clopidogrel.
CV = cardiovascular, GUSTO = Global Use of Strategies to Open Occluded Coronary Arteries, NSTE-ACS = non-ST-segment elevation acute coronary syndrome, STEMI = ST-segment elevation myocardial infarction, TIMI = thrombolysis in myocardial infarction; pts = patients.

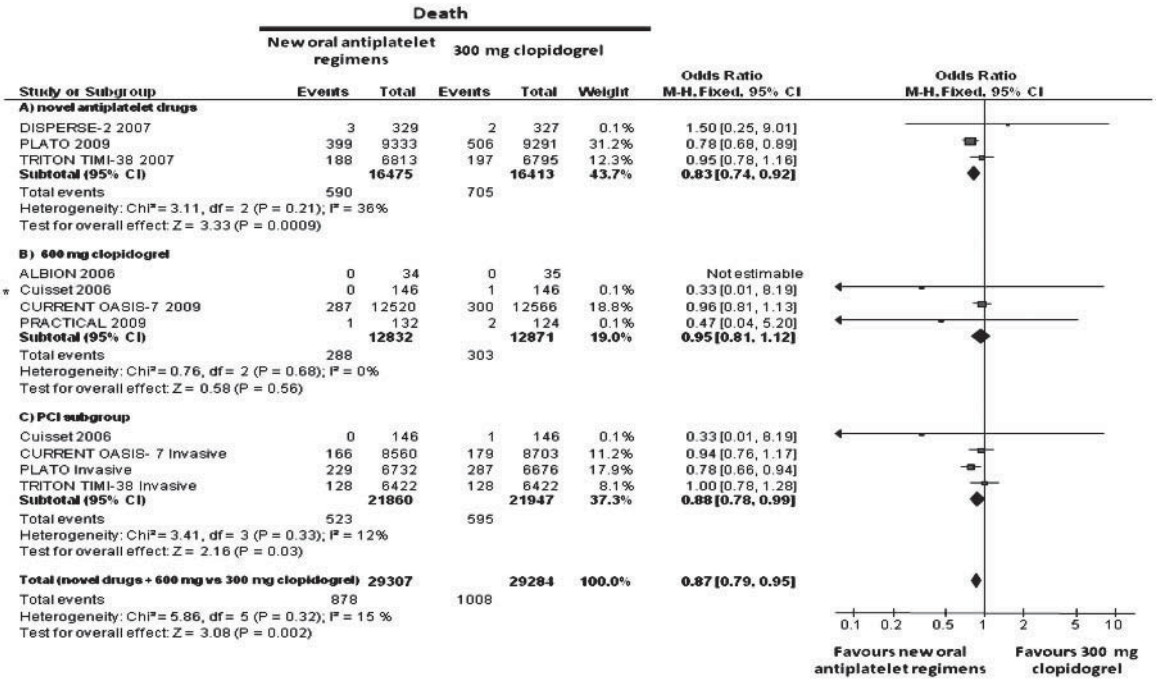

Figure 2. All-cause mortality in the overall population with ORs and 95% CI. (**A–C**) Prespecified subanalysis for mortality in the group of novel antitplatet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); ORs and 95% CI are reported. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial; * = cardiovascular mortality.

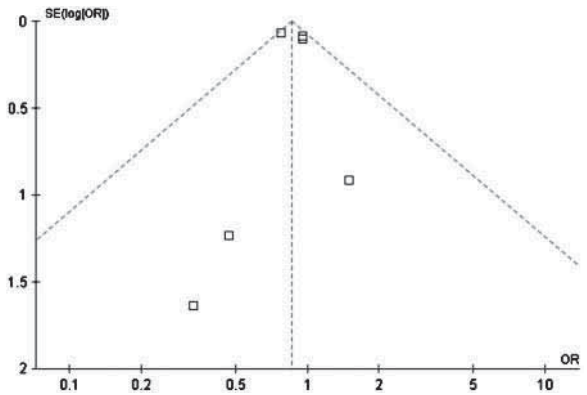

Figure 3. Funnel plot for mortality of the studies included in the meta-analysis. The SE of the ln OR was plotted against the OR for mortality. No skewed distribution was observed, suggesting no publication bias. ALBION study was not included in the graph because there was no computed effect size due to absence of events in the two arms (novel antiplatelet regimens vs. standard-dose clopidogrel).

with a higher rate of major bleedings (1.6% vs. 1.3%, OR = 1.25, 95% CI 1.02–1.53, $P = 0.03$, $P_{heter} = 0.45$) (Figure 6B: 600 mg clopidogrel).

Conversely, as compared with standard dose of clopidogrel, the new drugs did not significantly increase the rate of major bleeding complications (5% vs. 4.7%, OR = 1.06, 95% CI 0.96–1.17, $P = 0.25$, $P_{heter} = 0.10$) with the lower rates of bleedings confined to ticagrelor (Figure 6A: novel antiplatelet drugs). These results did not differ when the analysis was restricted to patients undergoing coronary intervention (Figure 6C: PCI subgroup).

Discussion

New antiplatelet regimens are regarded as major advance in cardiovascular therapy. The results of our meta-analysis of seven RCTs,[7–16] including 58 591 patients with ACS, showed that, when compared with standard-dose clopidogrel (300 mg loading dose), new antiplatelet regimens are associated with a significant reduction in mortality, reinfarction and in-stent thrombosis.

High-dose clopidogrel significantly increased the risk of major bleeding complications; an increased number of major bleedings was also observed with prasugrel, even though the overall subgroup of new antiplatelet drugs (prasugrel and ticagrelor) was not associated with an increased rate of major bleedings.

In terms of clinical efficacy and safety, the overall benefits were more pronounced with the new antiplatelet compound ticagrelor. The same clinical benefits observed in the overall analysis were consistent in the prespecified subgroup of patients

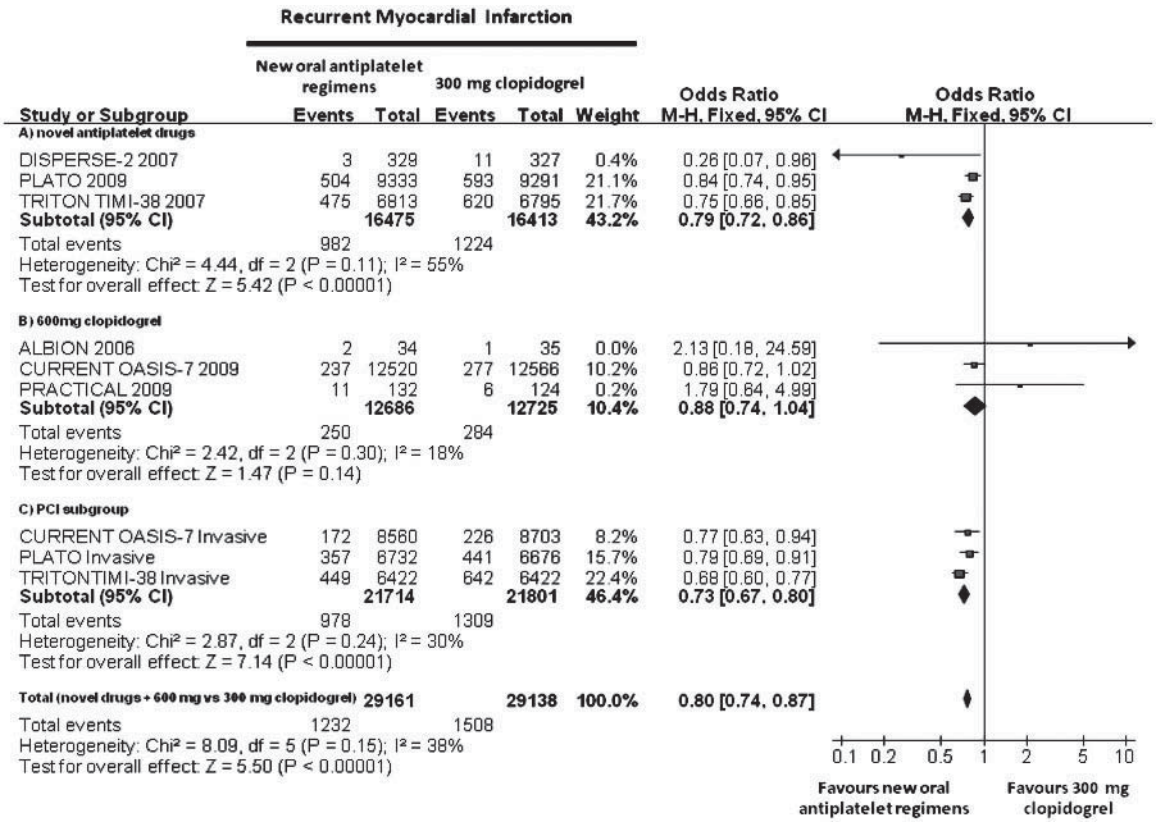

Figure 4. Recurrent myocardial infarction in the overall population, with ORs and 95% CI. (**A–C**) Prespecified subanalysis for myocardial infarction in the group of novel antitplatet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); ORs and 95% CI are reported. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

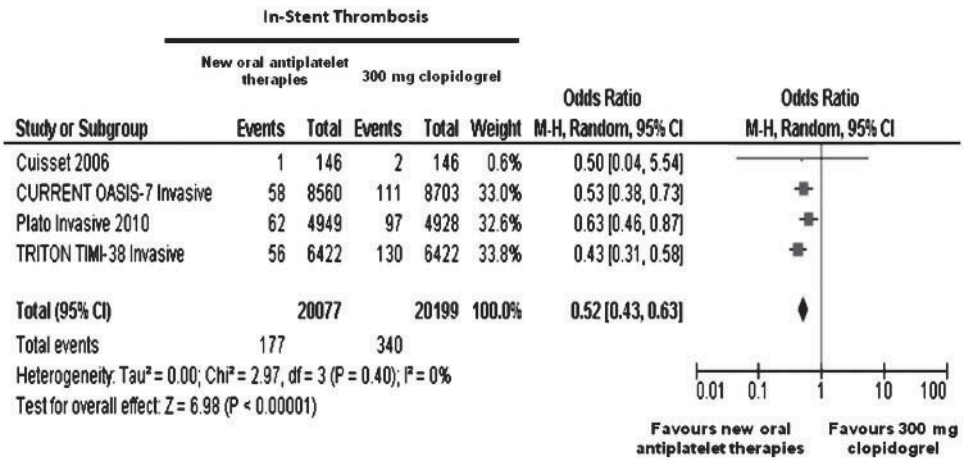

Figure 5. In-stent thrombosis in the overall population with ORs and 95% CI. The size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

undergoing PCI, where all the treatments did not increase the risk of major bleeding complications.

Standard-dose clopidogrel (300 mg bolus followed by 75 mg/daily) has been regarded for years as the gold standard of adjunctive antiplatelet therapy in patients with ACS treated with or without an interventional strategy.[1] Several limitations of clopidogrel[2–4] have raised the need for new therapies. First of all, many patients still have events despite dual antiplatelet therapy. Several factors may

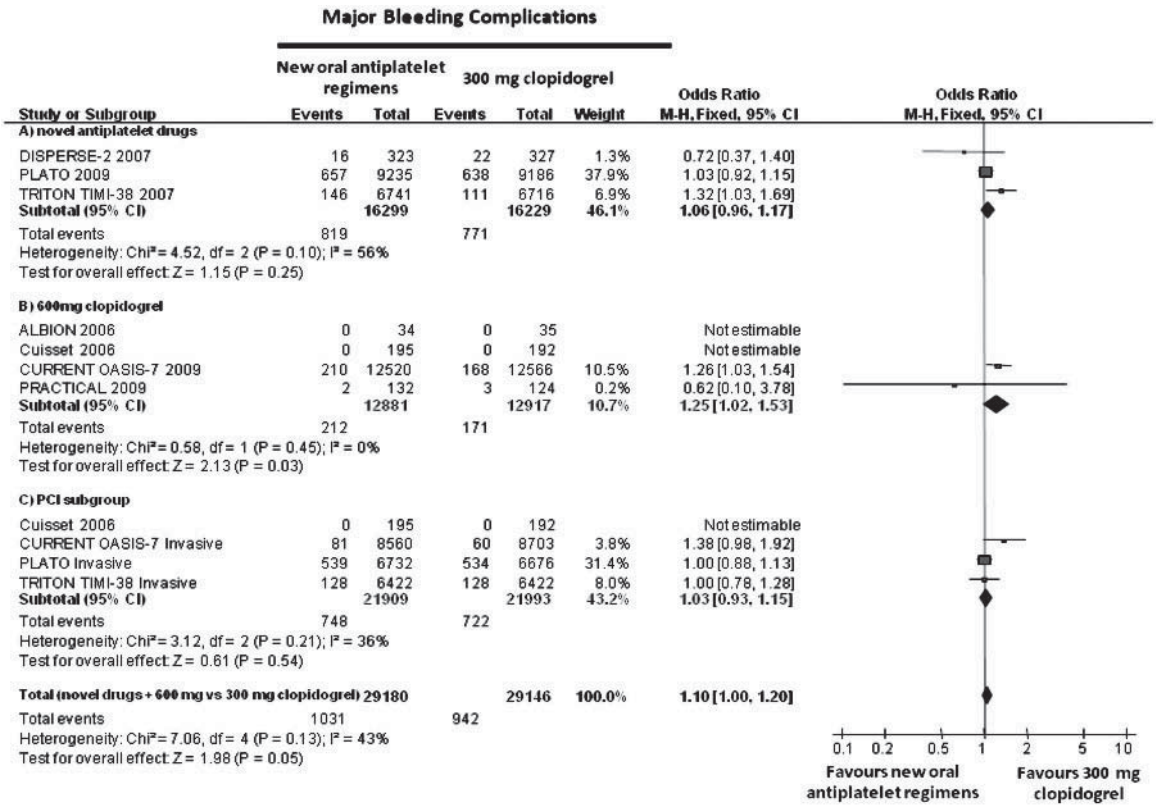

Figure 6. Major bleeding complications in the overall population with ORs and 95% CI. (**A–C**) Prespecified subanalysis for major bleedings in the group of novel antitplatet drugs (A), 600 mg of clopidogrel (B) and PCI subgroup (C); the size of the data markers (squares) is approximately proportional to the statistical weight of each trial.

contribute to clinical resistance to clopidogrel.[20] Due to its complex metabolic pathway, clopidogrel takes 4 h to reach peak platelet aggregation inhibition. Since many patients take clopidogrel loading dose just before PCI, they are at risk of ischemic periprocedural events. Furthermore, due to polymorphisms of several enzymes involved in the multistep metabolic pathway of clopidogrel, a large interindividual variability in platelet aggregation inhibition has been observed, with prevalence of resistance to clopidogrel ranging from 15% to 30%. Moreover, clopidogrel has irreversible effects that in some cases prevent from early administration before the procedure, especially in the setting of ACS where a relatively large proportion of patients (10–30%) has severe multivessel disease requiring bypass surgery, whereas a drug with reversible effects may overcome this limitation and increase the administration of early antiplatelet therapy.

However, a faster and stronger antiplatelet therapy may be associated with higher risk of bleeding complications that may counterbalance the benefits in terms of thrombotic complications.[5]

Several new therapeutic strategies have been proposed to overcome some limitations of standard-dose clopidogrel. High-dose clopidogrel has been shown to provide a faster and stronger inhibition of platelet aggregation with a lower percentage of resistance.

The CURRENT OASIS-7 trial showed that high-dose clopidogrel was associated with a slightly higher risk of bleeding complications [TIMI major bleedings: 210 (1.7%) vs. 168 (1.3%), $P = 0.03$] but benefits in reinfarction [237 (1.9%) vs. 277 (2.2%), $P = 0.09$], mainly due to a significant reduction of in-stent thrombosis [definite in-stent thrombosis 58 (0.7%) vs. 111 (1.3%); $P = 0.0001$).[14,15]

Prasugrel is a third-generation thienopyridine with a rapid and effective metabolic activation that is associated with a faster onset of action and an increased inhibition of platelet aggregation when compared to clopidogrel. Data from the TRITON-TIMI 38 showed significant benefits in terms of myocardial infarction and significant reduction in in-stent thrombosis.[7,8] Even though it was counterbalanced by a higher risk of major bleeding complications, the benefits in terms of thrombotic complications largely outweighed bleeding complications. Low body weight ($\leqslant 60$ kg), advanced age (>75 years) and previous stroke were predictors of

higher risk of bleeding complications, and in such patients the drug should not be administrated. However, a new ongoing trial, the TRILOGY trial, is investigating the benefits from a lower (half) dosage (30 mg bolus and 5 mg daily) in patients with ACS undergoing conservative therapy. In fact, one of the limitations of the TRITON-TIMI 38 trial was the enrolment of patients after initial angiography, but not at the very beginning of presentation of ACS (hospital admission).

Ticagrelor is a non-thienopyridine with a faster onset and offset of action and significantly higher inhibition of platelet aggregation as compared to 600 mg clopidogrel. One of the great advantages that make the molecule very appealing is the reversibility of its antiplatelet effect, with the drug administrated twice a day. This is extremely important, when the overall ACS population is taken into account. In fact, a considerable proportion of patients, ranging from 20% to 30%, undergo coronary artery bypass grafting (CABG) during hospitalization, where the risk of bleeding may become very high. Data from the large PLATO trial[9,10] showed a significant reduction in mortality, in addition to benefits in myocardial infarction and in-stent thrombosis. No difference was observed in terms of major bleeding complications. However, paradoxically, while a lower incidence of bleeding was observed in patients undergoing CABG, in non-CABG patients ticagrelor was associated with a significantly higher rate of major bleeding complications.

Our meta-analysis showed in 58 591 ACS patients that new oral antiplatelet therapies are associated with a significant reduction in mortality, recurrent myocardial infarction, especially with new drugs (prasugrel/ticagrelor). The benefits in mortality were mostly observed with ticagrelor, whereas the benefits regarding in-stent thrombosis were consistent with all the strategies. A higher risk of major bleeding complications was observed with both high-dose clopidogrel and prasugrel that disappeared in the analysis restricted to patients undergoing coronary angioplasty.

Limitations

This meta-analysis was not performed on individual patient's data that would have certainly improved the results, particularly by performing subgroup analyses. Furthermore, the trials included in our meta-analysis tested three different regimens (prasugrel, ticagrelor and high-dose clopidogrel) against standard-dose clopidogrel.

Conclusions

This meta-analysis of randomized trials conducted in ACS patients showed that new oral antiplatelet regimens to block platelet ADP-receptor are associated with a significant reduction in mortality, reinfarction, especially with ticagrelor and prasugrel. A higher risk of major bleeding complications was observed with both prasugrel and high-dose clopidogrel, that disappeared in the analysis restricted to patients undergoing coronary angioplasty, where clear and consistent benefits in terms of in-stent thrombosis were observed with all the new therapies as compared to standard-dose clopidogrel.

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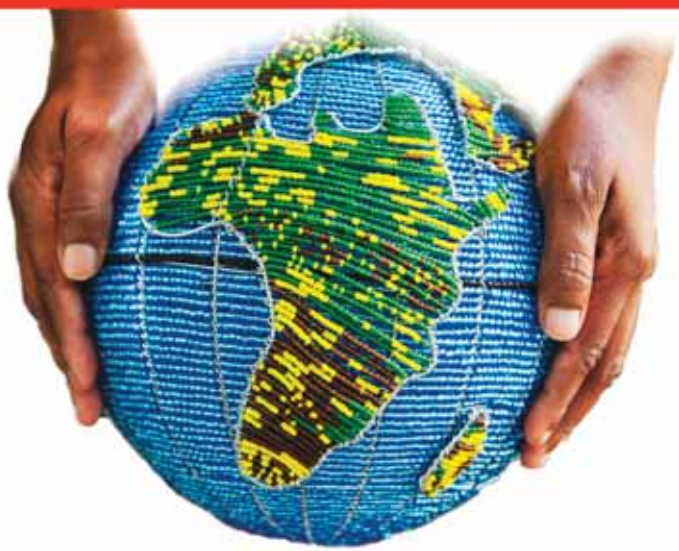
Award-winning inhaler innovation focusing on effective lung penetration[1,2,3] ...



- Effective fine particle generation[3]
- Higher and less variable lung deposition vs. pMDIs[2]
- Retains efficacy at inspiratory flow rates as low as 30 l/min[4]

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- Multiple-dose, user-friendly design[1,3]

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References: 1. Pharmacy Update Feb 11. Astrazeneca's Turbuhaler recognized at international Good Design Award. http://www.edoc.co.za/modules (Last accessed 20/5/2011). **2.** Thorsson L, Edsbäcker S, Conradson TB. Lung deposition of budesonide from Turbuhaler is twice that from a pressurized metered-dose inhaler P-MDI. *Eur Respir J* 1994;7:1839-1844. **3.** Borgström L, Asking L, Thorsson L. Idealhalers or realhalers? A comparison of Diskus and Turbuhaler. *Int J Clin Pract* 2005;59(12):1488-1495. **4.** Pederson S, Hansen OR, Fuglsang G. Influence of inspiratory flow rate upon the effect of a Turbuhaler. *Archives Dis Childhood* 1990;65:309-319.

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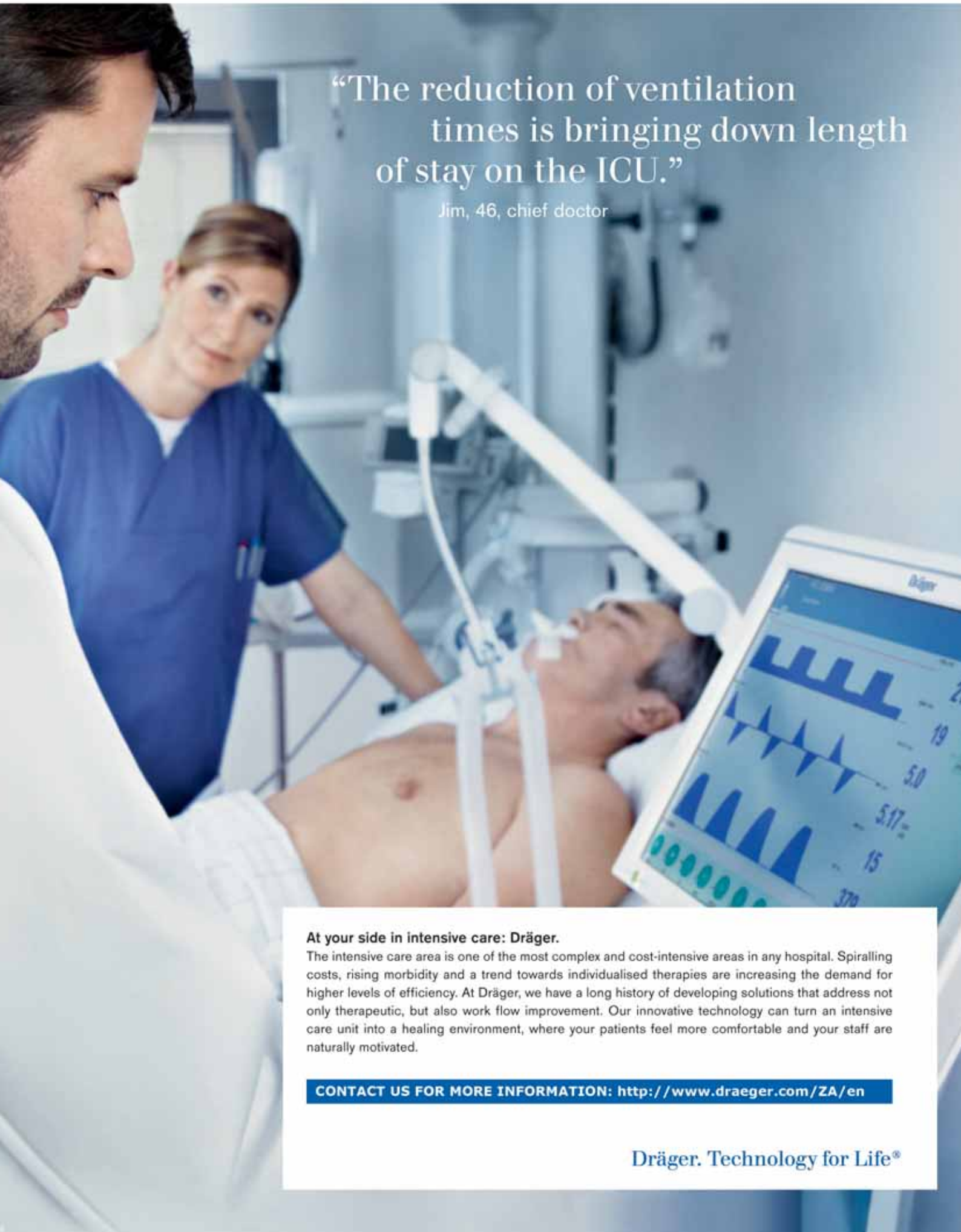

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