COMPLICATIONS AND FAILURES OF SECONDARY PREVENTION IN ACUTE ISCHAEMIC STROKE

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ABSTRACT

Complications and failures of secondary prevention of stroke:

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Stroke is a leading cause of death and the most common cause of disability in adults in the United Kingdom. Several treatments are effective in preventing stroke in the long term after TIA and minor ischaemic stroke, including aspirin, other antiplatelet agents, and blood pressure lowering drugs, statins and anticoagulation in atrial fibrillation. However, failure of secondary prevention to prevent recurrent vascular events is still a major clinical problem, as is the risk of bleeding associated with antiplatelet agents and anticoagulants.

This thesis determines the risks associated with urgent secondary prevention in the acute phase after TIA and minor stroke, particularly the reduction in risk of early recurrent stroke, the risk of bleeding with combination of aspirin and clopidogrel in the acute phase and whether or not there is a rebound increase risk of ischaemic stroke or recurrent TIA after withdrawal of a short course of clopidogrel.

I have shown that urgent and early treatment of ischaemic stroke with secondary prevention leads to an 80% reduction in recurrent stroke. I have also shown that an increased bleeding risk exists among aspirin naïve patients treated with combination antiplatelet medications compared to those already treated with aspirin. My work has also shown that discontinuation of clopidogrel following treatment for 30 days or more does not lead to a rebound increase in ischaemic stroke. Bleeding events are a frequent complication of antiplatelet treatment in TIA and ischaemic stroke. I have shown that the long term risk of bleeding in a population study treated with antiplatelets is 6% per 100 person years. Using this information I identified risk factors for bleeding to develop a clinical baseline bleeding model to identify those at higher risk of bleeding. Age was identified as a significnant risk factor for both bleeding and recurrent ischaemic risk. In addition, bleeding events are associated with higher rates of fatality and disability in the older population.

Finally, I have shown that the time trends in stroke recurrence differ depending on the presenting event i.e TIA or stroke. Stroke recurrence risk after minor stroke is delayed compared with TIA, and remains high during the late phase despite current best medical treatment. Blood pressure control and atrial fibrillation are risk factors for late stroke recurrence identifying the unmet need for better detection and treatment potentials to reduce late recurrent stroke.

Declaration

I certify that this thesis entitled “Complications and failures of secondary prevention of stroke” was performed whilst I was a full time postgraduate student at the University of Oxford.

I declare that I have personally been involved in recruiting many of the patients enrolled in the Oxford Vascular Study, which was used in this thesis. I personally entered or cleaned all of the data used in this thesis. The research contained herein is my own work. No portion of this work has been submitted in support of an application for any other degree.

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Introduction

My work has focused on two interrelated issues in the secondary prevention of stroke -failure of prevention and the risk of major bleeding on preventive treatment. However, as the efficacy and risks of secondary prevention are likely to differ to some extent between the acute phase and the long term phase, I have considered these two phases separately. For example, in the acute phase the benefits of secondary prevention in reducing the very high risk of early recurrent ischaemic events will probably outweigh the short-term risk of bleeding. In the longer term, however, different risk factors play a role in late stroke recurrence such as new onset atrial fibrillation, for example, and the cumulative risk of bleeding events will be much greater than during the acute phase.

1.1 The burden of ischaemic stroke

Arterial disease is the most prevalent chronic disease in the developed world,[1,2] and is rapidly increasing in importance in the developing world.[3,4] However,although arterial disease can cause stable or slowly progressive clinical syndromes, such as stable angina and intermittent claudication, the main clinical burden is acute,and usually ischaemic vascular events. Acute coronary syndromes (ACS) and stroke are the first and third leading causes of death in the developed world respectively and the two most common causes of death worldwide.[1,2] However, in addition to death, acute vascular events cause significant long term sequelae. For example, only about a third of strokes are fatal within a year, yet over half of the survivors are left with some disability and a third are functionally dependent after one year.[5] Stroke is the leading cause of neurological disability in the developed world and is a common cause of dementia, epilepsy, depression, falls and fractures.[6] Without more effective prevention, the burden of stroke will increase because of ageing populations in developed and developing countries.[7,8] There is evidence that primary prevention strategies are reducing the age-adjusted incidence of

first stroke, but improvements in secondary prevention after transient ischaemic attack and stroke are needed.[9, 10]

Acute Phase in the Management of TIA and Ischaemic Stroke

1.2 Early stroke risk following transient ischaemic attack

The importance of transient ischaemic attack (TIA lies mainly in the early risk of stroke and the long term risk of other vascular events. It is recognised that major stroke is often preceded by TIA.[11] A systematic review and meta-analysis of studies on the early risk of stroke following TIA showed the pooled risks of stroke were 3.1% [95% confidence interval (CI) 2.0-4.1] at 2 days and 5.2%(95% CI 3.9-6.5) at 7 days.[12] Recurrence of stroke continues to be a major risk for stroke survivors, despite advances in stroke prevention strategies and treatments.[10] An important part of the management of patients with a recent TIA is to reduce the very high risk of recurrent stroke in the first 3 months and the continuing long term risk of recurrent stroke, myocardial infarction and death due to vascular causes.

1.3 Identification of high risk TIA and stroke

Effective secondary prevention depends on identifying those at high risk of stroke recurrence and targeting treatment appropriately. There is evidence that the clinical features of a transient ischemic attack provide substantial prognostic information. Johnston et al [13] identified five risk factors independently associated with a high risk of recurrent stroke at three months: age over 60 years (OR 1.8; 95%CI 1.4-2.9), symptom duration greater than ten minutes OR 2.3(95% CI 1.3-4.2), motor weakness OR 1.9(95% CI 1.4-2.6), speech impairment OR 1.5 (95% CI 1.1-2.1), and diabetes mellitus OR 2.1(95% CI 1.1-2.7). A simple index with 1 point for each risk factor was useful in estimating risk at 3 months, which varied from 0% in patients with no risk factors to 34% in those with five risk factors.[13] Predictors of stroke in 7 days in the Oxford Vascular study

identified similar risk factors defined by a six point score ABCD (age >60 year=1, blood pressure systolic ≥140mmHg and or diastolic ≥90mmHg=1, clinical factors unilateral weakness=2, speech without weakness=1,duration of symptoms ≥60 minutes=2, 10-59 minutes=1,≤10=0) score. The corresponding 7 day risk of stroke was 0.4 %(95% CI 0.1.1) in patients with a score <5, 12.1 %(95% CI 4.2-20.0) with a score of 5 and 31.4 %(95% CI 16.0-46.8) with a score of 6.[14]

1.4 Secondary Prevention

Several treatments are effective in preventing stroke in the long term after TIA and ischaemic stroke, including aspirin, other antiplatelet agents, blood pressure lowering drugs, statins, anticoagulation in atrial fibrillation and endarterectomy for 50% or greater symptomatic carotid stenosis.[15-23] Clinical practice guidelines are generally based on randomised trials which evaluate one or at most two therapeutic strategies per study; the potential effects of combining multiple strategies for secondary prevention are unknown. As most of these strategies appear to be additive and independent in lowering cardiovascular risk, combined multiple approaches for the secondary prevention of stroke and TIA could reduce the risk of recurrent stroke by 80%.[24] However, failure of secondary prevention to prevent recurrent vascular events is still a major clinical problem, as is the risk of bleeding associated with antiplatelet agents. My work has focused on these two interrelated issues, at different time points of treatment, acute phase (<90 days) and chronic phase (≥ 90 days) as the benefits and risks of treatment are likely to differ between both phases.

1.4.1 Antiplatelet therapy in the secondary prevention of Stroke and TIA

Platelets play a pivotal role in the development of cardiovascular and cerebrovascular events and early use of antiplatelet drugs are widely used in secondary stroke prevention and acute coronary syndromes.[26] The Antiplatelet and Antithrombotic Trialists' collaborations reported

random assignment to any antiplatelet therapy compared with control was associated with an 11% reduction in odds of stroke, myocardial infarction, or death attributable to vascular causes among patients with acute ischaemic stroke and a 22% reduction for long term secondary prevention in patients with prior ischaemic stroke or TIA.[15]

Aspirin was the first antiplatelet agent used for treatment and prevention of acute ischaemic events and since then newer antiplatelet agents or combinations with aspirin have been used in acute coronary syndrome and TIA and stroke. Aspirin exerts its effect by inhibiting the cycloxygenase enzyme a key pathway of platelet aggregation leaving the adenosine diphosphate P2Y12 receptor unaffected.[26,27] Clopidogrel, a thienopyridine inhibits platelet aggregation by inhibiting this receptor. [26] In addition to its antiplatelet effect Clopidogrel may also has anti-inflammatory properties.[28]

The addition of clopidogrel to aspirin is associated with a marked reduction in platelet reactivity and has become the mainstay antiplatelet treatment strategy in early secondary prevention after acute coronary syndromes. It has been shown to significantly reduce the incidence of ischaemic cardiovascular events in patients treated either medically or with percutaneous coronary intervention.[29-33] For the primary endpoint (a composite of cardiovascular death, MI, or stroke) long term clopidogrel therapy plus aspirin in the CURE(The Clopidogrel in Unstable Angina to Prevent Recurent Events) trial was associated with a RRR 20% compared with aspirin alone (9.3% vs. 11.4%; p=0.00009).In addition, the benefit of clopidogrel was consistent for each component of the primary endpoint.[32] Further evidence of the benefit of dual antiplatelet therapy in the coronary vasculature was provided by the CREDO(Clopidogrel for the Reduction of Events During Observation) trial, which was designed to evaluate the efficacy of continuing clopidogrel, on top of standard therapy including aspirin for year following percutaneous coronary intervention. At 12 months, treatment with clopidogrel was associated with an RRR of 27% for the composite of death, MI, or stroke (p=0.02). [33] As in CURE, there was a consistent benefit of clopidogrel for each component of the composite endpoint.[32, 33]

The majority of strokes are non cardio embolic ischaemic strokes, and treatment with antiplatelet agents is the recommended first line therapy for secondary stroke prevention in these patients.[34] The most widely used effective antiplatelet regimens include aspirin, clopidogrel, and the combination of aspirin and dipyridamole. Aspirin reduces the risk of recurrent stroke and other major vascular events by at least 13 %(95% CI 6-19%) compared with control. Established alternatives to aspirin include clopidogrel and the combination of aspirin and extended release dipyridamole.[16-18, 35-40]

Clopidogrel is marginally more effective than aspirin. In the CAPRIE(A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events) trial it reduced the long term risk of stroke and other major vascular events by 8.7%(95% CI 0.3-16.5%) compared with aspirin alone in 19,185 patients at high vascular risk and by 7.3%(-5.7% to 18.7%) among a subgroup of 6431 patients with ischaemic stroke.[16,37] The combination of aspirin and ER(extended release) dipyridamole is also significantly more effective than aspirin alone in reducing the risk of stroke and other major vascular events (HR 0.82 ,95% CI 0.72-0.92) in patients with previous TIA or ischaemic stroke.[17] However a direct comparison of 75mg clopidogrel daily with the combination of 25mg aspirin and 200mg ER dipyridamole twice daily in 20,332 patients with acute ischaemic stroke in the PRoFess(Prevention Regimen For Effectively Avoiding Second Strokes) trial showed no significant difference between either regimen in the prevention of recurrent stroke (9.0% on aspirin plus ER diyridamole vs. 8.8% on clopidogrel.[39]
The benefits of combination aspirin and clopidogrel in the acute management of stroke and TIA are less clear.The MATCH (Management of ATherothrombosis with Clopidogrel in High risk patients with recent TIA or ischaemic stroke) study compared the effectiveness of monotherapy with an antiplatelet agent (clopidogrel) with that of the same agent in combination with aspirin. On the basis of previous trials investigators sought to determine whether the addition of aspirin to clopidogrel reduced the risk of vascular events after stroke and TIA.The mean time from qualifying event to randomisation in the MATCH trial was 26.7 days thus missing the potential

benefit of treatment in the acute phase. [40] The trial found that long term use (18months) of aspirin plus clopidogrel was no more effective than clopidogrel alone (RR 0.94(95% CI 0.84-1.05).

The benefits of long term combination dual antiplatelet medication were tested in another randomised controlled trial. Patients were randomised to receive aspirin (75-162mg) plus clopidogrel 75mg or placebo plus low dose aspirin with a median follow up of 28 months. All patients had either multiple atherothrombotic risk factors or a history of cerebrovascular, coronary or symptomatic peripheral arterial disease. There was no statistically significant difference between treatment groups in the rates of occurrence of primary efficacy endpoints recurrent stroke, MI or vascular death, RR 0.93(95% CI 0.83-1.05).[38]

For stroke and TIA patients in atrial fibrillation, warfarin is an effective secondary prevention strategy and reduces the risk of recurrent stroke in patients with TIA or minor ischaemic stroke by about 70%(hazard ratio 0.34, 95% CI 0.29-0.57).[41] Aspirin is less effective, resulting in a 20-30% risk reduction. In patients without atrial fibrillation presenting with a TIA or minor ischaemic stroke, warfarin is not better than aspirin as a secondary prevention agent.[42]

1.4.2 Role of statins in secondary stroke prevention:

Statins have also been shown to prevent stroke. The Heart Protection Study(HPS) showed that among 3289 people with a history of symptomatic ischaemic cerebrovascular disease random assignment to simvastatin 40mg daily for 4.8 years compared with placebo was associated with a significant reduction in major vascular events, RR 0.80(95% CI 0.71-0.92).[43] The SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels) study was the first to show the impact of statin treatment on secondary stroke prevention. SPARCL reported a 16% RRR (95% CI 1-29) in the risk of overall stroke with atorvastatin compared with placebo in patients with recent stroke or TIA, although atorvastatin increased the risk of haemorrhagic stroke.[20] A

systematic review based on four trials including the HPS and SPARCL demonstrated that in patients with a history of stroke or TIA, statins reduced the risk of ischaemic stroke by 20%(95% CI 8-30), although this beneficial effect was partly lost by an increase in risk of haemorrhagic stroke of 73%(95% CI 19-150)[44]

1.4.3 Blood pressure lowering in secondary stroke prevention:

While prevention of stroke must include adequate blood pressure (BP) control, the effects of control in the early secondary prevention of stroke are less clear. Meta-analyses indicate that modest BP reductions can decrease the risk of recurrent stroke by one third in primary prevention. [46] Lowering BP during the acute stroke remains controversial, however as too great a reduction in BP can interfere with cerebral perfusion and further exacerbate ischaemia. Earlier cohort studies show a J-shaped curve of BP and risk of stroke recurrence.[47] However, studies such as HOPE and PROGRESS and have failed to demonstrate this potential hazard at a lower BP.[19,48,49] Recent systematic reviews and meta-analyses have shown that blood pressure lowering agents in patients who have suffered a TIA or stroke significantly reduced the occurrence of subsequent stroke and cardiovascular events. [50-52]

1.4.4 Symptomatic Carotid Stenosis

Up to 15% of cerebral infarctions are estimated to be associated with embolic debris and thrombi originating from atherosclerotic plaques at the carotid bifurcation. [53] The risk of stroke in patients with carotid atherosclerosis is closely associated with the severity of luminal stenosis. [54-56] The risk of stroke in symptomatic patients (i.e., those who have had previous TIA or strokes) is 10% in the first year for those with severe lesions with the risk rising to 30-35% over the next 5 years.[57] Two pivotal trials (NASCET [the North American Symptomatic Carotid Endarterectomy Trial], and the ECST [the European Carotid Surgery Trial], have clearly shown the benefits of carotid endaterectomy compared with medical treatment in recently symptomatic patients with severe carotid stenosis.[58,59] Pooled analysis of these trials showed significant benefits of surgery

in the group with severe stenosis (70-99% stenosis in NASCET; absolute risk reduction of 16%; p<0.0001) after 5 years of follow up.[22] The risk of subsequent stroke in patients with carotid stenosis is highest in the first few weeks after onset of transient ischaemic attacks or minor strokes and this risk declines rapidly therefore a short window for effective stroke prevention exists in patients with significant stenosis.[60, 61]

1.5 Secondary prevention in the acute phase of TIA and minor ischaemic stroke

It is established that there is a high risk of ischaemic stroke following TIA in the acute phase (≤7 days) and in identifiable high risk groups,[3,7] which argues for particularly intensive treatment in acute phase. Evidence from randomised trials of acute coronary syndromes suggests the relative benefit of antiplatelet treatment is likely to be greater in the acute phase.[28-31]

Many stroke prevention trials have not separated early secondary prevention from long term secondary prevention. However, there is some evidence that the combination of aspirin plus clopidogrel may be more effective than aspirin alone in the acute phase. Firstly, in the CARESS trial, patients with recently symptomatic ≥50% carotid stenosis, the aetiological subgroup at highest risk of early recurrent stroke, combination of aspirin and clopidogrel (300mg loading then 75mg once a day) substantially reduced micro-embolic signals detected on transcranial Doppler imaging (a surrogate marker for cerebrovascular ischaemic events) in the ipsilateral middle cerebral artery and tended to reduce the risk of recurrent stroke.[62,63]

A similar reduction in microembolic signal rates was also reported in a randomised trial of aspirin alone versus aspirin plus clopidogrel in patients following carotid endarterectomy and in patients with symptomatic intracranial stenosis.[64,65] Secondly, in the MATCH trial of aspirin plus clopidogrel versus clopidogrel alone, combination therapy tended to be more effective than clopidogrel alone in the subgroup of patients randomized within 14 days of a TIA or stroke. However, the mean time from qualifying event to randomisation in the MATCH trial was 27 days thus missing the potential benefit of treatment in the acute phase.[40] Thirdly, the FASTER Trial (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence)

reported a trend towards a reduced early risk of stroke with aspirin plus clopidogrel (300mg load followed by 75 mg/day) versus aspirin alone in patients who have had a TIA or minor ischaemic stroke within the previous 24 hours. [66]

1.6 Bleeding and antiplatelet agents

A balance exists between the antithrombotic effect of antiplatelet agents and the risk of bleeding. As antiplatelet drugs exert their effect on haemostasis their beneficial effects cannot be dissociated from an increased risk of bleeding. Aspirin increases the risk of major bleeding by about 70% (risk ratio 1.71(95% CI 1.41-2.08).[67] The increased risk of bleeding is mainly due to gastrointestinal bleeding RR 2.07(95% CI 1.61-2.66); absolute annual increase 0.12 %(0.07-0.19%) and intracranial bleeding (RR 1.65 (95% CI 1.06-5.99); absolute annual increase 0.03 %(95% CI 0.01-0.08%).[67] Clopidogrel causes less gastrointestinal bleeding when compared to 325mg aspirin daily (RR 0.69(95%CI 0.48-1.00) in the CAPRIE trial. [16]

European stroke prevention study (ESPS-2) evaluated aspirin plus extended release dipyridamole versus aspirin alone after TIA or stroke and reported similar bleeding rates in patients receiving aspirin plus extended release dipyridamole compared with aspirin monotherapy.[18] However a direct comparison of 75mg clopidogrel daily with the combination of 25mg aspirin and 200mg ER dipyridamole twice daily in the PRoFESS trial showed the rate of haemorrhagic events whether minor or major, were 5.3% in the aspirin and dipyridamole group versus 4.9% with clopidogrel.[39]

The long term use of aspirin and clopidogrel in the MATCH trial increased the risk of life threatening bleeding (2.6% on aspirin and clopidogrel versus 1.3% on aspirin; absolute risk increase 1.3 %(95% CI 0.6-1.9%).[40] Rates of bleeding were similarly high in the CHARISMA (Clopidogrel for High Atherothrombotic Risk and Ischaemic Stabilisation, Management and Avoidance) trial that compared aspirin and clopidogrel versus aspirin and placebo, (rate of

moderate bleeding was 2.1% in the clopidogrel group and 1.3% in the placebo group.(RR, 1.62; 95% CI, 1.27-2.08; p<0.001).[38]

The long term dual antiplatelet trials in ischaemic stroke and TIA highlight the lack of overall benefit, due to a significant increased bleeding risk. The short term bleeding event rates in CURE showed an acceptable 1% increase in the incidence of major bleeding events in the clopidogrel group (3.7% vs. 2.7%; p<0.001).There was no significant increase in the incidence of life threatening major bleeding in the clopidogrel group. [32]

Although, both the efficacy and complications of therapy are dependent on a number of factors it is likely that the timing of treatment plays a significant role. In the CURE study patients were randomised within 24 hours of symptoms. MATCH recruited most patients several weeks after their presenting event thereby missing the acute phase when the risk of recurrent events is highest and the potential for prevention is greatest.

However, although it has been suggested that the risk of bleeding on short term treatment with aspirin plus clopidogrel early after TIA or minor ischaemic stroke might be smaller, [68] there are very few reliable data on the risk of bleeding in this situation. In the CARESS trial, short term administration of dual antiplatelets over 7 days resulted in no life threatening or major bleeding complications, although there was a small excess of minor bleeds (2/51 vs. 1/56).[63] However, in the FASTER pilot trial, there was a significant increase in the number of symptomatic bleeds on dual therapy, with a 90-day absolute risk of 3.0% (6/198).[66] Moreover, it cannot be assumed that the risks reported in the RCTs are reliable estimates of the risk in routine clinical practice, particularly in elderly patients. Furthermore, I cannot assume that any excess risk of combination therapy will be independent of prior antiplatelet treatment. It is possible, for example, that the risks of aspirin plus clopidogrel are greater in patients with no prior exposure to antiplatelet treatment than in patients who have tolerated aspirin for some time, therefore, I studied the risk

of bleeding among aspirin naïve patients treated with a combination of aspirin and clopidogrel in the acute phase of TIA and minor stroke.

1.7 Rebound thrombotic events

Another potential hazard of secondary prevention is the reported rebound effect that can occur following discontinuation of treatment. It is not uncommon to experience rebound activity following long term antagonism of physiological pathways, as shown by rebound elevation in blood pressure following withdrawal of long term beta blocker therapy, or rebound anginal symptoms following nitrate discontinuation.[69, 70]

The rebound effect following discontinuation of antiplatelets merits attention as the duration of treatment with antiplatelet agents varies among vascular diseases. The addition of clopidogrel to aspirin is associated with a marked reduction in platelet reactivity and a reduced risk of recurrent vascular events after acute coronary syndromes. [29-32] In patients undergoing stent implantation, addition of clopidogrel daily to aspirin is advocated for at least one month with bare metal stents, 3-6 months for drug eluting stents (DES), and ideally for up to one year.[71]

Premature discontinuation of clopidogrel in patients on aspirin and clopidogrel after acute coronary syndromes has been shown to be associated with a very substantial rebound increase in risk of stent thrombosis, stroke and death in stented patients [72-75] and probably also in patients who were not stented.[75] The proposed mechanism for these clustering of events is thought to be a transient hyperthrombotic state after stopping antiplatelet therapy.[72]

Clopidogrel causes a rebound hyper thrombotic effect possibly due to increased platelet activity and increased levels of inflammatory biomarkers.[76] Both are recognized as an important contributor to the development of atherothrombotic disease promoting plaque erosion and activating the coagulation cascade.

Interruption of clopidogrel therapy often precedes acute stent thrombosis and the increased morbidity and mortality following clopidogrel discontinuation is not restricted to patients having undergone angioplasty. Ho et al report in both medically and PCI treated patients discontinuation of clopidogrel was associated with a higher risk of adverse events in the first 90 days following clopidogrel cessation. [75] Limited published data suggest that the risk of recurrent ischaemic stroke is also increased after discontinuation of antiplatelet therapy in general after TIA or stroke.[77-79] For example, Sibon et al reported a 4.49% excess risk of ischaemic stroke associated with disruption of antiplatelet medications in the previous month.[77] Aspirin withdrawal may also increase thrombus stability by improving the efficacy of the fibrin cross link network. [80] This concordance between rebound platelet activation markers and occurrence of ischaemic events suggests a potential causal link. There are no published data on any possible rebound effect following discontinuation of a short course of clopidogrel in patients with a recent TIA or minor ischaemic stroke as follow up was not continued in the trials after discontinuation of trial treatment. I therefore studied the risk of rebound ischaemic events following discontinuation of a short course of clopidogrel among patients treated with aspirin and clopidogrel.

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1.8 Long term bleeding risk and antiplatelet medications:

In patients who are at high risk because they already have occlusive vascular disease, long term antiplatelet therapy reduces the risk of serious vascular events (non fatal MI, non fatal stroke or vascular death by about a quarter.[15] Efficacy outcomes of antiplatelet drugs in randomised controlled trials (RCTs) are well defined and incorporate a combination of cardiovascular death, acute myocardial infarction (AMI), stroke and recurrent ischaemic events. However, safety

outcomes such as bleeding are not as uniform and largely depend on the type of classification system used.[81, 82]

The incidence of major bleeding across antiplatelet studies ranges from 0.7-8.2% and is largely determined by their design, patient characteristics, treatment regimens, intervention rates, and the criteria used to define major bleeding.[83] Randomised controlled trials (RCTs) and systematic reviews are the most reliable methods of determining the effects of treatment.[84] If a beneficial effect of an antiplatelet treatment is shown from RCTs, it is likely that its relative effects are generalisable to other populations, however, the risks of treatment are less likely be so. RCTs probably underestimate the true extent of bleeding in clinical practice as patients perceived to be at high risk of complications including those of advanced age, for example are often excluded from clinical trials but constitute a significant proportion of patients treated for ACS, ischaemic stroke and TIA, thereby potentially limiting the generalisability of trial results.[81,82,84]

In addition, patients enrolled in RCTs are more likely to be treated according to defined protocols than in routine practice and so data derived from registry studies are more likely to reflect the frequency of major bleeding seen in the community. [84, 85] The relationship between bleeding and adverse clinical outcomes is well established.[86,87] Bleeding is an independent predictor of poor short and long term outcomes in acute coronary syndrome and ischaemic stroke. The majority of the risk of bleeding in ACS trials occurs in the acute phase after the initiation of therapy or intervention. [88,89] Given the strict eligibility criteria for acute coronary trials, those considered to be at high risk of bleeding would normally be excluded. Longer term trials of bleeding and antiplatelet therapy are limited as follow up rarely extends beyond 5 years. As trial patients often differ substantially from unselected patients treated in routine clinical practice, it would be useful to determine the real life incidence of bleeding in patients treated with antiplatelet agents following acute myocardial infarction, stroke or transient ischemic attack. I therefore, studied the long term risk of bleeding in a population based study of patients with acute coronary syndrome, TIA or stroke treated with antiplatelet medications.

1.9 Predictor of bleeding and antiplatelet medications:

Bleeding is an independent predictor of poor short and long term outcomes in ACS and ischaemic stroke. Major in-hospital bleeding has been strongly associated with increased rates of early and late mortality, MI, repeat revascularisation procedures, recurrent stroke and severe dependency on discharge. [86,87,90-95] Previous studies have associated certain clinical and procedural characteristics with bleeding complications following an acute ischaemic event and incorporated these predictors into a bleeding risk score. However, these scores were derived on ACS populations and may not perform well in patients with TIA or stroke. In addition, they incorporated acute treatment variables and acute interventions as part of their bleeding risk score, restricting use in long term prediction of bleeding. No bleed score exists, that incorporates baseline clinical characteristics in either ACS or stroke and TIA subgroups treated with antiplatelet agents. Identification of patients at higher risk of bleeding would thereby, prompt clinicians to make judicious treatment selection, carefully dose antithrombotic medications and select invasive strategies to minimise bleeding complications. [96, 97] I therefore, studied the risk factors for bleeding events in a population based study of patients with ACS, TIA or stroke treated with antiplatelet agents.

2.0 Long term risk of ischaemic stroke

Studies comparing stroke rates after TIA with expected stroke rates based on age and sex matched population controls have indicated the relative risk of stroke after TIA is highest during the early period after TIA and then declines over time, but remains elevated for several years [98,99] The early risk of major ischaemic stroke after a TIA or minor stroke is well defined,[7,12] but a considerable variation exists in the long term recurrence rates, with an absolute risk of recurrence within 5 years varying from 19% to 42% [100-103] This variation may be caused by

different definitions of stroke recurrence, differences in acute and preventative management or different methodology (hospital based, population based or clinical trial populations). Most randomised trials of interventions have follow up of only a few years. The effect of secondary prevention treatment in reducing long term stroke recurrence is largely unknown and it is uncertain to what extent effective treatment in the acute phase simply delays rather than prevents long term recurrent stroke. In addition, the estimates of treatment effects from trials may overestimate those in the long term prevention of stroke given that compliance in clinical practice is substantially lower than in closely monitored and motivated trial populations. [104,105] I therefore studied the long term risk of stroke in a population based study of patients with prior TIA or stroke on secondary prevention.

2.1 Predictors of late recurrent stroke

Patients with TIA and minor stroke are a heterogeneous group in terms of symptoms, risk factors, underlying pathology and prognosis. Risk factor control is an essential strategy for long term secondary stroke prevention and factors that increase the risk of a first ever stroke may not necessarily be as important in predicting a recurrent stroke. It is also not clear whether the same risk factors are associated with early and late recurrence and whether late recurrence occurs because of ineffective implementation or suboptimal management of original risk factors.[102,103,105] The relationship between risk factors such as hypertension and atrial fibrillation have been examined in several studies. At 1 year post stroke, past history of MI, stroke subtype, hypertension and atrial fibrillation were found to be predictive of early stroke recurrence.[106-108] At 5 years, hypertension and atrial fibrillation were found to be predictors. [106-109] At 10 years, older age, hypertension, diabetes and atrial fibrillation were found to be predictive of long term stroke recurrence.[106,110] However, studies regarding hypertension in stroke recurrence have been conflicting. The differences may relate to methodological problems such as retrospective BP documentation, lack of data on how BP was recorded and the frequency of BP readings. Observational studies tend to record history of blood pressure and do not take into account how

effectively BP is controlled during the follow period and few have assessed the impact of long term uncontrolled hypertension on stroke recurrence.[108] The issue of the quality of secondary prevention in long term stroke recurrence merits attention as previous studies report a large gap between recommended secondary prevention measures and their implementation [111-113]

It is unlikely given the multifactorial nature of stroke that long term control of a single risk factor will prevent long term stroke recurrence. It is plausible that in spite of improved adherence to preventative therapies such as antihypertensive treatment, lipid lowering therapy, aspirin,
the long term risk of stroke remains unchanged. More reliable methods of detection of atrial fibrillation, optimal control of blood pressure and further research into other undetermined risk factors might aid in the reduction of the risk of stroke. I therefore, studied whether different risk factors existed between early (<90 days) and late (≥ 90 days) recurrent ischaemic stroke events and whether detection and treatment of these risk factors could potentially reduce recurrent stroke event rates.

2.2 Summary

The early risk of stroke following TIA is high and a window of opportunity for early use of secondary prevention exists. Several treatments are effective in preventing stroke in the long term after a TIA or minor ischaemic stroke, including aspirin, other antiplatelet agents, BP lowering drugs, statins, anticoagulation for atrial fibrillation and carotid endarterectomy for 50% or greater symptomatic carotid stenosis. However, the effect of treatment in the reduction of recurrent stroke in the acute phase following TIA and minor stroke is unknown.

The major drawback of antiplatelet treatment in the acute phase of treatment is the risk of bleeding. Bleeding event rates reported in randomised controlled trials of antiplatelets vary due to the strict inclusion criteria upon entry to clinical trials. Most trials exclude elderly patients and those with prexisiting comorbidities. Data on bleeding event rates in acute phase of TIA and

minor stroke treated with antiplatelets have been limited. The extent to which prior antiplatelet use affects bleeding event rates among those treated with dual antiplatelet agents is of particular interest. Evidence is lacking in randomised trials whether bleeding event rates are higher in antiplatelet naïve patients treated with dual antiplatelet therapy. Furthermore, the effect of discontinuation of treatment in the acute phase is reported to increase the risk of rebound thrombotic events in those treated with dual antiplatelet therapy.There are no published data on any possible rebound effect following discontinuation of a short course of clopidogrel in patients with a recent TIA or minor ischaemic stroke as follow up was not continued after discontinuation of trial treatment.

A further limitation of secondary prevention after the acute phase is the lack of data on the effectiveness to prevent long term recurrent stroke. Considerable variation in the reported rates of long term recurrence in studies up to 5 years post stroke. It is also not clear whether the same risk factors are associated with early and late recurrence and whether late recurrence occurs because of ineffective implementation or suboptimal management of original risk factors.

Long term bleeding event rates are rarely reported beyond two years of follow up in randomised controlled trials of antiplatelet drugs. Registries and population cohorts have reported higher rates of bleeding when compared to randomised trials. Predictors of bleeding in acute coronary syndromes have been incorporated into bleed scores, but these assess the risk of in-hospital bleeding. No model has assessed risk factors for bleeding beyond the acute phase and existing scores include treatment variables in ACS.

2.3 Outline of thesis

The main source of data for my thesis has been the Oxford Vascular Study, a prospective population based study of all vascular events including TIA and stroke in a population of over 91,000 individuals registered with 63 general practitioners. Multiple overlapping methods of case-finding have been used to achieve nearly complete ascertainment of cases with stroke and these are detailed in the chapter 2.

The aims of this thesis are to study the complications and failures of secondary prevention in the acute and chronic phase of TIA and minor stroke.

Chapter 3. The effect of early use of existing secondary prevention and reduction in early risk of ischaemic stroke.

Chapter 4. Whether a higher risk of bleeding occurs in aspirin naïve patients treated acutely with dual antiplatelet treatment- aspirin and clopidogrel.

Chapter 5. Rebound thrombotic events following discontinuation of a short course clopidogrel in TIA and minor stroke.

Chapter 6. Determine risk and predictors of bleeding events on antilpatelet treatment

Chapter 7. The effect of age on bleeding rates in those treated with antiplatelet agents

Chapter 8 Determine the long term prognosis after TIA and stroke

Chapter 9. Incidence and clinical predictors of early versus late recurrent stroke (≥90 days)

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CHAPTER 2

Study Methods- case ascertainment

2.1	**The Oxford vascular Study**	**51**
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2.1 The Oxford Vascular Study (OXVASC)

The Oxford Vascular Study (OXVASC) is a study of all acute vascular events in a mainly urban population in Oxfordshire, United Kingdom (UK). Events included are: transient ischaemic attack (TIA), stroke, acute coronary syndrome (ACS) including unstable angina (UA), myocardial infarction (MI) and cardiac death, and acute peripheral vascular (PVE) events. The main aims of the study are to determine the incidence and case fatality of acute stroke, acute coronary syndromes and acute peripheral vascular disease events in the same population at the same time. This thesis uses data obtained during the first seven years of the study, unless otherwise stated.

2.1.1. Study population

The OXVASC study population comprises of all individuals registered with 63 general practitioners in nine general practices in Oxfordshire, UK (figure 1). In the UK, the vast majority of individuals register with a general practice, which provides their primary health care and holds a lifelong record of all medical consultations, and details of all medications, blood pressure, and investigations. In Oxfordshire, it is estimated that 97.1% of the true residential population is registered with a practice, the majority of non-registered individuals being young adults. All participating practices hold accurate age-sex patient registers and had collaborated on a previous population-based study, for which they were originally selected to be representative of the urban/rural mix and deprivation range of the Oxfordshire population as a whole.[1] The OXVASC population was 94% white, 3.1% Asian, 1.5% Chinese and 1.4% Afro-Caribbean.[2] Based on the Index of Multiple Deprivation (IMD),[3] the population included a broad range of deprivation.



OXVASC practice

1. Exeter, Kidlington, OX5 1AP
2. Kidlington & Yarnton, Kidlington, OX5 1AP
3. 19, Beaumont Street, Oxford, OX1 2NA
4. Bartlemas surgery, Oxford, OX4 1XD
5. Stert Street, Abingdon, OX14 3LB
6. Malthouse, Abingdon, OX14 3JY
7. Marcham Road, Abingdon, OX14 1BT
8. Berinsfield, OX10 7NE
9. Church Street, Wantage, OX12 9BN d

Figure 1.0 General practices in OXVASC, OXFORDSHIRE

2.1.2 Case Ascertainment

After a 3-month pilot, the study began on 01/04/2002 and is ongoing. Ascertainment includes combined prospective daily searches for acute events ("hot pursuit") and searches of administrative and diagnostic coding data ("cold pursuit"). Hot pursuit was based on: 1) Daily

searches of Emergency Department symptom / diagnosis registers; 2) Daily listing of all admissions from the study population; 3) Daily visits to the Medical Assessment Unit, Coronary Care Unit, Cardiology Ward, Acute Stroke Unit, and Vascular Surgery Ward, and to Neurology and Cardiothroracic Surgery Wards when indicated; 4) Daily identification via Bereavement Officers of patients dead on arrival at hospital or who died soon after; 5) Daily listing of all patients from the study population in whom a troponin level had been requested; 6) Review of outpatient clinics for patients with TIA and stroke, chest pain not requiring immediate admission to hospital, and peripheral vascular disease; 7) Daily assessment of all patients undergoing diagnostic coronary, carotid and peripheral angiography, angioplasty, stenting or vascular surgical procedures in any territory to identify prior acute events to estimate the completeness of ascertainment of non-fatal events by our other methods.

The methods of cold pursuit were: 1) Fortnightly visits to the study practices and monthly searches of practice diagnostic codes; 2) Monthly practice-specific list of all patients admitted to all acute and community NHS hospitals with ICD 10 diagnostic and procedure codes (Appendix 1); 3) Monthly listings of all referrals for brain, cerebrovascular, or carotid imaging; 4) Monthly visits to the Coroner's Office; 5) Review of all death certificates in the study general practices; 5) Practice-specific listings of all ICD-10 death codes registered centrally. Patients found on GP practice searches who had an event whilst temporarily out of Oxfordshire are included, but visitors who were not registered with one of the study practices were excluded.

2.1.3 Clinical assessment and investigation

A study clinician assessed patients as soon as possible after the event in hospital or at home. Data is collected using event-specific forms, for TIA and stroke, ACS (Appendix 2 and 3) or PVE. This includes timing, history of presenting condition, diagnostic information, risk factors and subsequent management. Those cases with no typical history or ECG changes but a raised troponin I have core risk factor data recorded.

For all deaths that are not recorded as being of clearly non-vascular aetiology that occurred outside hospital and/or prior to assessment, we obtained an eyewitness account of the clinical event and reviewed any relevant medical records and autopsy report.

All surviving patients are followed-up by a research nurse at 1, 6, 12 and 60 months after the event and all recurrent vascular events were recorded (Appendix 4), together with the relevant clinical details and investigations. Recurrent events are also recorded as part the ongoing OXVASC ascertainment methods.

2.2 Definitions and diagnosis

Standard definitions of TIA and stroke are used.[4,5] and acute coronary events are defined using published criteria[6] based on available history, ECG findings, cardiac biomarkers (mainly troponin I), autopsy or death certificate. Non-ST elevation (NSTEMI) and ST-elevation myocardial infarction (STEMI) are defined using standard criteria.[7] Troponin-I is measured with the Bayer Centaur assay using the manufacturer's normal range. ECGs are assessed by objective measurements based on the Minnesota criteria,[8] but formal blinded Minnesota coding is not done. Definite/probable unstable angina was defined as new cardiac symptoms or a changing symptom pattern with positive ECG findings, a positive stress test, or a small rise elevation in troponin that did not meet the criteria for an MI. [9] Possible unstable angina was defined as cases with a suggestive clinical presentation but without any of these additional features are classified as possible unstable angina in the absence of any alternative diagnosis made by the managing clinician. Sudden cardiac deaths are coded according to recent recommendations for epidemiological studies,[6] and required a definite history of preceding symptoms consistent with acute coronary ischaemia, or post-mortem evidence of either significant coronary atherosclerosis or acute thrombosis, or a documented myocardial infarction during the previous 28 days.[6] Sudden deaths were coded as probable cardiac deaths in the absence of the above

characteristics if the person had a past history of ischaemic heart disease. Other sudden out-of-hospital deaths were coded as unclassifiable.

Acute peripheral arterial events are defined as those affecting a limb or an organ other than the heart or the brain/eye. Aortic events included ruptured or acutely symptomatic aortic aneurysm or dissection. Acute thrombo-embolic events included all documented cases of limb or visceral ischaemia of clearly acute onset. Critical limb ischaemia included rest pain and/or ulceration of sufficient severity to warrant hospital admission that was thought to be secondary to large- or small-vessel disease.

In view of previous data on the inaccuracy of death certification of coronary heart disease and stroke,[5,6] all deaths in the OXVASC population that were recorded and assigned were coded as follows (in increasing order of validity):

i. *All certified deaths due to vascular disease*: All deaths with the underlying cause coded for the purposes of national statistics as being due to "ischaemic heart disease" (ICD I219,I251,I259), "cerebrovascular disease" (ICD I607, I609, I610,I619, I620,I634,I635, I639,I64X,I678,I679, I694, I698), or "peripheral vascular disease" (ICD I709, I710, I711, I713, I714, I718, I719 ,I728, I739).

ii. *All certified acute vascular deaths*: All deaths where the underlying cause of death was coded for the purposes of national statistics as being due to "acute ischaemic heart disease" (ICD I219, I251), "acute cerebrovascular disease" (ICD I607, I609, I610, I619, I620, I634, I635, I639, I64X), or "acute peripheral vascular disease" (ICD I710, I711, I713, I714, I718, I719, I728).

iii. *Probable or definite acute vascular deaths*: All deaths in (ii) excluding unclassifiable sudden deaths (as defined below) and other deaths that after evaluation of the clinical and/or post-mortem data were considered to have been incorrectly attributed (i.e. there was definite evidence of another cause), and with the addition of any deaths not in (ii) that were considered by the OXVASC researchers to have been due to an acute vascular event. This definition includes all probable or definite sudden cardiac deaths as defined in the methods section.

iv. Definite acute vascular deaths: All deaths in (iii) excluding sudden deaths for which the only supporting evidence was a previous history of symptomatic vascular disease in the relevant arterial territory (unless there was a documented acute myocardial infarction, acute stroke or acute peripheral vascular event within the previous 28 days).

Unclassifiable deaths, which were mainly out-of-hospital deaths, were deaths certified as having a vascular cause which had no witness description of the event or of preceding symptoms to suggest acute vascular disease in a specific territory, no post-mortem evidence of an acute vascular event or other cause of death, no post-mortem evidence of clinically significant coronary atherosclerosis, and no past history of symptomatic vascular disease in a relevant arterial territory.

2.2.1 Designation of events

All events are categorised as first-ever incident, or recurrent, based on clinical history. A first-ever stroke in a patient with a previous TIA is coded as incident, but a first-ever TIA in a patient with a previous stroke is coded as recurrent.[4] Similarly, a first-ever NSTEMI, STEMI or sudden cardiac death that occurred in a patient with a previous episode of unstable angina is coded as incident. However, a first-ever STEMI or a sudden cardiac death in a patient with a previous myocardial infarction is coded as a recurrent coronary event.

2.3 Ethical approval

All patients eligible for the study are given an information sheet (Appendix 5). If the patient is willing to decide about participation in the study immediately, then written consent is obtained (Appendix 6). If the patient requests a period of time to consider the decision then this is respected. Surrogate consent is obtained from next of kin if required (Appendix 7). The Oxford Vascular Study has received a favourable ethical opinion from the Oxfordshire Regional Ethics Committee A (Ref: 05/Q1604/70).

2.4 Summary

The Oxford Vascular Study (OXVASC) in a prospective population study of the incidence and outcome of all acute vascular events in a defined population in Oxfordshire, UK. The study uses multiple overlapping sources of case identification, to ensure near complete ascertainment. This method is considered to be the “gold standard” for incidence studies of both stroke and myocardial infarction.[10,11]

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CHAPTER 3

Reduction in risk of early recurrent stroke by urgent treatment of TIA and minor stroke.

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3.1 Abstract

Background: The risk of major stroke in the week after a TIA or minor stroke is up to 10%. An observational study of the impact of the phased introduction of rapid assessment and treatment for TIA and minor stroke was performed to assess whether early treatment reduced recurrent stroke and whether bleeding complications were increased.

Methods: In a population-based study of all TIA and stroke in 91,000 individuals (Oxford Vascular Study), a prospective before (phase-1: 01/04/02-30/09/04) versus after (phase-2: 01/10/04-31/3/07) study of the impact on recurrent stroke following changes to the management of TIA and stroke, more urgent assessment; and immediate treatment in clinic rather than subsequent initiation of treatment in primary care. Case-ascertainment, investigation and follow-up were otherwise identical in both periods. The primary outcome was 90-day risk of stroke and bleeding event rates classified by the CURE criteria after seeking medical attention.

Results: 620(337 TIA, 283 stroke) were referred for outpatient assessment, and 591(95.3%) of those were referred to the EXPRESS clinic. Baseline characteristics, delays in seeking medical attention, and referral rates were similar in the two periods, but median delay to assessment in the EXPRESS clinic fell from 3(IQR 2-5) days in phase-1 to 1(0-3) day in phase-2 ($p<0.0001$). Consequently, the 90-day risk of recurrent stroke among referrals to the EXPRESS clinic fell from 10.3% (32/310) to 2.1% (6/281) (p 0.0001). The 30 day risk of major bleeding in phase 1 0.32% (1/310) and 0.70 %(2/281) in phase 2 defined by the CURE criteria.

Conclusion: In a population-based study, including all patients presenting with TIA or minor stroke irrespective of age, early initiation of treatment prevented 80% of early recurrent strokes

without increasing the risk of major bleeding. Further follow-up is required to determine long-term outcome.

3.2 Introduction

The risk of major stroke in the week after a TIA or minor stroke is up to 10%.[1-3] These "warning" events provide a short window of opportunity for prevention,[4] Several treatments are effective in preventing stroke in the long-term after a TIA or minor ischaemic stroke, including aspirin,[5] other antiplatelet agents,[6-8] blood pressure lowering drugs,[9] statins,[10] anticoagulation for atrial fibrillation,[11] and endarterectomy for ≥50% symptomatic carotid stenosis.[12,13] Assuming that these effects are independent, use of all of these interventions in appropriate patients would be predicted to reduce the long-term group risk of recurrent stroke by 80-90%.[14] Moreover, evidence from trials of treatment in acute stroke and acute coronary syndromes suggests that the relative benefits of several of these intervention are, if anything, likely to be even greater in the acute phase.[15-20]

I aimed to determine the effect of more rapid treatment after TIA and minor stroke. Given the predicted benefits of early secondary prevention, and emerging evidence of substantial benefits of early endarterectomy for symptomatic carotid stenosis,[12] an observational study of the phased introduction of early assessment and treatment (Early use of EXisting PREventive Strategies for Stroke – EXPRESS Study), nested within a population-based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study - OXVASC) was performed.[21,22] I also aimed to determine whether bleeding complications were increased due to the early initiation of treatment between both phases.

3.3 Methods

The methods of OXVASC and details of the study population have been reported previously.[21,22] Briefly, the study population comprised all 91,000 individuals, irrespective of age, registered with 63 family physicians in nine general practices in Oxfordshire, UK. In the UK, almost all individuals register with a general practice, which provides their primary health care and holds a lifelong medical record. OXVASC was approved by our local research ethics committee and began on 01/04/02 after a 3-month pilot to ensure reliable case ascertainment. This report concerns all events identified in the study population in the first five years, with follow-up to 30/06/07.

3.3.1 Case Ascertainment

The EXPRESS study intervention was the reduction in delay to assessment and initiation of treatment via the study clinic on 1st October 2004.In phase-1 (01/04/02-31/09/04) of OXVASC, a daily TIA and stroke clinic to which collaborating family doctors referred the vast majority of patients with suspected TIA and minor stroke in the study population was arranged. Thus, although it was an improvement on the standard weekly TIA clinic, it did not ensure immediate treatment. In phase 2 a “no appointment necessary” clinic to which collaborating family doctors were asked to send all patients immediately after presentation, and at which treatment was initiated immediately if the diagnosis was confirmed.

The treatment protocol was aspirin in patients not already on antiplatelet therapy (300mg loading and 75mg daily), or clopidogrel if aspirin was contraindicated; simvastatin (40mg daily); blood pressure lowering unless systolic blood pressure <130mmHg on repeated measurement (increase existing medication if required, or start perindopril 4mg daily + indapamide 1.5mg

daily); and anticoagulation as required. In patients seen within 48 hours of their event or those seen within 7 days who were thought to be at particularly high early risk, [1] clopidogrel (300mg loading and 75mg daily to be stopped after 30 days) was recommended in addition to aspirin. Brain imaging was required prior to starting combination antiplatelet treatment after a minor stroke.

Bleeding events were identified by regular face-to-face follow-up, diagnostic coding in primary care, secondary care and blood transfusion data. In both study periods, patients were assessed by a study physician in a standardised manner.[21,22] Detailed data were collected on the times and methods of first contact with medical attention after the presenting event.[23] All cases were reviewed with the senior study neurologist (PMR) and classified as TIA, stroke, or other condition using standard definitions.[21,22]

3.3.2 Definitions and analysis

All patients in OXVASC were followed-up by a research nurse or clinical research fellow after 1,6,12 and 24 months and asked about any new neurological symptoms and any bleeding that had required medical attention. Current medication was recorded and two measurements of resting blood pressure (5 minutes apart) were made. If a recurrent vascular event was suspected at a follow-up visit, the patient was re-assessed and investigated by a study physician. Details of all potential recurrent strokes within 90-days of seeking medical attention were reviewed at the end of the EXPRESS study by an independent neurologist blinded to the phase of the study. The definition of recurrent stroke used in OXVASC required a sudden new symptomatic neurological deterioration on a background of stability or improvement following the presenting event. Gradual or stuttering progression after an initial event was not coded as a

recurrent stroke. Strokes occurring within 24 hours of an initial TIA/minor stroke were included - if the recurrence occurred prior to complete symptomatic resolution of the initial event the initial event was coded as a stroke. Bleeding events were classified by the CURE trial criteria.[18] Major bleeding was defined as substantially disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or more units of blood. Major bleeding was further subclassified as life threatening if it was fatal, if it lead to a decrease in haemoglobin of 5g/dl, if it caused significant hypotension requiring intravenous inotropes or surgical intervention, if it resulted in symptomatic intracranial haemorrhage, or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as bleeding not requiring transfusion.

The study denominator and stroke risk were defined from the point at which patients with TIA or stroke first sought medical attention (e.g. contact with their primary care practice, emergency department, or other services). I limited analysis to the first presentation in each phase of the study. However, since exclusion of patients from analysis in phase-2 if they had also presented in phase-1 could have caused bias (patients were not excluded from phase-1 if they had had a previous event prior to the study), patients who presented in both phases were included in the analysis of each. To avoid any possible bias due to "carry-over" effects of improved long-term treatment in phase-1 (compared to that prior to the study) on outcome of any subsequent events in phase-2, all analyses were also done for incident first-ever events only.

The primary outcome was the 90-day risk of recurrent stroke. Patients who were referred to the EXPRESS clinic but had a recurrent stroke necessitating hospital admission prior to clinic assessment were coded as EXPRESS clinic cases. To exclude any bias due to temporal changes in referral patterns and to determine the impact of the EXPRESS clinic on the whole population I also analysed stroke risk in all patients who sought medical attention with a TIA or stroke of any severity, both overall and stratified by place of treatment: acute hospital services

(i.e. patients who self-referred to the emergency department or emergency ambulance services or were referred directly to hospital after contacting their primary care practice); outpatient services (i.e. referred to EXPRESS or other clinic); or care by family physician without referral to hospital. Analyses were also stratified according to the type of presenting event (TIA or stroke).

3.4 Results

Of the 1278 patients in OXVASC who presented with a TIA or stroke (634 in phase-1 and 644 in phase-2) 607 were referred or presented direct to hospital, 620 were referred for outpatient assessment, and 51 were not referred to secondary care.95%(n=591) of all outpatient referrals were to the study clinic. Table 3.1

Among patients referred to the EXPRESS clinic, there were no major differences between phase-1 and phase-2 that might have been expected to affect the risk of early recurrent stroke after seeking medical attention. The characteristics of all patients seeking medical attention were similar in the two periods, other than a small increase in premorbid use of statins in phase-2 Table 3.2

Reliable 90-day follow-up was available for all presentations with TIA or stroke in the study population irrespective of where they initially sought medical attention or were subsequently referred. The 90-day risk of recurrent stroke after all TIA or stroke presentations in the whole population fell from 9.9% in phase-1 to 4.2% in phase-2 (63/634 vs 27/644, p=<0.0001.

The remainder of the results applies to patients referred to the EXPRESS clinic only. Of the 620 referrals (283 stroke and 337 with TIA) to outpatient services, 591 (95.3%) were referred direct to the EXPRESS clinic (310 in phase-1 and 281 in phase-2), and 29 (13 and 16) to other clinics

(mainly ocular ischaemic events). Among the 591 referrals to the EXPRESS clinic with probable or definite TIA or stroke, who represented 56.0% of the 1060 referrals to the clinic during the study period with suspected events, the 90-day risk of stroke risk fell from 10.3 % in phase-1 to 2.1% in phase-2 (32/310 vs 6/281, p=0.0001).The median delay from seeking medical attention in primary care to assessment in the EXPRESS clinic fell from 3 days in phase-1 to less than 1 day in phase-2 (p<0.0001). Median time from seeking medical attention to first prescription of other treatments (mainly statin or blood pressure lowering drugs) that were recommended to primary care in phase-1 was 20 days (IQR = 8 – 53). The equivalent delay in phase-2 was 1 day (IQR = 0 -3, p<0.0001) because treatment was initiated in the EXPRESS clinic.

Early treatment did not increase the 30-day risk of bleeding events requiring medical attention in referrals to the EXPRESS clinic in either phase of the study period in spite of early initation of treatment. Table 3.3 The 30 day risk of major bleeding in phase 1 was (1/310), 0.32% and (2/281) 0.70% in phase 2 defined by CURE criteria.

Process of care in patients referred to the EXPRESS clinic, assessed at the one-month follow-up clinic, showed that those referred in phase-2 were more likely to be taking a statin (63.5% vs 83.8%, p<0.0001) and to have been treated with aspirin and clopidogrel (8.1% vs 46.5%, p<0.0001), reflecting the fact that treatment was initiated in the clinic in phase-2. Similar numbers of patients had carotid endarterectomy for recently symptomatic stenosis during the two periods (17 vs 15), but surgery was performed earlier in phase-2 (<7 days: 0 vs 6, p=0.006; <30 days: 2 vs 10, p=0.001).

Table 3.1: Number of patients seeking medical attention after a first event, stratified by place of initial referral, or by type of presenting event.

	Phase 1	Phase 2	Total
Outpatient care			
Referred to EXPRESS clinic	310	281	591
Referred to other clinics	13	16	29
Presented TIA	165	172	337
Presented with Stroke	158	125	283
Hospital-based care			
Discharged from AE	33	54	87
Inpatient Care	252	268	520
Presented with TIA	56	67	123
Presented with Stroke	229	255	484
Not referred to secondary care			
Presented with TIA	12	13	25
Presented with Stroke	14	12	26
Whole population			
Presented with TIA	233	252	485
Presented with Stroke	401	392	793

Table 3.2. The baseline clinical characteristics of all patients with first presentations with TIA or stroke during the two study periods who were referred to EXPRESS clinic.

	Phase 1(310)	Phase 2(281)	p
Age <80	207(67%)	189(67%)	1.00
≥80 years	103 (33%)	92 (33%)	0.92
Male sex (%)	141 (45%)	132(47%)	0.82
TIA	156 (50%)	160 (57%)	0.40
Hypertension	167 (54%)	164 (59%)	0.60
Diabetes	36 (12%)	37 (13%)	0.61
Previous MI	36 (12%)	29 (10%)	0.65
Previous angina	57 (18%)	42 (15%)	0.38
Prior antiplatelet	139 (45%)	109 (39%)	0.36
Prior statin	63(20%)	89(32%)	0.018

Table 3.3 The 30-day risk of bleeding events requiring medical attention after all first presentations with TIA or stroke during the two study periods.

Type of bleeding	Phase 1	Phase 2
Symptomatic intracerebral haemorrhage	0	0
Symptomatic haemorrhagic transformation of infarction	0	0
Major GI Bleeding	1	1
Minor GI Bleeding	2	3
Major Genitourinary Bleeding	0	1

3.5 Discussion

I have shown using a population-based study of all patients presenting with TIA or stroke in the whole population irrespective of age that urgent assessment and early initiation of a combination of existing preventive treatments can reduce the risk of early recurrent stroke by about 80% after TIA or minor stroke.

Although this study is not a randomized comparison it has produced results that are reliable. Firstly, there was no temporal change in rates of referral to the clinic. Secondly, there was no change in the delay to seeking medical attention after a TIA or minor stroke, or in the number of patients having early recurrent stroke prior to seeking medical attention. Thirdly, there was no change in the methods of either our face to face follow-up of patients or our ascertainment of strokes in the population. Fourthly, there was no change in our definition of recurrent stroke, and all outcomes were independently audited at the end of the study blind to the phase of the study.

There was also no evidence of confounding (i.e. that some other factor had changed between phase-1 and phase-2 in addition to the study intervention. There was also no evidence of any substantial change in the characteristics of patients presenting with TIA or stroke between the two periods, other than a small increase in the proportion on premorbid statin treatment – due mainly to representation of patients treated in phase-1.

The observed reduction is consistent with that predicted to result from the earlier use of the combination of treatments given.[14] Secondly, the low risk of recurrence in phase-2, particularly in patients with TIA who were referred to the EXPRESS clinic, is entirely consistent with data now emerging from other studies in which patients with TIA are treated urgently and intensively [24-26]whereas the high risk in phase-1 is consistent with similar studies in which patients were not treated urgently [27-31]

In certain respects, our population-based methodology has produced results that are more useful than those that would have been produced in randomized trial. Firstly randomised trials recruit only a small proportion of patients in the population with the disease of interest, and those recruited almost always differ from those not recruited in relation to age, sex, race, social class, educational status, patient preference and severity of disease.[32] By nesting our study in a population-based study of all TIA and stroke I avoided such recruitment bias. For example, a third of the patients treated in the EXPRESS clinic were aged over 80 years (and about 10% were over 90), all of whom would have been excluded from most trial protocols used in vascular disease.[32] The data on the effect of the intervention on the whole population also facilitates much more complete and informative assessments based in a "real world" setting.

This study has a number of shortcomings. In particular, I do not know what the relative effect of each of the different treatments used was on the risk of early recurrent stroke. It is possible that one or more of the treatments was ineffective, but it is unlikely that any was significantly harmful, given the very low risk of both early recurrent stroke and major bleeding in phase-2. Simply giving aspirin (with a loading dose of 300mg) more quickly after the presenting event is likely to have accounted for a substantial proportion of the benefit. The relative reduction in the 14-day risk of recurrent ischaemic stroke with aspirin in major acute ischaemic stroke is about 30%, [16,17] and could well be larger in patients with TIA or minor stroke.

Importantly, I do not know what proportion of the benefit of early treatment observed in phase-2 was due to the higher use of the combination of aspirin and clopidogrel. The greater use of clopidogrel in phase-2 was mainly due to the higher-proportion of patients seen within the very-high risk first 48 hours after TIA or minor stroke than in phase-1, but was also due to the fact that

we prescribed medication in the clinic rather than simply making a recommendation to the family doctor which was not always acted upon. In other words, it was a direct consequence of the two changes to the EXPRESS clinic that comprised the study intervention – rather than a confounding factor.

Although the MATCH trial of aspirin plus clopidogrel versus clopidogrel alone showed no benefit of longer-term combination treatment, there was a beneficial tend in the subgroup of patients randomized within 7 days of a TIA or stroke.[33] In the CARESS trial, patients with recently symptomatic ≥50% carotid stenosis, the aetiological subgroup at highest risk of early recurrent stroke, combination of aspirin and clopidogrel (300mg loading then 75mg once a day) substantially reduced micro-embolic signals (MES) in the ipsilateral middle cerebral artery detected on transcranial doppler and tended to reduce the risk of recurrent stroke. [20] A similar reduction in MES rates was also reported in a randomised trial of aspirin alone versus aspirin plus clopidogrel in patients prior to carotid endarterectomy.[34]

Most recently, the FASTER Trial (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence) reported a trend towards a reduced early risk of stroke with aspirin plus clopidogrel (300mg load followed by 75 mg/day) versus aspirin alone in patients who have had a TIA or minor ischaemic stroke within the previous 24 hours.[35] The combination of aspirin and clopidogrel does, however, have a greater risk of major bleeding than aspirin alone when given in long-term secondary prevention.[33,36,37] However, although it has been suggested that the risk of bleeding on a short course of aspirin plus clopidogrel early after TIA or minor ischaemic stroke might be smaller, there are very few reliable data.[38]

In addition more data from randomized trials on the risks and benefits of blood pressure lowering in the acute phase after TIA and minor stroke may also be required, depending on the results of ongoing randomized trials in the acute phase after major stroke.

Our results have several implications for the future provision of clinical services for TIA and minor stroke. Firstly, that urgent assessment and treatment is indeed highly effective in reducing the early risk of stroke after TIA and minor stroke. Secondly, the long delays to initiation of treatment in primary care that can occur if treatment is not started in secondary care. The high risk of early recurrent stroke in patients referred to the EXPRESS clinic in phase-1 was clearly a reflection of the fact that even if patients sought medical attention immediately and were seen quickly in the clinic there were substantial delays to the subsequent prescription of treatment in primary care. Further research is required into the causes of this delay, but a policy of initiation of treatment in secondary care, if not already given in primary care, is clearly sensible in TIA and minor stroke. Thirdly, our results suggest that in patients with a recent TIA (and minor stroke with the exception of combination antiplatelet treatment prior to brain imaging) a combination of preventive treatments should be initiated immediately they seek medical attention, either in primary care or in the emergency department.

In conclusion, this population-based study of all patients presenting with TIA or minor stroke irrespective of age has shown that early initiation of existing treatments can prevent about 80% of early recurrent strokes. Further follow-up is required to determine long-term outcome, but these results have immediate implications for service provision and public education about TIA or minor stroke.

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Chapter 4

Risk of bleeding with combination of aspirin and clopidogrel in aspirin naïve patients in the acute phase after TIA or minor ischaemic stroke.

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4.1 Abstract

Background: Aspirin plus clopidogrel (A+C) may be more effective than aspirin alone (AO) acutely after TIA and minor stroke, but the risk of bleeding in the acute phase is uncertain. I determined this risk, focusing particularly on aspirin naïve patients.

Methods: I studied consecutive referrals to the EXPRESS study clinic from 1/4/02-1/4/08. A 30-90-day course of A+C was given to patients presenting acutely. Bleeding events were identified by face-to-face follow-up, diagnostic coding, and blood transfusion data. Unpublished data from the FASTER Pilot Trial were also studied

Results: Among 633 EXPRESS patients treated with aspirin (+/- clopidogrel) there were 12 spontaneous bleeds (6 minor, 6 major/life-threatening) within 90-days after assessment, with a higher risk on A+C vs AO (8/247 vs 4/386, p=0.047 overall; 5/247 vs 1/386, p=0.03 for major/life-threatening bleeds). The excess of major/life-threatening bleeds on A+C vs AO was seen in aspirin-naive patients, (4/137 vs 0/273, p=0.01) but not in prior-aspirin patients (1/110 vs 1/113, p=0.98). All symptomatic bleeds in the FASTER Pilot also occurred in aspirin-naïve patients randomized to A+C (6/104 vs 0/94, p=0.03). In a pooled analysis, major/life-threatening bleeding on A+C occurred 9/241 aspirin-naïve patients (90-day risk=4.8%, 1.6-8.0) versus 1/204 prior-aspirin patients (p=0.009).

Conclusion: Although based on relatively few outcomes, the high risk of major bleeding on A+C acutely after TIA or minor stroke in aspirin-naive patients is a cause for concern. The potential risk to patients is sufficient to mandate detailed monitoring of bleeding risk in ongoing trials and stratify results by whether patients were aspirin-naïve.

4.2 Introduction

Antiplatelet treatment is indicated in most patients with TIA and minor ischaemic stroke. Given the high early risk of major stroke a short course of treatment with aspirin plus clopidogrel (A+C) might be particularly beneficial. [1, 2] Although the MATCH trial of A+C versus clopidogrel alone showed no benefit of longer-term combination treatment, there was a beneficial trend in the subgroup of patients randomized within 7 days of a TIA or stroke.[3] In the CARESS trial, patients with recently symptomatic ≥50% carotid stenosis, the aetiological subgroup at highest risk of early recurrent stroke, A+C substantially reduced micro-embolic signals (MES) and tended to reduce the risk of recurrent stroke.[4,5] A similar reduction in MES was also reported in a randomised trial of aspirin only (AO) versus A+C prior to carotid endarterectomy.[6] Most recently, the FASTER Pilot (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence) reported a trend towards a reduced early risk of stroke with A+C versus AO in patients with TIA or minor ischaemic stroke in the previous 24 hours.[7]

The combination of A+C does have a greater risk of major bleeding than AO when given long-term, but the risk of bleeding on a short course of treatment early after TIA or minor ischaemic stroke might be lower.[3,8] In the EXPRESS Study, early preventive treatment after TIA and minor stroke, including the use of A+C in high-risk patients, reduced early recurrent stroke by 80% without increasing bleeding complications, but safety data were not reported separately for patients given A+C.[9] In the FASTER Pilot, there was a 3.0% (6/198) 90-day risk of symptomatic bleeds on A+C.[7] However, the risks might be greater in routine clinical practice, particularly in elderly patients, and also in patients with no prior exposure to aspirin (aspirin-naïve). I therefore studied the safety of acute treatment with A+C in consecutive patients referred to the EXPRESS study clinic. I stratified the risk of bleeding by age and by prior antiplatelet treatment, and validated our observations using data from the FASTER Pilot.

4.3 Case Ascertainment

I studied all patients with TIA or minor stroke referred to the EXPRESS study clinic from 01/04/02-31/03/08. The clinic is nested in a population-based study of all TIA and stroke (Oxford Vascular Study - OXVASC) and sees over 95% of patients with suspected TIA and minor stroke in the study population.[9-12] All patients were given aspirin if not on antiplatelet therapy (300mg loading and 75mg daily), or clopidogrel (300mg loading and 75mg daily) if aspirin was contraindicated; or anticoagulation as required. In patients seen within 48 hours of their event or those seen later who were thought to be at particularly high early risk (e.g. ABCD score>4), a 30-day course of clopidogrel was given in addition to aspirin with a recommendation that it be substituted with dipyridamole 200mg twice daily after 30-days.[14] Brain imaging was required prior to starting combination antiplatelet treatment after a minor stroke to exclude haemorrhage. Patients with recent gastrointestinal or other bleeding, gastrointestinal or urological malignancy, coagulation disorders, or other known bleeding tendency were not given A+C.[9]

All medication prescribed in the clinic or recommended to the GP was recorded and data on prescriptions were obtained from the collaborating GP practices. All patients were followed-up by a research nurse or clinical research fellow after 1 and 6 months and asked about any bleeding that had required medical attention. In addition, diagnostic coding in primary and secondary care and blood transfusion data were searched to ensure complete ascertainment of all bleeding events for which medical attention was sought. Bleeding events were categorized as life threatening, major or minor by the CURE Trial criteria.[12] Major bleeding was defined as substantially disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or more units of blood. Major bleeding was further

subclassified as life threatening if it was fatal, if it lead to a decrease in haemoglobin of 5g/dl, if it caused significant hypotension requiring intravenous inotropes or surgical intervention, if it resulted in symptomatic intracranial haemorrhage, or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as bleeding not requiring transfusion.

4.3.1 Definitions and analysis

Baseline characteristics of patients started on A+ C vs AO were compared with χ^2 test or t test. Only a 30-day course of A+C was recommended. However, because some patients in phase-1 of EXPRESS did not start medication immediately and some GPs in both phases continued the combination for more than 30 days our primary analysis was a Kaplan-Meier time to event analysis of the 90-day risk with censoring at the time that clopidogrel was actually stopped. The risk of bleeding was stratified according to whether patients were aspirin naïve. In view of the small number of outcome events the Fisher exact test was used for all comparisons. All analyses were performed with SPSS software version 15.0.

The validity of associations between antiplatelet treatment and bleeding in the EXPRESS clinic cohort was tested in data from the FASTER Pilot.[7] FASTER Pilot was a randomized trial of A+C (300mg load followed by 75 mg/day) versus AO in patients with TIA or minor ischaemic stroke within the previous 24 hours, with patients also randomized to simvastatin 40mg daily versus placebo. Treatment was continued for 90 days and bleeding complications were identified by face-to-face follow-up. Prior use of aspirin, H2 antagonists and proton pump inhibitors was recorded. Exclusion criteria included contraindications to use of study medication (ie known bleeding diathesis or hepatic dysfunction) and the long-term use of non-steroidal anti-inflammatory drugs but not COX-2 inhibitors. Severity of bleeding events during follow-up was

classified as mild, moderate or severe, which equated to the minor, major or life-threatening categories in the CURE trial criteria repectively.[7,12]

4.4Results

824 patients with suspected TIA and minor stroke were seen in the EXPRESS clinic, of which 386 (47%) were subsequently treated with AO, 247 (30%) with A+C, 38 (4.6%) with clopidogrel alone, 49 (5.9%) aspirin plus dipyridamole, and 43 (5.2%) with warfarin. During the first 90-days of follow-up one minor bleed occurred in patients on clopidogrel only, one minor bleed in patients on warfarin and no bleeds in patients on aspirin plus dipyridamole.

The remainder of the results refer only to the 633 patients treated with AO (n=386) or A+C (n=247). 347 (54.8%) presented with TIA and 286 (45.2%) with a minor stroke. Mean age was 71 years and 177 (28%) were ≥80 years. 125 (19.7%) patients had a previous TIA or stroke. At the time of assessment in the EXPRESS clinic, 594 (93.8%) patients had a NIHSS score of 3 or less.[13]

228 (36%) patients were on antiplatelet treatment prior to their presenting event: 212 on aspirin alone, 8 on A+C, 4 on aspirin plus dipyridamole, and 4 on clopidogrel alone. Premorbid aspirin dose was 75mg in 213 (93%). Table 1 shows that the baseline characteristics of patients stratified according to what treatment they received after assessment in the EXPRESS study clinic and whether or not they were aspirin naïve. The median delay from seeking medical attention to prescription of treatment was 1 (IQR 0-3) days in patients treated with A+C and 3 (IQR 1-6) days in those treated with AO.A+C was prescribed in the EXPRESS clinic for 30 days, but 46 patients continued treatment for up to 90 days.

Twelve spontaneous bleeds (6 minor, 3 major, 3 life-threatening) occurred during the 90-days after clinic assessment, with a tendency towards a higher risk of major or life-threatening bleeds

in patients aged ≥80-years (4/177 vs 2/456, p=0.055). The overall risk of bleeding was higher on A+C than on AO (8/247 vs 4/386, p=0.047), particularly for major or life-threatening bleeds (5/247 vs 1/386, p=0.03). However, the excess of major or life-threatening bleeds A+C versus AO was only seen in aspirin-naive patients, (4/137 vs 0/273, p=0.01) and not in patients on prior aspirin (1/110 vs 1/113, p=0.98). This risk appeared to be particularly high in aspirin naive patients aged ≥80-years on A+C (2/19, 9.5%). Among all 824 patients referred the study clinic, all 90-day life-threatening spontaneous bleeds occurred in the aspirin-naive group given A+C (3/137 vs 0/687 in all other patients, p=0.004).

Only one of the 12 patients who had a bleed on AO or A+C had a history of previous GI bleeding or peptic ulcer disease. Table 4.1 shows that there were no major differences in measured risk factors for GI bleeding between aspirin-naive patients and the prior aspirin patients among the 247 patients treated with A+C. History of peptic ulcer disease was slightly more frequent in the prior aspirin group and use of non-steroidal anti-inflammatory drugs was slightly more frequent in the aspirin-naïve group. To identify whether there might have been any unmeasured differences in clinical characteristics between aspirin-naive patients and the prior aspirin patients among the 247 patients treated with A+C that might have increased the risk of major or life-threatening bleeds in the aspirin-naïve subgroup, I determined the risk of major bleeding during the 12 months after clopidogrel was stopped and the patients were left on aspirin alone or changed to aspirin plus dipyridamole. The subsequent one-year risk was 1/108, 0.9% (0-2.8) in the aspirin-naive patients versus 1/72, 1.8 %(0-5.3) in the prior aspirin patients (p=0.79).

Table 4.1 Baseline characteristics of the EXPRESS clinic patients with TIA or ischaemic stroke who were treated with aspirin alone or aspirin plus clopidogrel, stratified according to whether they were on prior aspirin at the time of their presenting event.

	Aspirin-naïve			Prior Aspirin		
	0-A	**0-A+C**	**p**	**A-A**	**A-A+C**	**p**
	n=273	**n=137**		**n=113**	**n=110**	
Baseline characteristics						
Age (years)	69.7	67.64	0.27	76.81	74.89	0.15
Male sex	124	62	1.00	47	65	0.01
History of peptic ulcer	23	8	0.43	9	12	0.49
Anti- inflammatory use	36	22	0.45	16	13	0.69
Prior gastrointestinal bleed	10	4	0.78	2	2	1.00
Prior acid suppression use	20	14	0.35	12	22	0.06
SSRIs	3	5	0.12	6	8	0.59
Prior MI	5	6	0.19	16	20	0.47
Previous TIA	19	5	0.26	18	17	1.00
Previous stroke	12	3	0.40	27	24	0.75
Prior PVD	7	5	0.54	8	8	1.00
Angina	9	4	1.00	24	35	0.10
Hypertension	94	74	<0.0001	73	74	0.79
Hyperlipidaemia	41	35	0.015	36	61	<0.0001
Cardiac failure	14	2	0.13	12	10	0.82
Diabetes	25	9	0.18	14	17	0.56
Venous thombosis	13	4	0.44	4	5	0.75
Smoking			0.028			0.75
Never	138	51		48	46	
ex-smoker	91	54		56	52	
current smoker	44	32		9	12	
Bleeding Events						
Life threatening/Major	**0**	**4 (2.9%)**	**0.01**	**1 (0.9%)**	**1 (0.9%)**	**1.0**
Gastrointestinal	0	2		1	0	
Intracranial	0	1		0	0	
Other	0	1		0	1	
Minor	**2 (0.73%)**	**2 (1.5%)**	**0.60**	**1 (0.9%)**	**1 (0.9%)**	**1.0**
Gastrointestinal	1	1		0	1	
Other	1	1		1	0	

0-A= aspirin naive treated with aspirin only, **0-A+C**= aspirin naïve treated with A+C**, A-A=** prior aspirin treated with aspirin**, A-A+C** prior aspirin treated with A+C

SSRI- selective serotonin reuptake inhibitors, **MI**= myocardial infarction, **PVD**= peripheral vascular disease, **TIA**= transient ischaemic attack.

In the 198 patients randomized to A+C in the FASTER Pilot, there were five major or life threatening bleeds (2.5%, 1.08-5.77) during the 90-days of scheduled treatment (2 intracerebral haemorrhages, a haematoma at the site of carotid endarterectomy, a gastrointestinal bleed, and anaemia requiring blood transfusion secondary to stomach cancer that presented during follow-up), and one minor bleed (table 4.2) All six bleeds occurred in patients who were aspirin-naïve (6/104 vs 0/94, p=0.03, Fisher exact test).

Table 4.2 Baseline characteristics of the FASTER Pilot patients who were randomised to aspirin alone versus aspirin plus clopidogrel, stratified according to whether they were on prior aspirin at the time of their presenting event.

		Aspirin-naïve			Prior Aspirin	
Treatment Assignment	**Placebo n=118**	**Clopidogrel n=104**	**p**	**Placebo n=76**	**Clopidogrel n=94**	**p**
Age	68.7	67.0	0.14	71.4	73.7	0.20
Female sex	54	45	0.66	46	40	0.02
Previous TIA	11	13	0.45	20	19	0.35
Previous Stroke	4	0	0.13	13	12	0.52
Prior PVD	1	3	0.34	2	2	1.0
Angina	4	4	0.75	2	12	0.02
Hypertension	57	43	0.30	49	49	0.11
Hyperlipidaemia	9	6	0.61	6	7	1.0
Cardiac failure	1	0	1.0	1	1	1.0
Diabetes	12	12	0.83	6	12	0.33
Smoking within the past year	29	39	0.04	19	15	0.14
Bleeding events						
Life threatening/Major	**0**	**5(4.8%)**	**0.02**	**0**	**0**	
Gastrointestinal	0	2		0	0	
Genitourinary	0	0		0	0	
Intracranial	0	2		0	0	
Other	0	1		0	0	
Minor	**0**	**1(0.1%)**	**0.47**	**0**	**0**	
Other	0	1		0	0	

0-A= aspirin naive treated with aspirin only, **0-A+C**= aspirin naïve treated with A+C**, A-A**= prior aspirin treated with aspirin**, A-A+C**= prior aspirin treated with A+C

SSRI- selective serotonin reuptake inhibitors, **MI**= myocardial infarction, **PVD**= peripheral vascular disease, **TIA**= transient ischaemic attack.

Figure 4.1 shows the crude 90-day risks of major or life threatening bleeds in patients treated with A+C in the EXPRESS study clinic cohort and the FASTER Pilot cohort. The pooled crude risks were 3.7% (1.9-5.6) in aspirin-naïve patients and 0.5% (0-2.1%) in prior-aspirin patients (difference - p=0.009). The pooled odds of having a major or life-threatening bleed on A+C versus AO were 15.4 (1.9-122) in aspirin-naïve patients versus 0.9 (0.1-9.2) in patients on prior aspirin.

Figure 4.1 The 90-day crude risk of major and life threatening bleeding on aspirin plus clopidogrel early after TIA or minor stroke stratified according to prior aspirin use.

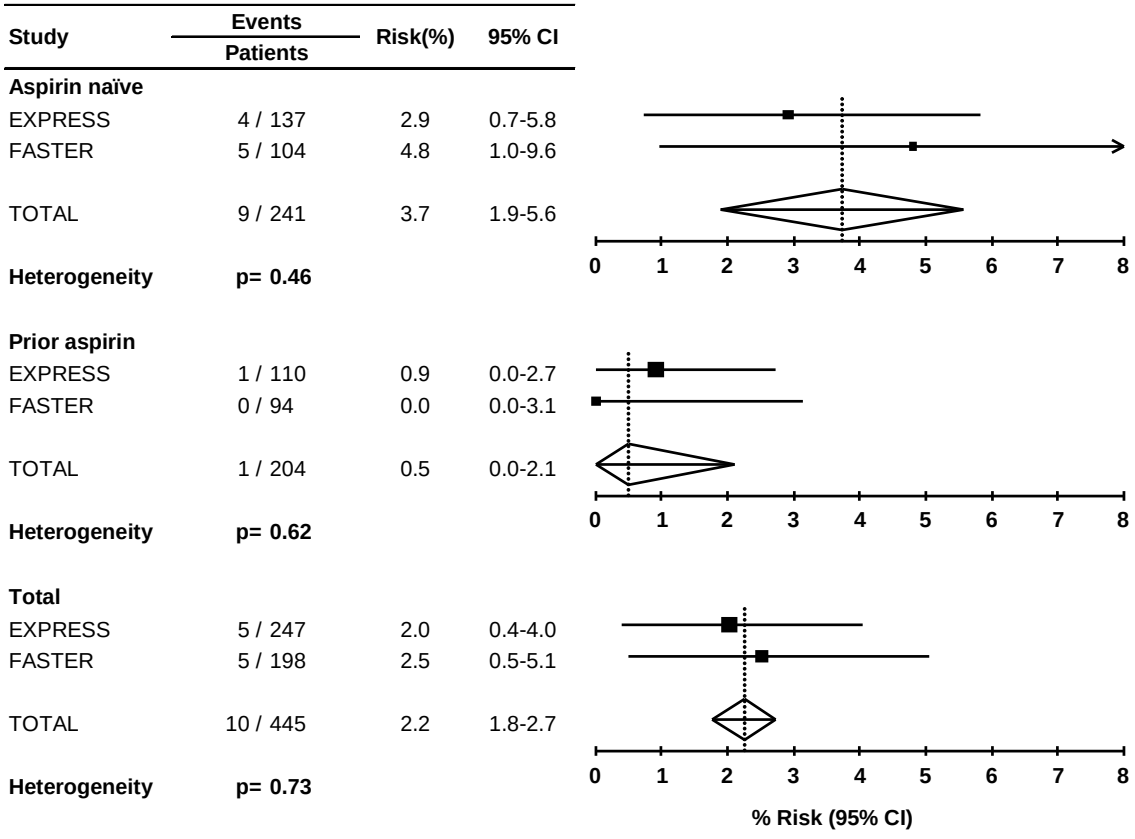
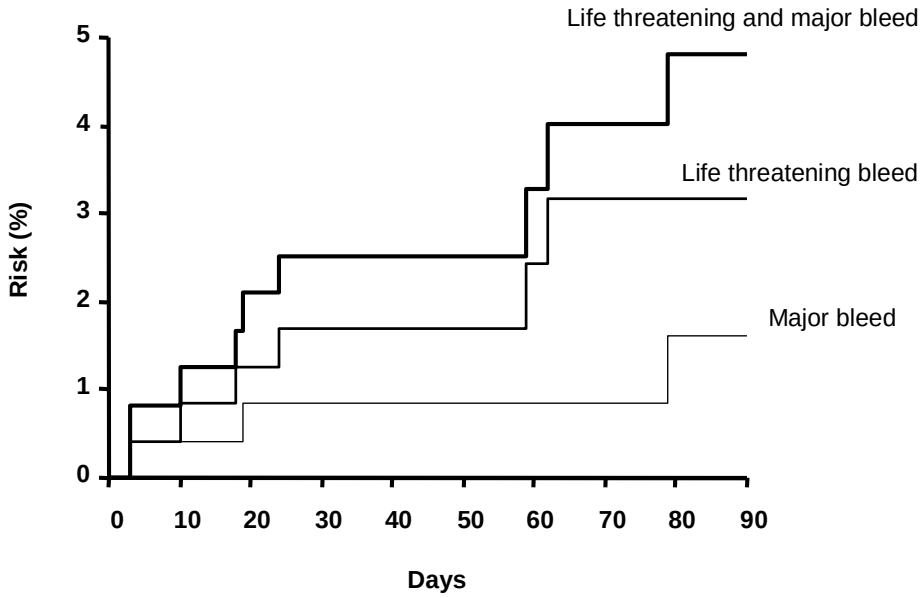


Figure 4.2 shows the 90-day actuarial risk of major and life-threatening bleeding in a pooled analysis of aspirin-naïve patients from the EXPRESS and FASTER cohorts combined censoring patients at the time that clopidogrel was stopped. The 90-day risk of major or life-threatening bleeding was 4.8% (1.6-8.0).



4.5Discussion

In randomised trials of acute stroke and acute coronary syndromes the benefit of antiplatelet treatment is greatest in the acute phase.[12] Combination treatment in high-risk patients in the first few days after a TIA or minor ischaemic stroke might therefore be beneficial even though longer-term treatment with A+C is associated with a significant bleeding risk.[3, 11] However, I have shown that the risk of bleeding on A+C is also high in the acute phase after TIA and minor stroke. Although the confidence intervals around our estimates of 90-day risk of bleeding were wide, the risks were consistent in the EXPRESS study clinic and the FASTER Pilot cohort. Risk of major or life-threatening bleeds was particularly high in aspirin-naïve patients and in those aged ≥80-years. Previous trials of A+C have not reported the risk of bleeding in patients who were aspirin-naïve prior to their vascular event, but an analogous increased risk of bleeding among treatment-naïve patients is recognized in warfarin trials.[14]

My observation that the risk of major bleeding on A+C appears to be greater in the acute phase after TIA and minor ischaemic stroke than on longer-term treatment in previous trials is plausible.[3,8,15] Firstly, patients treated acutely might be more susceptible to haemorrhagic complications due to spontaneous stress gastric ulceration and haemorrhagic transformation of an infarct. The ulcerogenic effect of aspirin is likely to be attributed to its direct effect on the gastric mucosa due to impairment of prostaglandin E2 production in addition to its effect on platelet function. Although clopidogrel does not cause mucosal injury through direct exposure and does not affect cytoprotective prostaglandin E2 production, it may exacerbate the mucosal injury due to aspirin by impairing ulcer healing through its anti-angiogenic actions.[16-18.] Secondly, the previous large trials might also have applied exclusion criteria more strictly in relation to

factors that might lead to any increased risk of GI bleeding, which tend to be more frequent in routine clinical practice, particularly in elderly patients.[19,20] Finally, in trials such as MATCH [3] and CHARISMA[8] the vast majority of patients are likely to have been on aspirin for some time after the initial TIA or stroke and prior to randomisation in the trial (mean delay was 27 days in MATCH; all patients had events within the previous 5 years in CHARISMA). Recruited patients would therefore be more likely to be aspirin-tolerant.

My analyses have a number of shortcomings. Firstly, my analyses of the EXPRESS study clinic cohort were observational and I cannot therefore exclude the possibility that the differences in rates of bleeding were due to some other difference between the patient groups unrelated to the antiplatelet regimens. Equally, the analysis of the FASTER Pilot data represents an unplanned subgroup analysis of randomised controlled trial data. Secondly, the number of major or life-threatening bleeds during the first 90-days of follow-up was small and so the confidence intervals around our risk estimates are wide and I had insufficient events to allow multivariate adjustment for baseline clinical characteristics. However, the difference in bleeding risk observed in the EXPRESS study clinic cohort between patients on AO versus A+C was very similar to that in the randomised comparison in the FASTER Pilot. Moreover, although the difference in bleeding risk on A+C between those who had had premorbid aspirin and those who were aspirin-naïve was based on small numbers, the hypothesis was proposed prior to looking at the data and the observation was highly consistent in two independent studies, with a pooled significance of p=0.009.

Further studies of the balance of risks and benefits of A+C versus AO in acute TIA and minor stroke are still justified, albeit with careful monitoring of differences in risk of bleeding between aspirin-naïve patients and those on prior aspirin. There is no evidence of immediate efficacy (i.e.

within hours) of adding dipyridamole to aspirin, but there is probably a tangible risk of haemorrhage.[21] A recent pilot trial of triple antiplatelet therapy (aspirin, dipyridamole and clopidogrel) suggests that the haemorrhage risks might be multiplicative.[22] In the meantime, given the high proportion of GI bleeds in patients taking A+C, concurrent prescription of H2 receptor antagonists might be sensible, given the potential adverse interaction between some proton pump inhibitors and clopidogrel.[23,24]

In summary, clinicians should be aware that the risk of major bleeding on A+C in patients with recent TIA or minor stroke is significant, although the risk of recurrent stroke at 90 days is greater than the risk of bleeding especially in high risk patients. Until further data on the balance of risks and benefits are available from ongoing randomized controlled trials, clinicians should probably only use combination A+C in aspirin-naïve patients if they consider that the early risk of ischaemic stroke is very high (ABCD2 score >4 or evidence of large artery atherosclerosis). As short a course of combination treatment as possible would also be advisable in order to minimize the risk of bleeding (a 14-day course is used in FASTER-2), and it is essential to ensure that patients and referring clinicians are informed not to continue treatment thereafter. More research is also required on the effectiveness of gastric protection in patients on antiplatelet therapy after recent TIA or stroke.

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CHAPTER 5

Low risk of rebound events after a short course of clopidogrel in acute TIA or minor stroke

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5.1Abstract

Introduction: The combination of aspirin and clopidogrel is indicated after acute coronary events and possibly for a short period after TIA or minor ischaemic stroke. Early discontinuation of clopidogrel results in a transient “rebound” increase in risk of recurrence in acute coronary syndromes, but there are no published data on any similar rebound effect in patients with TIA or stroke that might inform the design of clinical trials of aspirin and clopidogrel in the acute phase.

Methods: A 30-day course of aspirin and clopidogrel (both 75mg daily) was given to high risk patients with TIA or minor ischaemic stroke seen acutely in the EXPRESS study clinic from 01-04-2002 to 31-03-09. Clopidogrel was stopped after 30 days and aspirin continued. Recurrent events were ascertained at face-to-face follow up.

Results: 320 patients were prescribed a 30-day course of aspirin and clopidogrel acutely after TIA or minor stroke. There were 5 recurrent ischaemic strokes and 7 TIAs during the aspirin and clopidogrel treatment period, but no strokes and 4 TIAs during the 30-days after stopping clopidogrel. A similar temporal trend in stroke risk was seen in the 487 patients prescribed aspirin alone in the acute phase, with 12 and 5 strokes in the equivalent time periods. The upper 95% confidence interval of the observed 0% risk of stroke during the 30-days after stopping clopidogrel was 1.15% overall.

Conclusion: Although larger studies are required, our findings suggest there is unlikely to be a large rebound effect after discontinuation of a 30-day course of clopidogrel in acute TIA and minor ischaemic stroke. However, planned trials of aspirin and clopidogrel in the acute phase after TIA or stroke should still follow-up beyond the cessation of clopidogrel treatment.

5.2 Introduction.

Antithrombotic therapy is recommended after transient ischaemic attack (TIA) and ischaemic stroke.[1] Addition of clopidogrel to aspirin reduces risk of recurrent events after acute coronary syndromes (ACS). [2-4] Given the high early risk of stroke following TIA and minor stroke,[5] a short course of treatment with aspirin plus clopidogrel might also be beneficial. Current trial evidence is limited,[6-9] but larger trials are planned.[10, 11] However, the optimal duration of dual treatment to prevent early recurrence without excessive increased bleeding risk is unknown. Premature discontinuation of clopidogrel after ACS

is associated with a substantial rebound increase in risk of recurrent events in stented patients [12-15] and probably also in patients who are not stented,[15] and clinical guidelines were revised accordingly.[16-18] Limited published data suggest that the risk of recurrent ischaemic stroke is also increased after discontinuation of antiplatelet therapy in general after TIA or stroke,[19-21] but there are no published data on any rebound effect following discontinuation of a short course of clopidogrel in this group. No unpublished data are available from the CARESS Trial[7] (personal communication, Hugh Markus), the Leicester trial[8] (personal communication, Ross Naylor), or the FASTER pilot[9] (personal communication, James Kennedy) because follow up was not continued after discontinuation of trial treatment. In the absence of trial data, I sought to identify any rebound effect after discontinuation of a 30-day course of clopidogrel in consecutive patients treated with aspirin and clopidogrel after TIA or minor ischaemic stroke in our population-based cohort study.

5.3Methods

The methods of the Oxford Vascular study (OXVASC) and details of the EXPRESS study clinic have been reported previously.[22-24] Briefly, the study population comprised all 91,000 individuals,

irrespective of age, registered with 63 family physicians in nine general practices in Oxfordshire, UK. Standard definitions of transient ischaemic attack and stroke were used.

This report concerns all patients with TIA or minor stroke referred to the EXPRESS study daily outpatient clinic during the first seven years of OXVASC from 1/4/2002-31/3/2009. Over 95% of patients with suspected TIA and minor stroke in our study population are referred directly to our study clinic by their family practitioner or from accident and emergency.[22] The same antiplatelet treatment protocol after TIA or minor ischaemic stroke was used throughout.

5.3.1 Case ascertainment

All patients were given aspirin if not already on antiplatelet therapy (300mg loading and 75mg daily), or clopidogrel if aspirin was contraindicated; and anticoagulation as required. In patients seen within 48 hours of their event or those seen later who were thought to be at particularly high early risk, (ABCD score >4 or large artery aetiology), clopidogrel (300mg loading followed by 75mg daily once daily) was given in addition to aspirin with a recommendation that it be stopped after 30-days and substituted with dipyridamole 200mg twice daily. Brain imaging was required prior to starting combination antiplatelet treatment after a minor stroke to exclude cerebral haemorrhage. Patients with recent symptomatic gastrointestinal or other bleeding events, those with gastrointestinal or urological malignancy, or coagulation disorders, or other known severe increased tendency for bleeding were not given aspirin plus clopidogrel. [23]

Patients were assessed by a study physician in the EXPRESS clinic in a standardised manner. Detailed data were collected on times and methods of first contact with medical attention after the presenting event. All patients were followed-up by a research nurse or clinical research fellow after 1,6,12 and 24 and 60 months and asked about new neurological symptoms, medication compliance and any bleeding that had required medical attention. All medication prescribed in the clinic or recommended to the family physician was recorded and data on

prescription of all medications after the presenting TIA or stroke were obtained from the databases of the collaborating primary care practices.

Severity of stroke was assessed with the National Institutes of Health Stroke scale (NIHSS). Other vascular outcomes were also identified on follow-up. Acute coronary events were defined as ST-elevation myocardial infarction (STEMI) and non-ST elevation myocardial infarction (N-STEMI) by using standard criteria.[25] Acute peripheral arterial events were defined as ischaemic events affecting a limb or organ other than the heart, brain or eye.

5.3.2 Definitions and analysis

All patients with TIA or minor ischaemic stroke referred to the EXPRESS clinic were included.

Baseline characteristics of patients started on aspirin and clopidogrel at clinic and those started on aspirin alone were compared by use of χ^2 test for categorical variables and a t test for continuous variables. Although it was recommended that clopidogrel be stopped after 30-days, some patients continued clopidogrel in addition to aspirin (deliberately or inadvertently) for longer before stopping. I therefore compared the risk of recurrent ischaemic events during 30 days prior to discontinuation with that during the 30-days after discontinuation. In a sensitivity analysis, I restricted this comparison to those patients in whom the recommendation to stop clopidogrel at exactly 30-days had been adhered to. All analyses were performed with SPSS software version 15.0.

5.4Results

Of the 952 patients with TIA or minor stroke seen in the EXPRESS clinic from 1st April 2002 to the 31st March 2009, 522 (54.8%) presented with TIA and 430 (45.2%) with a minor stroke. Mean age was 71 years and 271 (29%) were ≥80 years. 114 (12%) patients had a previous TIA and 105 (11%) had a previous stroke. At the time of assessment in the EXPRESS clinic the

median NIHSS score was 0 (IQR 0-1), 894 (94%) patients had a score of 3 or less, and 933 (98.1%) had a score of 5 or less.

338 (36%) patients were on antiplatelet treatment prior to their presenting event: 308 (91%) on aspirin alone, 8 (0.8%) on aspirin plus clopidogrel 75mg daily and 11 (1.2%) on aspirin plus dipyridamole. 11(1.2%) patients were on clopidogrel 75mg alone and none were on dipyridamole alone prior to their event. Premorbid aspirin dose was 75mg in 267(87%) cases.
Following assessment in the clinic, 487 (51%) patients were treated with aspirin only and 320 (34%) with aspirin plus a short course of clopidogrel. The remainder of the results refer only to these 807 patients.

Baseline characteristics of the aspirin and clopidogrel and the aspirin-only treated groups are shown in Table 1. There were no major differences in measured risk factors between the aspirin and clopidogrel and the aspirin treated groups except a higher prevalence of hyperlipidaemia, hypertension and ≥50% symptomatic carotid artery disease in the aspirin and clopidogrel group, as expected on the basis of our preferential use of combination treatment in higher-risk patients with large artery disease.

Table 5.1: Baseline characteristics of the aspirin and clopidogrel group and the aspirin only group.

	Aspirin + clopidogrel n=320	Aspirin only n=487	p
Age	70(13)	71.7(13)	0.17 [3]
Male sex	164 (51)	223 (46)	0.13
Prior TIA	31 (10)	58 (12)	0.36
Prior Stroke	29 (9)	58 (12)	0.25
Prior angina	47(15)	61 (13)	0.39
Prior MI	30 (9)	36 (7)	0.36
Prior PVD	15(5)	21 (4)	0.86
Hypertension	182 (57) [1]	237 (49)	0.03
Hyperlipidaemia	122 (38) [2]	124 (26) [1]	<0.0001
Cardiac failure	16 (5)	40 (8)	0.09
Diabetes	39 (12)	57 (12)	0.82
Anti- inflammatory use	35 (14)	64 (15)	0.91
Venous thombosis	13 (4) [1]	20 (4)	1.0
Post event acid suppression	113 (35)	75 (15)	<0.0001
Smoking			0.36
Never	134 (42)	228 (47)	
ex-smoker	135 (42)	191 (40)	
current smoker	51 (16)	68 (14)	
≥50% symptomatic carotid stenosis	49(15)	50(10)	0.04
CEA for (≥50%) stenosis	19(6)	17(3.5)	0.11

Data are n (%) are for Fishers exact test unless stated otherwise.

[1] one case missing

[2] two cases missing

[3] t-test

During the 30 days prior to stopping clopidogrel there were 5 ischaemic strokes (1.6%) and 7 TIAs in the aspirin and clopidogrel group. During the 30 days after stopping clopidogrel there were no strokes and 4 TIAs. The upper 95% confidence interval of the observed 30-day stroke risk after discontinuation of clopidogrel was 1.15%. A similar temporal trend in stroke risk was seen in the 487 patients prescribed aspirin alone in the acute phase, with 12 and 5 strokes in the equivalent time periods (although aspirin was of course not stopped). The number of ischaemic events in other arterial territories was small (table 2), such that the temporal trends in risk of all major acute vascular events were similar to those for stroke alone.

Table 5.2: Risk of recurrent ischaemic events stratified according to the timing of discontinuation of clopidogrel in patients given a short course of clopidogrel in addition to aspirin and in the equivalent periods in patients treated with aspirin alone.

Time period *	**Aspirin + clopidogrel** (n=320)	**Aspirin only** (n=487)	**p**
Risk of ischaemic stroke			
-30-0 days	5/318(1.6)	12/487(2.5)	0.41
0-30 days	0/316(0)	5/485(1.0)	0.07
30-60 days	1/315(0.3)	4/482(0.8)	0.37
Risk of TIA			
-30-0 days	7/318(2.2)	5/487(1.0)	0.16
0-30 days	4/316(1.2)	3/485(0.61)	0.34
30-60 days	5/315(1.6)	3/482(0.62)	0.18
Risk of ischaemic stroke, myocardial infarction or acute peripheral vascular events			
-30-0 days	6/318(1.9)	14/487(2.8)	0.40
0-30 days	0/316	6/485 (1.2)	0.048
30-60 days	1/315(0.3)	4/482 (0.82)	0.37
Risk of ischaemic stroke, TIA, myocardial infarction or acute peripheral vascular events			
-30-0 days	13/318(4.0)	19/487(3.9)	0.83
0-30 days	4/316(1.2)	9/485 (1.8)	0.53
30-60 days	6/315(1.9)	7/482 (1.5)	0.62

* -30-0 days represents the 30-days prior to stopping clopidogrel; 0-30 days represents the 30 days after clopidogrel was stopped; and 30-60 days represents the period 30-60 days after clopidogrel was stopped.

Aspirin and clopidogrel was prescribed in the EXPRESS clinic for 30 days, but 103 (32%) of patients continued clopidogrel in addition to aspirin (deliberately or inadvertently) for longer before stopping. However, exclusion of these cases from the above analyses did not alter the findings. 49 patients treated with aspirin and clopidogrel had ≥50% symptomatic carotid stenosis, of whom 19 subsequently had endarterectomy with a median time to carotid endarterectomy of 39 (IQR 12-69) days. The upper 95% confidence interval of the observed 0% stroke risk after discontinuation of clopidogrel in these 49 patients was 7.2% and so clinically significant stroke risk cannot be excluded. However, there were 4 TIAs during follow-up in this group, all of which occurred during the 30-day period on aspirin plus clopidogrel, with no events during the subsequent 30 day "rebound" period.

Patients and GPs were advised to start Dipyridamole 200mg twice daily following the 30 day course of clopidogrel. However, an audit of 50 consecutive cases showed that only 21(42%) had ever started dipyridamole, and the median delay from stopping clopidogrel to starting dipyridamole was 49 days.

5.5Discussion

I observed no rebound increase in risk of stroke during the 30 days after discontinuation of a short course of clopidogrel in TIA or minor stroke. The number of patients studied (n=320) was not very large, but the upper 95% confidence interval of the observed stroke risk after discontinuation of treatment was relatively low nevertheless (1.15%) and ours is the only published cohort of patients treated with aspirin plus clopidogrel acutely after TIA or stroke with follow up after discontinuation of clopidogrel. Moreover, no data are available on the risk of vascular events after discontinuation of clopidogrel in patients randomized to aspirin and clopidogrel in the CARESS,[7] Leicester,[8] or FASTER Pilot trials.[9] Furthermore, our sample of 320

patients is actually larger than the aspirin and clopidogrel groups in all three of these trials combined, and our subset of 49 patients with ≥50% symptomatic carotid stenosis is equivalent to the aspirin and clopidogrel groups in the Leicester [8] and CARESS [7] trials which were done in this specific patient group.

It is important to stress that no conclusions about efficacy can be drawn from our comparison of the aspirin plus clopidogrel group with the aspirin-only group. Rather I simply looked at the temporal trend in event rates within the aspirin and clopidogrel group in order to try to detect a "rebound effect". I presented the event rates during the equivalent periods in the aspirin-only group simply to give an idea of the temporal trends in event rates that might be expected in the absence of discontinuation of antiplatelet treatment.

Given the strong evidence of a rebound risk of acute ischaemic events after discontinuation of clopidogrel in patients with prior acute coronary events,[12-15] the lack of an obvious rebound effect in our study requires explanation. First, the difference may reflect the fact that patients with stroke and TIA are a more heterogeneous group compared to patients with acute coronary events. The subgroup most analogous to cohorts with acute coronary events is probably those patients with ≥50% symptomatic carotid stenosis, and the upper 95% confidence interval of our 0% 30-day rebound stroke risk in the 49 such patients in our study was 7.2% and so a clinically important rebound effect in this group cannot be excluded. Second, the rebound effect upon discontinuation of clopidogrel is more likely to occur in those patients with acute coronary syndrome who have coronary stents compared to those without.[12-14] A small number of case reports highlight premature discontinuation of aspirin and clopidogrel as a potential cause of late carotid stent thrombosis [26, 27] but carotid endarterectomy was the standard treatment for revascularization of extracranial carotid occlusive disease in our study. Third, a rebound phenomenon assumes that the treatment has had some beneficial effect in the first place. It is, of course, possible that the combination of agents is actually no more effective than aspirin

alone, in which case I would not expect to see a rebound effect after withdrawal of clopidogrel. However, the results in trials in acute coronary events, [3,28-30] and the data available so far from trials in patients with TIA or minor stroke,[6-9] suggest that there probably is some benefit - the uncertainty in patients with TIA or stroke being more related to whether the risk of bleeding outweighs such benefit. [31]

One potential shortcoming of our study was a theoretical possibility that our advice to primary care physicians that dipyridamole should be commenced after stopping clopidogrel might have reduced any rebound risk of ischaemic events. However, the majority of patients did not go onto dipyridamole and there was a considerable delay to prescription in those who did.

Our results have implications for the design of trials of aspirin plus clopidogrel in patients with TIA or minor stroke. I observed no rebound increase in risk of stroke or TIA after discontinuation of a 30-day course of clopidogrel, but larger studies are required and ongoing trials that use a limited duration of clopidogrel should follow-up patients beyond the cessation of trial treatment in order to document any rebound effect.[10,11,32] In terms of more immediate implications for clinical practice, although use of aspirin plus clopidogrel in the acute phase after TIA or minor stroke is not supported by substantial trial evidence, a short course of combination treatment is used in some centres. Our findings suggest that a 30-day course of clopidogrel is likely to be sufficient (assuming that it actually is of some benefit), given the lack of an obvious rebound effect. It is important to stress, however, that our results do not provide any evidence on the risks of discontinuation of clopidogrel prior to 30 days, as is often required, for example, by some surgeons in patients due to undergo carotid endarterectomy.

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Chapter 6

Population based study of the risks and predictors of bleeding on antiplatelet treatment: towards development of a bleed risk model in routine practice

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6.1 Abstract

Introduction: Antiplatelet drugs are effective for preventing recurrent ischaemic events or death in patients with acute coronary syndromes (ACS), transient ischaemic attack (TIA) and ischaemic stroke. However they increase the risk of major gastrointestinal or intracranial bleeds. In contrast to risk stratification for ischaemic events, where a range of validated scores exist, there is currently no universally accepted risk score for the stratification of bleeding risk in the short or long-term in ACS, TIA or ischaemic stroke patients treated with antiplatelet drugs**.**

Methods:

A bleed risk model in the population based cohort of the Oxford Vascular Study (OXVASC) was derived. The risk model was derived first in the stroke and TIA patients ascertained throughout the OXVASC study period (April 1, 2002 to March 31st 2008) and validated in the cohort of ACS patients ascertained in OXVASC throughout the same period. Similarly, the risk model was used to determine recurrent ischaemic risk (stroke, MI, sudden cardiac death (SCD). Quintiles of bleeding and ischaemic risk were calculated for each individual. Each bleed risk factor was tested independently in a univariate regression analysis and multivariable regression analysis was then used to assess the independent effect of each prognostic variable. Model discrimination was assessed using the area under the receiver operating curve (AUROC).

Results: Of 2116 eligible patients, 826(39%) presented with ACS (ACS), and 1290(61%) with TIA or ischaemic stroke. 8 independent predictors of bleeding were identified in the stroke/TIA cohort. The cumulative 3 year risk of major bleeding in the validation cohort, increased with increasing risk score, 3.0% for the lowest risk quintile to 22.3% for the highest. AUROC=0.67 (95%CI 0.58-0.75) however, the risk of ischaemic events also increased, 13.85% lowest quintile to 34.98% for the highest quintile AUROC 0.57(95% CI 0.51-0.62). The score also predicted

severity of bleeding events AUROC=0.51(95% CI 0.41-0.60) for minor bleeding and AUROC=0.76 (95% CI 0.60-0.91) for fatal bleeding events.

Conclusions: The OXVASC bleed model quantifies long term risk of bleeding in those treated with antiplatelets. However, bleed risk was proportional to ischaemic risk, which might reduce the clinical utility of risk assessment. My aim for further research is to develop a simple scoring model that would aid bleeding risk assessment in the future.

6.2 Introduction

Antiplatelet drugs are effective for preventing recurrent ischaemic events or death in patients with acute coronary syndromes (ACS), transient ischaemic attack (TIA) and ischaemic stroke. Against this benefit they increase the risk of major gastrointestinal or intracranial bleeds.[1,2] Particularly as newer and more potent antiplatelet therapies are emerging, [3-7] it is important to consider their risks in the real world setting. Indeed, bleeding has been the focus of recent American and European cardiology guidelines which stress the importance of balancing antithrombotic effectiveness against risks. [8-10] However, in contrast to risk stratification for ischaemic events, where a range of validated scores exist, there is currently no accepted risk score for the stratification of bleeding risk in the short or long-term after ACS, TIA or ischaemic stroke.[11-13]

Previous studies of bleeding complications following an acute ischaemic event (almost all in patients with ACS) have identified several clinical and procedural predictors, including advanced age,[14-23] female sex,[14-17,19,20,24-28] history of bleeding,[16,19,26,29] baseline anaemia,[14,17,28] renal insufficiency,[14-19,27,28,30-32] lower body weight,[28] hypertension,[15,16,18,24,28,30] diabetes, [14,19,28,] prior history of cancer,[19,29] prior peptic ulcer disease [29,33] cancer,[19,29] stroke severity,[34,35] prior peripheral arterial disease or stroke,[15,23,24,28] admission heart rate,[23,28] procedural hypotension [18]

ST deviation or elevation [14,16] raised cardiac markers [14,16] use of glycoprotein 11b/111a inhibitors,[17,18,20,24,26] antiplatelet therapy,[26,34] low molecular weight heparin,[14,16,17,20] fibrinolysis,[16,24,26] selective serotonin inhibitor use(SSRI),[36,37] and invasive procedures [15-18,20,24,26,31] In addition, three models for assessment of risk of in-hospital bleeding after ACS have been derived and validated. Nikolosky et al derived an eight-point score using trial data on patients undergoing percutaneous coronary intervention (PCI).[17] The other two models (GRACE; CRUSADE) were derived from ACS and non-ST-elevation myocardial infarction (NSTEMI) database registries and are again limited to short-term risk of in-hospital bleeding.[16,28] Both scores included treatment variables which limit their ability to assess bleeding risk at presentation.[16,28] A longer term bleeding risk model was recently developed to predict bleeding risk in stable patients with or at risk of atherothrombosis treated with antithrombotics using the REACH(Reduction of Atherothrombosis for Continued Health) registry.[38]

However, although a model to predict the long-term risk of bleeding on antiplatelet treatment would appear to be necessary, it may be less clinically useful than it might appear at first sight. Bleeding is clearly an important outcome in its own right, and can be fatal, but it is also an independent predictor of increased rates of early and late mortality, recurrent MI, repeat revascularisation procedures and recurrent stroke.[14-16,24,25,39,40] It is quite possible therefore that patients identified by a model to be at high risk of bleeding on antiplatelet treatment, in whom it might therefore be suggested that treatment be withheld, would also be at particularly high risk of ischaemic events and thus also be the very group in which absolute benefit from antiplatelet drugs would be greatest. Thus, although the precise pathophysiogical mechanisms by which the risks of bleeding and of ischaemic events may be linked are not well understood,[41,42] this ischaemic/bleeding balance has been the focus of several recent and ongoing antiplatelet trials.[3-6,43] However, in contrast to the numerous studies of the risks of warfarin in routine clinical practice,[44-47] there has been remarkably few studies of the incidence, risk factors and outcomes of bleeding complications on aspirin and other antiplatelet drugs in routine practice.

I therefore sought to determine the long-term risk of bleeding complications in a population-based study of all patients with a recent TIA, ischaemic stroke, or ACS treated with antiplatelet drugs, to derive a predictive risk model, and to determine the association between risk of bleeding and risk of recurrent ischaemic events.

6.3 Methods

I derived the bleed score in the population based cohort of the Oxford Vascular Study (OXVASC). The methods of OXVASC and details of the study population have been reported previously. Briefly, the study population comprised all 91,000 individuals, irrespective of age, registered with 63 family physicians in nine general practices in Oxfordshire, UK.[48] In the UK, almost all individuals register with a general practice, which provides their primary health care and holds a lifelong medical record. This report concerns all bleeding events following ischaemic events in two arterial territories, coronary (acute myocardial infarction) and cerebrovascular (acute TIA and ischaemic stroke) in the study population in the first six years with follow up until 31/3/2008. Details of the methods of ascertainment have been published previously, and direct assessment has shown it to be near complete. [48-51]

6.3.1 Derivation cohort

All patients, irrespective of age presenting to medical attention with TIA or stroke in the study population were ascertained from inpatient admissions, Accident and Emergency, EYE hospital, OXVASC clinic and other outpatient clinics. Standard definitions of stroke and TIA were used which have been reported previously.[49] All premorbid medications and medications at the time of treatment and discharge and follow up were recorded. In patients seen within 48 hours of their event or those seen later who were thought to be at particularly high early risk (e.g. ABCD score>4), a 30-day course of clopidogrel was given in addition to aspirin with a recommendation that it be substituted with dipyridamole 200mg twice daily after 30-days.[14] Brain imaging was

required prior to starting combination antiplatelet treatment after a minor stroke to exclude haemorrhage. Patients with recent gastrointestinal or other bleeding, gastrointestinal or urological malignancy, coagulation disorders, or other known bleeding tendency were not given A+C.[9] Patients who were treated on warfarin premorbidly or following an acute ischaemic event were not included.

6.3.2 Validation cohort

Acute coronary events were defined as ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI) by using standard criteria.[51] All premorbid medications and medications at the time of treatment, discharge and follow up were recorded. In addition use of fibrinolytics and further interventions such as percutaneous coronary stenting or angioplasty and coronary artery bypass grafting were recorded.

Standard clinical characteristics were routinely collected in both cohorts during initial assessment. A prior vascular event included a previous myocardial infarction, TIA or ischaemic stroke. Anaemia was defined according to the World Heath organisation (WHO), baseline haemoglobin less than 13g/l in men and less than 12g/l in women.[52] Renal failure was defined as any documented history of chronic renal failure (glomerular filtration rate of <30ml/minute estimated using the Cockroft and Gault formula) [53] previous gastrointestinal bleed included a history of upper or lower gastrointestinal haemorrhage, weight was measured in kilograms and frailty was defined by Strawbridge criteria as having problems in 2 or more of the 4 domains (physical function, nutrition, cognition and sensory impairments). [54]

6.3.3 Ascertainment of bleeding events

Bleeding events were defined as bleeding requiring medical attention, episodes of purpura or bruising were not included. Prospective daily searches of all bleeding events in the study population were done. In order to ensure complete ascertainment, all hospital-care and primary-care coding and blood transfusion data were searched for all bleeding events for which medical attention was sought. Patients were asked on follow up about bleeding events and general practice databases were searched for any bleeding events requiring medical attention. Bleeding events were classified by the CURE criteria. Major bleeding was defined as substantially disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or more units of blood. Major bleeding was further subclassified as life threatening if it was fatal, if it lead to a decrease in haemoglobin of 5g/dl, if it caused significant hypotension requiring intravenous inotropes or surgical intervention, if it resulted in symptomatic intracranial haemorrhage, or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as bleeding not requiring blood transfusion.[55]

6.3.4 Derivation of bleed risk model

Categorical variables are expressed as frequencies and percentages and continuous variables are expressed as means and standard deviations (SD) if appropriate. Continuous variables were tested and investigated for non linearity and cut off values were determined to create a binary variable when appropriate. Based on previous literature of risk factors for increased bleeding risk, baseline characteristics were arranged in a dichotomous fashion were screened as candidate predictor variables at risk of bleeding as an endpoint. (Appendix 8) Age and sex and other potential risk factors were tested independently in a univariate regression analysis and factors with a significance of $p< 0.10$ were tested in a multivariate regression analysis.

6.3.5 Validation of the risk model

The risk model was derived in OXVASC patients ascertained throughout the study period (April 1, 2002 to March 31st 2008) and validated in the ACS patients ascertained during the same period. (6.7 Appendix) I used this model to produce quintiles of bleeding risk in the whole population and compared their observed risk in the TIA/stroke cohort (internal validation) with the ACS cohort (external validation) The performance of the bleeding model was tested in the derivation and validation cohort. Area under the receiver operator curve (AUROC) and 95% CIs were calculated as a measure of predictive ability with ideal prediction producing a value of 1.00, whereas no better than chance prediction is represented by 0.50.Probablity values that I quote are based on the difference between the observed predictive value(AUROC) and chance(ie, no predictive value).

6.4 Results

Of 2116 patients, 1290(61%) presented with an acute cerebrovascular event (derivation cohort), and 826 (39%) with ACS event (validation cohort). In the cerebrovascular group 512(39.6%) had TIA and 778(60.3%) acute ischaemic strokes. In the ACS group 542(65.6%) were NSTEMI, and 284(34.3%) were STEMI. Mean age was 73 years and 767(36.2%) were >80 years. The baseline characteristics of the derivation and validation cohort are described in (Table 6.1)

Table 6.1 Baseline characteristics of derivation cohort (stroke/TIA) and validation cohort (ACS) in OXVASC 2002-2008 (n=2116)

	Derivation cohort n=1290	Validation cohort n=826	p
Age (years) [1]	71.3	74.2	<0.0001
Sex (females)	681(53)	289(35)	<0.0001
Prior vascular event[2]	430(33)	242(29)	0.05
Hypertension	719(56)	420(51)	0.03
Diabetes	152(12)	148(18)	<0.0001
Prior peptic ulcer disease	55(4)	78(9)	1.00
Smoking-Current	174(14)	197(24)	<0.0001
SSRI	63(5)	35(5)	0.83
PPI	280(21)	172(21)	0.66
Anti inflammatory use	160(12)	87(11)	0.21
Chronic liver disease	20(2)	22(3)	0.08
Prior GI bleed	89(7)	61(7)	0.66
Cancer	140(11)	78(9)	0.30
Chronic renal failure	14(1)	29(4)	<0.0001
Weight (kg) [1]	73.2	77.3	<0.0001
Frail	251(26)	145(20)	0.005

[1] t statistic

[2]Prior stroke/TIA/myocardial infarction or peripheral vascular event

SSRI =selective serotonin inhibitors,PPI =proton pump inhibitors,GI bleed= gastrointestinal bleed

A total of 249(12.2%) first bleeding events occurred, including 26(10.4%) intracranial, 146(58.6%) gastrointestinal, 27(10.8%) epistaxis, 29(12%) genitourinary, and 21(8.4%) other bleeds. Bleeding severity classified by the CURE trial criteria and included 116(5.7%) minor, 54(2.6%) major, 62(3.0%) life threatening, and 17(0.80%) fatal haemorrhages. A total of 133(6.5%) major, life threatening and fatal bleeding events occurred, 26(17.4%) intracranial, 85(57.0%) gastrointestinal, 2(1.3%) epistaxis, 4(2.7%) genitourinary, and 16(10.7%) other. The time course for bleeding events in the derivation cohort showed a constant bleeding risk over time, whereas a front loading of bleeding in the first month was seen in the validation cohort. (Figure6.1)

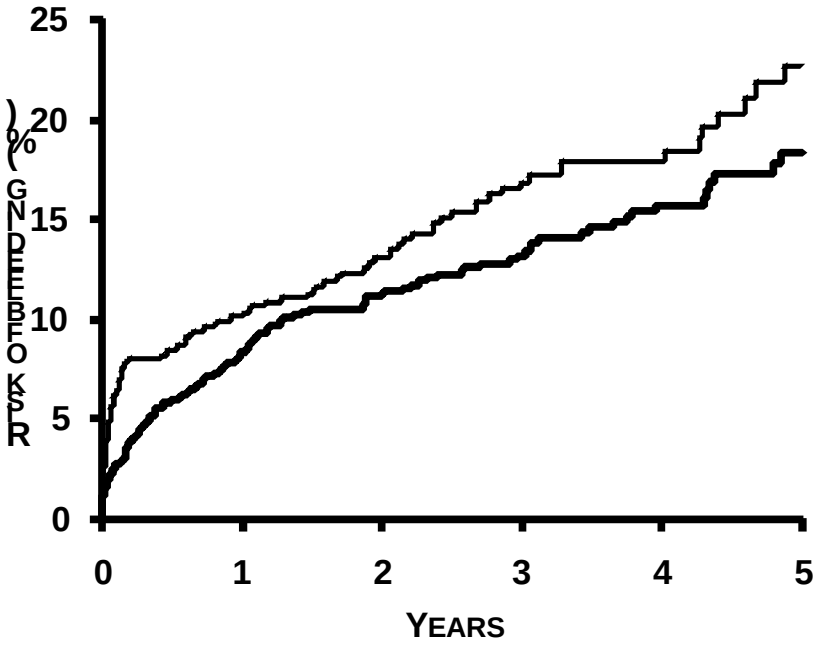


Figure 6.1 Risk of bleeding in ACS and stroke/TIA cohort of the OXVASC population (2002-2008)

I derived the predictors of all bleeding events in the OXVASC population using univariate and multivariate cox regression analysis, Table 6.2. Univariate predictors of bleeding were older age,

male sex, prior vascular disease, previous gastrointestinal bleed, history of peptic ulcer disease, history of cancer, SSRI use, low body weight, baseline anaemia, chronic renal failure, and frailty. From the multivariate analysis the factors independently associated with bleeding were male sex, prior vascular disease, previous GI bleed, cancer, peptic ulcer disease, low body weight (kg), chronic renal failure and frailty.

To account for an increased bleeding risk in those treated with aspirin and clopidogrel in the acute phase, the bleed model was re-derived in the stroke/TIA cohort excluding those aspirin and clopidogrel bleeding events during the first 30 days of treatment was similar.

Table 6.2 Univariate, and Multivariate analyses for all bleeds in TIA and stroke cohort.

		Univariate Analysis		Multivariate analysis	
Risk Factor	**Events/patients (%)**	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (per year)		1.03(1.02-1.05)	<0.0001	1.01(0.99-1.03)	0.13
< 65	17/265(6.4)	1	0.001		
65-74	33/298 (11.1)	1.77 (0.99, 3.18)			
75-84	60/440 (13.6)	2.50(1.46-4.28)			
>85	32/254 (12.6)	3.08(1.71-5.56)			
Female sex	73/670(10.9)	0.92(0.66-1.28)	0.61	0.70(0.48-1.02)	0.06
Prior vascular event[1]	68/402(16.9)	2.09(1.50-2.91)	<0.0001	1.65(1.17-2.33)	0.004
Cancer	22/137(16.1)	1.70(1.08-2.68)	0.02	1.52(0.96-2.42)	0.07
Prior GI Bleed	18/83(21.7)	2.44(1.49-4.00)	<0.0001	2.34(1.41-3.89)	0.001
Prior peptic ulcer	20/92(21.7)	2.07(1.29-3.32)	0.003	1.71(1.04-2.79)	0.03
Weight per kg		0.98(0.97-0.99)	0.002	0.98(0.97-0.99)	0.03
SSRI use	10/63(15.9)	1.73(0.91-3.30)	0.09	1.40(0.72-2.72)	0.31
Baseline anaemia	20/103(19.4)	1.93(1.20-3.09)	0.007	1.27(0.75-2.15)	0.36
Renal failure	4/14(28.6)	5.85(2.15-15.86)	0.001	2.90(0.96-8.79)	0.06
Frail	42/245(17.1)	2.68(1.82-3.95)	<0.0001	1.77(1.20-2.61)	0.004
Diabetes	19/144(13.2)	1.18(0.73-1.91)	0.50		
Hypertension	75/701(10.7)	0.89(0.64-1.24)	0.48		
CCF	13/108(12)	1.33(0.75-2.36)	0.32		
Atrial fibrillation	22/181(12.2)	1.42(0.90-2.24)	0.32		
Anti inflammatory drug use	21/157(13.4)	1.14(0.72-1.82)	0.56		

[1]Prior stroke/TIA/myocardial infarction or peripheral vascular event

SSRI =selective serotonin inhibitors,PPI =proton pump inhibitors, GI bleed= gastrointestinal bleed

I used these models to produce quintiles of bleeding risk in the whole population and compared their observed risk in the stroke/TIA cohort (internal validation) with the ACS cohort (external validation group). (Table 6.3)

The cumulative 3 year risk of major bleeding and ischaemic events in the validation cohort, increased with increasing risk score, 3.0% for the lowest risk quintile to 22.3% for the highest. AUROC=0.67 (95% CI 0.58-0.75, log rank test <0.0001). The model also predicted severity of bleeding events AUROC=0.51(95% CI 0.41-0.60) for minor bleeding and AUROC=0.76 (95% CI 0.60-0.91) for fatal bleeding events. In addition, the risk of ischaemic events also increased, 13.85% lowest quintile to 34.98% for the highest AUROC 0.57(95% CI 0.51-0.62, log rank test 0.01). The model predicted fatal ischaemic events (ischaemic stroke/MI and SCD) across quintiles less well 3.85% to 8.70% from the lowest to highest quintile AUROC 0.57(95% CI 0.49-0.64)

In order to further assess the validity of our model I performed a cross over internal validation using the ACS model and validating in the stroke and TIA cohort. (Table 6.4) Using this method the cumulative 3 year risk of major bleeding and ischaemic events in the validation cohort(stroke/TIA), increased with increasing risk score, 4.5%% for the lowest risk quintile to 25.8% for the highest. AUROC=0.64 (95% CI 0.59-0.68, log rank test <0.0001). In addition, the risk of ischaemic events also increased, 9.54% lowest quintile to 35.6% for the highest AUROC 0.59(95% CI 0.55-0.63, log rank test <0.0001). Fatal ischaemic events increased from 0% lowest quintile to 15.13% highest quintile AUROC 0.74(95% CI 0.69-0.79).

Table 6.3 Validation of model in ACS cohort. Observed: Events/patients (E/P), cumulative 3 year % in ACS cohort

		Observed: Events/patients (cumulative 3 year risk %)					
Quintiles of risk	**Median Predicted risk (%)**	**All Bleeds**	**Minor bleeds**	**Major/LT Bleeds**	**Fatal bleed**	**Ischaemic Stroke/MI/SCD**	**Fatal Ischaemic**
		E/P (3 year cum risk %)	**E/P (3 year cum risk %)**	**E/P (3 year cum risk %)**	**E/P (3 year cum risk %)**	**E/P (3 year cum risk %)**	
5(highest)	27.55	36/151(40.15)	11/151 (15.44)	20/151(22.26)	5/151(5.73)	30/151(34.98)	7/151(8.70)
4	15.16	18/156 (16.73)	5/156 (4.58)	12/156(11.30)	1/156(1.01)	31/151(28.04)	15/156(13.15)
3	10.55	11/153(8.84)	7/153(6.16)	3/153(2.02)	1/153(0.74)	29/153(24.03)	9/153(7.31)
2	8.15	19/165(14.33)	10/165(7.94)	8/165(5.52)	1/165(0.98)	25/165(17.75)	9/1665(6.85)
1(lowest)	5.98	12/161 (9.37)	8/161(6.38)	4/161(3.05)	0/161	17/161(13.85)	4/161(3.85)
ROC	0.62(95%CI, 0.55-0.68)		0.51(95% CI, 0.41-0.60)	0.67(95% CI, 0.58-0.75)	0.76(95% CI, 0.60-0.91)	0.57(95% CI, 0.51-0.62)	0.57(0.49-0.64)

Area under the curve

Table 6.4 ACS model validation in Stroke/TIA cohort. Observed: Events/patients (E/P), cumulative 3 year % in ACS cohort

		Observed: Events/patients (cumulative 3 year risk %)					
Quintiles of risk	Median Predicted risk (%)	All Bleeds E/P (3 year cum risk %)	Minor bleeds E/P (3 year cum risk %)	Major/LT Bleeds E/P (3 year cum risk %)	Fatal bleed E/P (3 year cum risk %)	Ischaemic Stroke/MI/SCD E/P (3 year cum risk %)	Fatal Ischaemic
5(highest)	30.32	43/254(25.78)	24/254 (14.46)	18/254(11.24)	1/254(0.68)	55/254(35.56)	21/254(15.13)
4	17.98	33/284 (17.16)	6/284(2.66)	23/284(12.74)	4/284(2.05)	53/284(26.18)	19/284(8.67)
3	14.32	26/252(13.64)	15/252(8.12)	11/252(5.51)	0/252	53/252(26.13)	9/252(4.21)
2	11.51	16/270(7.04)	8/270(3.79)	7/270(2.92)	1/270(0.37)	31/270(14.06)	1/270(0.74)
1(lowest)	8.69	7/197 (4.57)	5/197(3.15)	2/197(1.42)	0/197	17/197(9.54)	0/197
ROC Area under the curve		0.64(95%CI, 0.59-0.68)	0.61(95% CI, 0.53-0.69)	0.65(95% CI, 0.56-0.71)	0.65(95% CI, 0.49-0.81)	0.59(95% CI, 0.55-63)	0.74(0.69-0.79)

Discussion

The bleed risk model predicts baseline risk of bleeding reasonably well in ACS, stroke and TIA patients treated with antiplatelet agents. The absolute risk of bleeding per 100 person years in the OXVASC population was 5.98% for all bleeds presenting to medical attention and 3.15% for major bleeding events. Gastrointestinal bleeding was the commonest major bleeding event as shown in previous studies**.** [30,34] The risk of bleeding in acute ischaemic events is dependent on a number of factors and this is reflected by the number of risk score models being developed. [16,17,28] Moreover, a comparison between risks of bleeding between trials is difficult as different bleeding criteria are used to define bleeding severity. [56]

In our study, male sex, prior vascular disease, chronic renal failure, previous GI bleed, prior history of peptic ulcer disease, lower body weight, history of cancer, and frailty were associated with an increased risk of bleeding. Increasing age, baseline anaemia, and use of SSRIs, were significant risk factors in univariate testing but were not significant during multivariate testing. Prior studies have identified prior vascular disease as a risk factor for bleeding. [15,23,24,28] Vascular events such as myocardial infarction may lead to hypoperfusion of gastric and or intestinal mucosa leading to ulceration, bleeding and hypotension.[15,23,24,28] Chronic renal failure is a predictor of increased mortality and bleeding events in ACS.[14-19,27,28,30-32] This may due to the effect of renal dysfunction on platelet function and the coagulation cascade but mainly for the effect of dosing in antiplatelet and antithrombotic medications. Consistent with previous studies, previous GI bleed is an important predictor of bleeding that may indicate a predisposition to develop peptic or duodenal erosions or ulcers. [16,29] Prior history of cancer was associated with gastrointestinal bleeding requiring blood transfusion in acute ischaemic stroke.[19,29] Although only identified in this study in univariate testing, an increased risk of upper GI bleeding with SSRI use has been reported.[36] The biological effects of SSRIs on activated platelets inhibits platelet aggregation by depleting the serotonin content of platelets.[36,37] Baseline anaemia is a high risk

marker for haemorrhagic complications and suggests underlying bleeding sites or haemorrhagic diathesis. [14,23,33]

A novel and important practical finding in this study is the association of bleeding and frailty. Frailty is defined as having problems in 2 or more of the 4 domains (physical function, nutrition, cognition and sensory impairments).[54] The increased risk of bleeding in association with frailty remained following multivariate adjustments. In contrast to other studies diabetes and female sex were not risk factors for bleeding. Diabetes may impair mucosal integrity leading to more severe ulceration and abnormal haemostasis through its effects on mucosal circulation [57] The relationship between bleeding and sex is conflicting in previous studies, and it appears that it is the overall prevalence of risk factors rather than sex that determines the risk of bleeding and mortality. [14-17,19,20,24-28] Women have been shown in previous models to be at a higher risk of bleeding but women are often older with reduced creatinine clearance and lower weight.

The mechanism by which bleeding impacts on adverse outcomes are likely multifactorial including the deleterious effect of anaemia, transfusion of red cells and discontinuation of antiplatelet drugs with rebound prothrombotic effects that could potentially precipitate recurrent ischaemia events in an already frail population.[58] The risk of bleeding events and risk of ischaemic events are correlated in this study, and this ischaemia/ bleed balance has been the focus of ongoing trials as it is quite possible that patients identified to be at high risk of bleeding on antiplatelet treatment, in whom it might therefore be suggested that treatment be withheld, would also be at particularly high risk of ischaemic events and thus also be the very group in which absolute benefit from antiplatelet drugs would be greatest. [3-6,42]

This study is unique as it includes patients of all ages, no exclusion criteria, and long term follow arranged face to face to predict bleeding risk in those treated with antiplatelet drugs. The predictive model from GRACE and the risk score from REPLACE 2 apply only to in hospital

bleeding and include treatment variables (invasive procedures and antithrombotics) that limits their utility for assessing bleeding risk at presentation.[16,17] Patients perceived to be at high risk of complications including those of advanced age and renal insufficiency, are often excluded from clinical trials but constitute a significant proportion of the patients treated for ACS, ischaemic stroke and TIA, thereby limiting the generalisability of results of studies from which they are excluded.[7,59,60] An important and practical finding in this study is that a third of our population is older than 80 years and significant comorbidity, thereby increasing the generalisability and clinical applicability of the score to a real world setting.

This study has a number of shortcomings. First, there was significant clinical heterogeneity between the cerebrovascular and the acute coronary group(validation cohort). Interventional strategies and dual antiplatelet therapy are used more frequently in the ACS group and a higher early risk of bleeding would be expected. However the purpose of this score was to identify potential baseline variables prior to use of these interventions among both populations treated with antiplatelet agents and the score validated well in the ACS cohort. Second, our study is limited by the inherent drawbacks of using prognostic scores in clinical practice.[61,62] The bleed score that is proposed should be independently (externally) validated to ensure that the clinical predictors are not due to chance and how likely a score it is to do in clinical practice. Third, variations in the definitions of bleeding in various trials exist making comparisons between bleeding events among trials difficult.[56] I defined bleeding severity by using the CURE trial criteria which uses a combination of clinical and laboratory data and is independently associated with an increased risk of mortality.[55] Fourth, this model predicts risk of bleeding in secondary prevention and it is likely that bleeding risk factors are different in primary prevention.

The OXVASC bleed model quantifies long term risk of bleeding in those treated with antiplatelets, which enhances the baseline risk assessment for ACS, TIA and stroke care. In addition it predicts severity of bleeding events.However, bleed risk was proportional to ischaemic risk, which might reduce the clinical utility of risk assessment.

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6.7 Appendix (Table 6.5)

Multivariate analyses for all and major bleeds in TIA/stroke and ACS cohort.

	All Bleeds		Major Bleeds	
Risk Factors	**HR (95% CI)**	**p**	**HR (95% CI)**	**p**
Age (per year)	1.01(1.003-1.02)	0.01	1.03(1.01-1.05)	<0.0001
Female sex	0.77(0.58-1.03)	0.07	0.63(0.42-0.93)	0.02
Prior vascular event[1]	1.45(1.12-1.88)	0.005	1.38(0.96-1.97)	0.07
Cancer	1.46(1.02-2.10)	0.03	1.73(1.09-2.76)	0.02
Prior GI Bleed	3.18(2.25-4.48)	<0.0001	2.03(1.21-3.41)	0.007
Prior peptic ulcer	1.53(1.03-2.28)	0.03	1.57(0.93-2.66)	0.08
Weight (kg)	0.99(0.98-1.002)	0.11	0.98(0.97-1.002)	0.10
SSRI use	1.55(0.96-2.49)	0.06	1.68(0.90-3.15)	0.10
Baseline anaemia	1.14(0.84-1.54)	0.39	0.94(0.61-1.47)	0.81
Renal failure	3.96(2.30-6.81)	<0.0001	4.32(2.13-8.78)	<0.0001
Frailty	1.65(1.21-2.24)	0.001	1.50(0.99-2.26)	0.05

[1]Prior stroke/TIA/myocardial infarction or peripheral vascular event

SSRI =selective serotonin inhibitors,PPI =proton pump inhibitors, GI bleed= gastrointestinal bleed

CHAPTER 7

The effect of age on bleeding outcomes

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7.1 Abstract

Introduction: Randomised trials have shown that antiplatelet drugs are effective for preventing recurrent ischaemic events or death in patients with acute coronary syndromes (ACS), transient ischaemic attack (TIA) and ischaemic stroke across all age groups. Against this benefit they increase the risk of major gastrointestinal and intracranial bleeds which risk might have been underestimated in trials.Our aim was to determine rates and effects of bleeding events associated with antiplatelet therapy in elderly patients (≥70 years old) in a population based study of ACS, stroke or TIA.

Methods: A bleed risk model was derived in the stroke and TIA patients ascertained throughout the OXVASC study period (April 1, 2002 to March 31st 2008) and validated in the cohort of ACS patients ascertained in OXVASC throughout the same period. The risk model was also used to determine recurrent ischaemic risk (stroke, MI, sudden cardiac death (SCD). Deciles of bleeding and ischaemic risk were calculated for each individual stratified by age <70 years and ≥70 years. Data on mortality and disability were collected.

Results:

2116 patients, 826(39%) presented with ACS, and 1290(61%) with stroke/TIA. 741(36%) were <70 years and 1302(64%) ≥70 years old. During 4421 patient-years of follow up, a total of 249(12.2%) first bleeding events occurred and severity was classified by the CURE trial criteria. The annual rate of major bleeding increased with age from (1.37%, 95% CI 1.40-2.46) at <70 years to (4.50%, 95% CI, 4.00-6.20) ≥70 year group. Predictors of all bleeding events in the OXVASC stroke/TIA population using univariate and multivariate cox regression analysis were derived and these models were used to produce deciles of bleeding risk in the whole population and their observed risk compared in the <70 years and ≥70 years cohorts. Risk of bleeding ranged from 6.77% to 22.26% from the lowest to highest decile in those ≥70 years and from 0%

to 12% in the <70 years cohort. Recurrent ischaemic event risk, a composite of ischaemic stroke, MI and sudden cardiac death, increased similarly from 22.0%-44.7% from lowest to highest decile score risk in those ≥70 years and from 8.48-23.8% in those <70 years. The proportion of bleeding events that were fatal in the stroke/TIA cohort by age were (1/31, 12.9% fatal extracranial haemorrhage at <70 years) and 5/15(33.3%) fatal intracranial haemorrhages (ICH), and 3/102(2.94%) fatal extracranial haemorrhages in ≥70 years. The proportion of events that were disabling following ICH were 3/5(60%) <70 years, and 13/15(86.6%) in ≥70 years and 0/36 <70 years versus 39/102(38.2%) in ≥70 years secondary to extracranial haemorrhages.

Conclusion:

The risk of bleeding increases with age in patients treated with antiplatelet agents. In addition to increased fatality, rates of disability following a bleeding event were increased in the elderly cohort. Future trials should aim to include elderly patients as data cannot always be extrapolated from younger trial patients in terms of absolute risks and benefits of treatment in this cohort.

7.2 Introduction

The prevalence of coronary heart disease and stroke increases with increasing age.[1,2] Antiplatelet drugs are effective for preventing recurrent ischaemic events or death in patients with acute coronary syndromes (ACS), transient ischaemic attack (TIA) and ischaemic stroke across all age groups. Against this benefit they increase the risk of major gastrointestinal or intracranial bleeds.[3,4] The relationship between bleeding and adverse clinical outcomes is well established. Bleeding is an independent predictor of poor short and long term outcomes in acute coronary syndrome and ischaemic stroke. Major in-hospital bleeding has been strongly associated with increased rates of early and late mortality, MI, repeat revascularisation procedures, recurrent stroke and severe dependency on discharge.[5-12]

The relationship between age as an important predictor of both fatal and non fatal complications following percutaneous or surgical coronary revascularisation procedures has been identified in several studies. In particular, age has been found to be associated with an increased risk of death, vascular complications, major bleeding and transfusion requirements following PCI. [13-17] Increasing age is associated with an increased risk of intracranial bleeding following use of thrombolytic and antithrombotic treatment in ACS and acute ischaemic stroke.[18-22] In addition, increased age is an independent predictor of short and long term post stroke mortality, recurrent stroke and poor functional outcome.[22-25]

Intracranial haemorrhages are considered more severe than extracranial haemorrhages, as it is assumed that extracranial haemorrhages especially of gastrointestinal origin are more likely to be reversible making residual deficits uncommon. Outcomes following intracranial and extracranial haemorrhages in ischaemic events have been reported among warfarin users,

however less is known about the effect of age and outcomes following bleeding events with antiplatelet agents.[26]

As newer and more potent antiplatelet medications are emerging, we need to consider the overall efficacy in older age so those at greatest risk of ischaemia and lowest risk of bleeding events are identified and treated. Although randomised trials are probably the most reliable way of determining the effects of treatment, they probably underestimate the true extent of bleeding in clinical practice, as those of advanced age and comorbidity are often excluded from clinical trials but constitute a significant proportion of the patients treated for ACS, ischaemic stroke and TIA, thereby limiting the generalisability of their results.[27-29] Extrapolating data from younger to older patients may appear reasonable in most cases, however, the variation in the extent of atherosclerosis, functional and cognitive status, comorbid conditions, and pharmacokinetics must be considered when weighing the risks and benefits from therapies and interventions. The mean age of trial populations in TIA/stroke is 66 years, thereby limiting applicability for those over 70 years.[30-36]

My aim was to determine the rates and effects of bleeding events associated with antiplatelet therapy in elderly patients (>70 years old) using a population based study (OXVASC) of all ACS, stroke and TIA patients.

7.3 Methods

The methods of OXVASC and details of the study population have been reported previously. Briefly, the study population comprised all 91,000 individuals, irrespective of age, registered with 63 family physicians in nine general practices in Oxfordshire, UK.[37] In the UK, almost all individuals register with a general practice, which provides their primary health care and holds a lifelong medical record. This report concerns all bleeding events following ischaemic events in

two arterial territories, coronary (acute myocardial infarction) and cerebrovascular (acute TIA and ischaemic stroke) in the study population in the first six years with follow up until 31/3/2008. Details of the methods of ascertainment have been published previously, and direct assessment has shown it to be complete. [37-39]

7.3.1 Definitions

Acute coronary events were defined as ST elevation myocardial infarction (STEMI) and non ST elevation myocardial infarction (NSTEMI) by using standard criteria.[40] All premorbid medications and medications at the time of treatment, discharge and follow up were recorded. In addition use of fibrinolytics and further interventions such as percutaneous coronary stenting or angioplasty and coronary artery bypass grafting were recorded.

All patients presenting to medical attention with TIA or stroke in the study population were ascertained from inpatient admissions, Accident and Emergency, EYE hospital, OXVASC clinic and other outpatient clinics. Standard definitions of stroke and TIA were used which have been reported previously.[38] All premorbid medications and medications at the time of treatment and discharge were recorded. In patients seen within 48 hours of their event or those seen later who were thought to be at particularly high early risk (e.g. ABCD score>4), a 30-day course of clopidogrel was given in addition to aspirin with a recommendation that it be substituted with dipyridamole 200mg twice daily after 30-days. Brain imaging was required prior to starting combination antiplatelet treatment after a minor stroke to exclude haemorrhage. Patients with recent gastrointestinal or other bleeding, gastrointestinal or urological malignancy, coagulation disorders, or other known bleeding tendency were not given A+C. Patients who were treated with warfarin premorbidly or following an acute ischaemic event were not included.

Standard clinical characteristics were routinely collected during initial assessment. A prior vascular event included a previous myocardial infarction, TIA or ischaemic stroke. Anaemia was

defined according to the World Health Organisation (WHO), baseline haemoglobin less than 13g/l in men and less than 12g/l in women.[41] Renal insufficiency was defined as any documented history of chronic renal failure (glomerular filtration rate of <30ml/minute estimated using the Cockroft and Gault formula)[42] previous gastrointestinal bleed included a history of upper or lower gastrointestinal haemorrhage, weight was measured in kilograms and frailty was defined by Strawbridge criteria as having problems in 2 or more of the 4 domains (physical function, nutrition, cognition and sensory impairments.[43]

Patients were followed up face-to-face at 30, 90 days, 6 months, 1 year and 5 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. Functional and cognitive assessments at follow up clinics included modified Rankin scale,[44] Barthel score,[45] Rivermead mobility index [46] and Folsteins mini mental exam.[47] All deaths during follow-up were recorded with cause of death. The cause of death was determined from death certificates, coroners reports and coding from the Office for National Statistics National Health Service Central Register and then categorized into

- fatal stroke, in patients who died as a direct result or complication of stroke within 6 months of the event
- myocardial infarction or sudden cardiac death
- non-vascular death
- peripheral vascular disease death, in patients who died due to an acute peripheral vascular event such as an abdominal aortic aneurysm rupture or a complication of limb ischemia.

7.3.2 Ascertainment of bleeding events

Bleeding events were defined as bleeding requiring medical attention, episodes of purpura or bruising were not included. Prospective daily searches of all bleeding events in the study population were done. In order to ensure complete ascertainment, all hospital-care and primary-care coding and blood transfusion data were searched for all bleeding events for which medical attention was sought. Patients were asked on follow up about bleeding events and general practice databases were searched for any bleeding events requiring medical attention. Each patients functional disability following a bleeding event was determined on the basis of a physicians review of the medical records following a bleeding event and at follow up clinic. Disability was categorised using a modified Rankin scale, the categories were fatal event, major disability (i.e, deficit that prevented independent living), minor disability (ie, residual deficit that did not interfere with independent living) and no disability.[44]

Bleeding events were classified by the CURE criteria. Major bleeding was defined as substantially disabling with persistent sequelae, intraocular bleeding leading to significant loss of vision or bleeding requiring transfusion of 2 or more units of blood. Major bleeding was further subclassified as life threatening if it was fatal, if it lead to a decrease in haemoglobin of 5g/dl, if it caused significant hypotension requiring intravenous inotropes or surgical intervention, if it resulted in symptomatic intracranial haemorrhage, or if it necessitated transfusion of 4 or more units of blood. Minor bleeding was defined as bleeding not requiring blood transfusion.[48] Bleeding events secondary to trauma were not included. Sites of bleeding were defined as intracranial (intracerebral, subdural or subarachnoid haemorrhage), extracranial (upper and lower gastrointestinal, genitourinary and other).

7.3.3 Statistical analyses

Values are reported as absolute numbers with percentages for categorical variables and as means with standard deviations for continuous variables. I used the χ^2 test to compare categorical variables between patients who did and those who did not develop bleeding events stratified by age <70 years and ≥70 years throughout the study period. A total of 32 baseline characteristics arranged in a dichotomous fashion were screened as candidate predictor variables at risk of bleeding as an endpoint. Each factor was tested independently in a univariate regression analysis and a multivariable regression analysis was then used to assess the statistical significance of each prognostic variable

7.4 Results

Of 2116 patients, 826(39%) presented with ACS (ACS) and 1290(61%) with acute cerebrovascular events. Of the ACS population 542(65.6%) were NSTEMI and 284(34.3%) were STEMI. In the cerebrovascular group 512(39.6%) had TIA and 778(60.3%) acute ischaemic strokes. 741(36%) were <70 years and 1302(64%) ≥70 years old.

A total of 249(12.2%) first bleeding events occurred and consisted of 26(10.4%) intracranial, 146(58.6%) gastrointestinal, 27(10.8%) epistaxis, 29(12%) genitourinary, and 21(8.4%) other bleeds. Bleeding severity was classified by the CURE trial criteria and included 116(5.7%) minor, 54(2.6%) major, 62(3.0%) life threatening, and 17(0.80%) fatal haemorrhages. A total of 133(6.5%) major (i.e. major, life threatening or fatal) bleeding events occurred, 26(17.4%) intracranial, 85(57.0%) gastrointestinal, 2(1.3%) epistaxis, 4(2.7%) genitourinary, and 16(10.7%) other.

The annual rate of both major and minor bleeding is increased with age. (Figure 7.1) and this effect remained excluding cases treated with aspirin and clopidogrel in ACS and stroke and TIA.

(Figure 7.2).In addition the annual rate of ischaemic events increased with age.(Figure 7.3)The baseline characteristics of this group stratified by age <70 years and ≥70 years showed a higher rate of prior vascular disease and vascular risk factors (hypertension and hyperlipidaemia), prior antiplatelet and antihypertensive treatment among the older cohort. In addition a higher rate of peptic ulcer disease, prior gastrointestinal bleed, cancer and lower body weight was shown in the ≥70 year olds. (Table 7.1)

I derived the predictors of all bleeding events in the OXVASC population using univariate and multivariate cox regression analysis (Table 7.2). Univariate predictors of bleeding were older age, male sex, prior vascular disease, previous gastrointestinal bleed, history of peptic ulcer disease, history of cancer, SSRI use, low body weight, baseline anaemia, chronic renal failure, and frailty. From the multivariate analysis the factors independently associated with bleeding included male sex, prior vascular disease, previous GI bleed, cancer, peptic ulcer disease, low body weight (kg), chronic renal failure and frailty.

I used these models to produce deciles of bleeding risk in the whole population and compared their observed risk in the <70 years and ≥70 years cohorts (Table 7.2 and 7.3).The risk of bleeding ranged from 6.77% to 22.26% from the lowest to highest decile in those ≥70 years and from 0% to 12% in the <70 years cohort. (Table 7.2 and 7.3) Recurrent ischaemic event risk, a composite of ischaemic stroke, MI and sudden cardiac death increased similarly from 22%-44.7% from lowest to highest decile score risk in those ≥70 years and from 8.48-23.8% in those <70 years (Table 7.2 and 7.3)

The proportion of bleeding events that were fatal in the stroke/TIA cohort by age were (1/31, 12.9% fatal extracranial haemorrhage at <70 years) and 5/15(33.3%) fatal intracranial haemorrhages (ICH), and 3/102(2.94%) fatal extracranial haemorrhages in ≥70 years. The

proportion of events that were disabling following ICH were 3/5(60%) <70 years, and 13/15(86.6%) in ≥70 years and 0/36 <70 years versus 39/102(38.2%) in ≥70 years secondary to extracranial haemorrhages.(Figure 7.4 and 7.5)

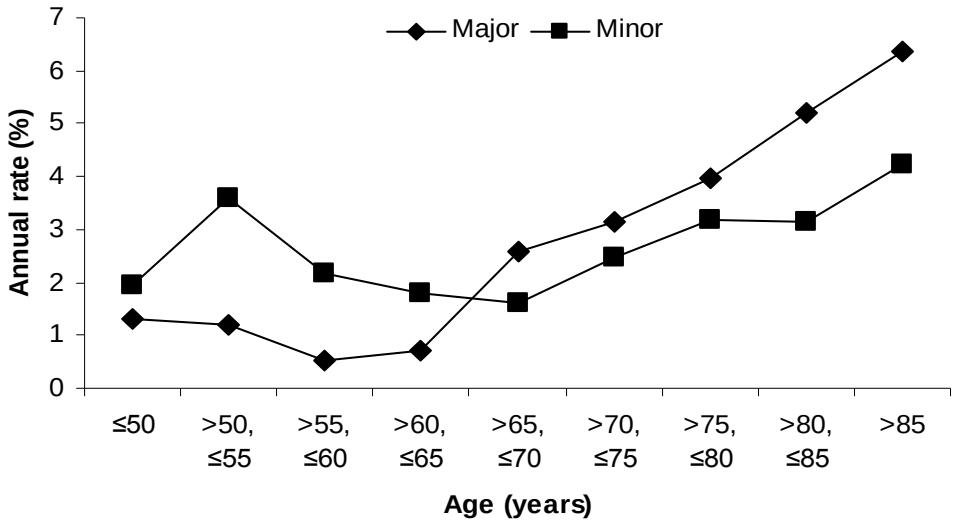


Figure 7.1 Annual rate of major and minor bleeding events by age in the Oxford Vascular Study 2002-2008

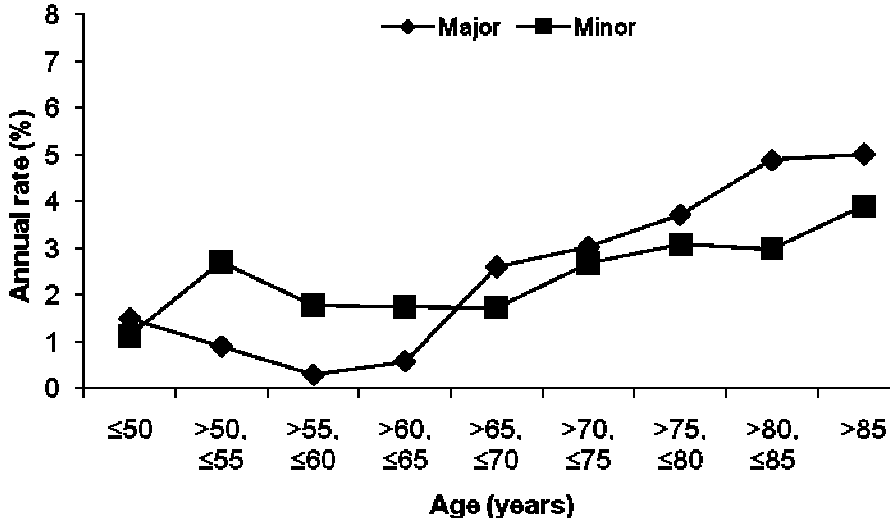


Figure 7.2 Annual rate of major and minor bleeding events excluding aspirin and clopidogrel cases in the Oxford Vascular study 2002

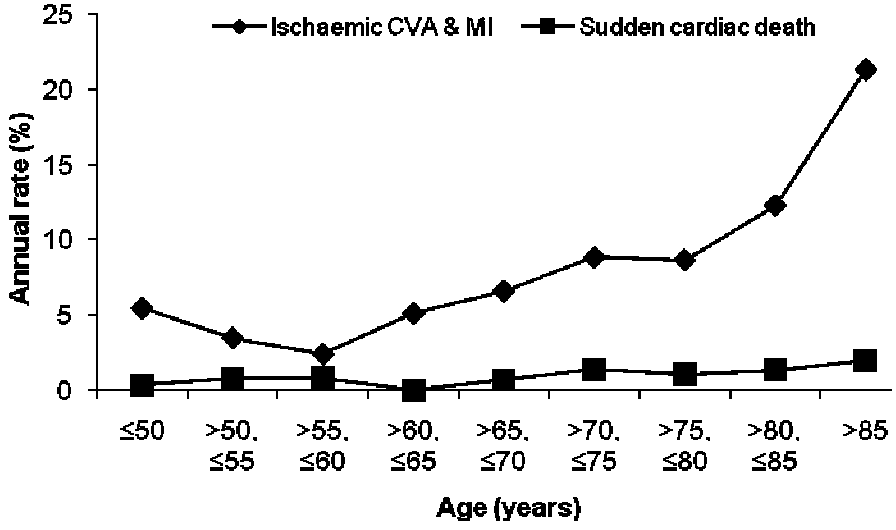


Figure 7.3 Annual rate of ischaemic events by age in the Oxford Vascular study 2002-2008

Table 7.1 Baseline characteristics of <70 year old and ≥70 years in ACS and stroke/TIA Oxford Vascular Study 2002/2008.

	<70 years n=741(36)	**≥70 years n=1302 (64)**	**p**
Female sex	244 (33)	690 (53)	<0.0001
Prior Vascular disease[1]	138 (19)	470 (36)	<0.0001
PVD	26(3.5)	89(7)	0.001
Hypertension	337 (46)	754 (58)	<0.0001
Hyperlipidaemia	221 (30)	331 (25)	0.03
Cardiac failure	37 (5)	184 (14)	<0.0001
Diabetes	118 (16)	164 (13)	0.03
Peptic ulcer disease	36(5)	116(9)	0.001
Previous Gastrointestinal bleed	29(4)	109(8)	<0.0001
Prior SSRI use	31(4)	67(5)	0.38
Chronic renal failure	14(2)	27(2)	0.87
Chronic liver disease	18(2)	21(2)	0.24
Previous history of cancer	43(6)	163(13)	<0.0001
Baseline anaemia	135(18)	226(17)	0.63
Frailty	46(7)	335(33)	<0.0001
Current smoker	227 (31)	133 (10)	<0.0001
Weight [2]	81.3	70.8	<0.001
Prior Antiplatelet	194(26)	655(50)	<0.0001
Prior statin use	169(23)	321(25)	0.36
Prior Antihypertensive use	323(44)	814(63)	<0.0001
Anti- inflammatory use	91 (12)	149 (11)	0.56

Data are n (%) are for Fishers exact test unless stated otherwise.

[1] prior vascular disease is any previous myocardial infarction, TIA or ischaemic stroke.

[2] t-test

[3] PVD peripheral vascular event

Table 7.2 Observed Events/patients, cumulative 3 year risk % (se) in <70 years

Deciles	Median Predicted risk (%)	All Bleeds n/n (%)	Major Bleeds n/n (%)	Ischaemic Stroke/MI/SCD n/n(%)
10	22.79	17/74 (27.14)	8/74 (12.05)	13/74 (23.84)
9	13.02	7/74 (12.42)	5/74 (8.60)	16/74 (23.46)
8	10.92	5/74 (8.21)	1/74 (1.52)	4/74 (6.42)
7	9.34	9/74 (13.53)	3/74 (4.37)	4/74 (6.20)
6	8.53	3/74, (4.57)	1/74 (1.35)	5/74 (8.35)
5	7.92	1/75 (1.89)	1/75 (1.89)	7/75 (11.38)
4	7.43	4/74 (6.77)	1/74 (1.35)	5/74 (8.32)
3	6.93	0/74 (0)	0/74, (0)	7/74, (12.34)
2	6.30	4/74 (7.60)	0/74 (0)	13/74 (21.40)
1	5.46	5/74 (9.01)	0/74 (0)	6/74 (8.48)
ROC				
Area under the curve		0.67	0.80	0.54

Table 7.3 Observed: Events/patients, cumulative 3 year risk % (se) in ≥70 years

Deciles	Median Predicted risk (%)	All Bleeds n/n (%)	Major Bleeds n/n (%)	Ischaemic Stroke/MI/SCD n/n (%)
10	41.15	32/130 (44.28)	17/130 (22.26)	31/130 (44.72)
9	27.13	25/130 (26.78)	13/130 (12.60)	32/130 (38.76)
8	21.93	19/130 (25.05)	13/130 (18.40)	23/130 (23.98)
7	17.84	17/130 (20.75)	14/130 (18.30)	27/130 (29.97)
6	15.61	12/131 (12.67)	10/131 (10.06)	19/131 (22.56)
5	13.64	12/130 (13.49)	8/130 (9.10)	24/130 (25.32)
4	12.08	14/131 (13.71)	8/131 (7.83)	36/131 (36.22)
3	10.69	11/130 (11.33)	5/130 (5.00)	27/130 (28.90)
2	9.67	13/130 (12.90)	7/130 (6.57)	19/130 (20.55)
1	8.43	11/130 (10.84)	7/130 (6.77)	23/130 (21.99
ROC Area under the curve		0.61	0.60	0.53

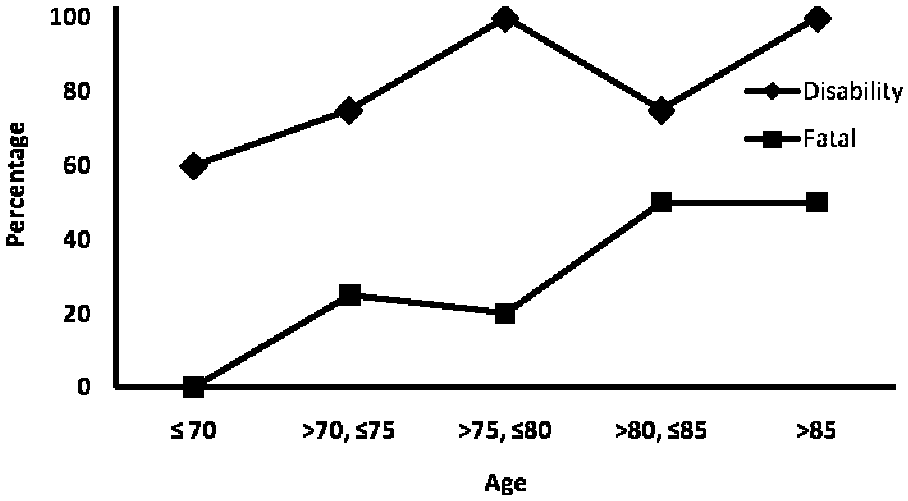


Figure 7.4 Proportion of ICH bleeds that are disabling or fatal by age among stroke and TIA cohort of the Oxford Vascular study 2002-2008

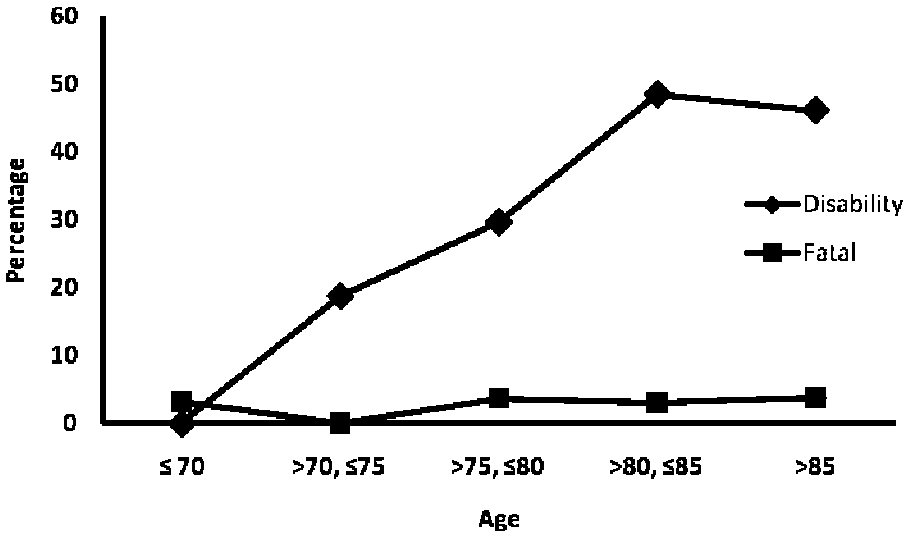


Figure 7.5 Proportion of extracranial bleeds that are disabling or fatal by age among stroke and TIA cohort of the Oxford Vascular study 2002-2008

Discussion

In this study the risk of all or major bleeding events increases with age in patients treated with antiplatelet agents. Risk factors for gastrointestinal bleeding in community dwelling older persons were advanced age, male sex, premorbid cardiovascular disease, use of multiple medications and prior disability.[49,50] In the ACS and stroke/TIA cohort of this study, multivariate analysis identified age, prior vascular disease, cancer, previous gastrointestinal bleed, previous peptic ulcer disease, low body weight, SSRI use, baseline anaemia, renal failure and frailty as independent predictors for bleeding events in those treated with antiplatelet agents.

The three fold increased risk of major bleeding in those ≥70 years observed in this study is clinically plausible as the presence of local vascular changes or more advanced vascular disease has been postulated as a potential explanation for the increased incidence of bleeding complications in elderly patients. The baseline differences among <70 and ≥70 year cohorts in this study showed a higher rate of prior vascular events and vascular risk factors, compared with younger patients.The observed bleeding and ischaemic event risks were correlated in both cohorts as patients identified to be at high risk of bleeding on antiplatelet treatment, were also at particularly high risk of ischaemic events.[51-55]

I found higher rates of fatality and disability following bleeding events among the older cohort. When the type of bleeding event was considered, a greater rate of major disability was seen following ICH and extracranial haemorrhages in particular gastrointestinal haemorrhage. Intracranial haemorrhages are considered more severe than extracranial haemorrhages, as it is assumed that extracranial haemorrhages especially of gastrointestinal origin are more likely to be reversible making residual deficits uncommon.The mechanism by which a bleeding event impacts on functional independence are likely multifactorial including the deleterious effect of anaemia, transfusion of red cells and discontinuation of antiplatelet drugs that could potentially

precipitate recurrent ischaemic events in an already frail population.[56] Aging itself, imparts a number of physiological changes to the gastrointestinal tract. The increased prevalence of Helicobacter pylori and a number of age related physiological changes to the gastrointestinal tract lead to a higher rate of complications and peptic ulcer disease related mortality.[57] Extracranial bleeding events in younger patients resulted in no disability, however, to ensure that disability was not just attributed to ageing itself , a detailed review of all cases identified decline in mobility and cognition, reduced physiological reserve and recurrent ischaemic events as the underlying reasons for subsequent disability following a bleeding event.

This study is unique as it is a prospective population based study that includes patients of all ages, with limited exclusion criteria, long term face to face follow up, and reliable ascertainment of all bleeding events through GP coding, inpatient admissions, hospital coding and blood transfusion data. Patients perceived to be at high risk of complications including those of advanced age and renal insufficiency, are often excluded from clinical trials but constitute a significant proportion of the patients treated for ACS, ischaemic stroke and TIA, thereby limiting the generalisability of results of studies from which they are excluded.[27-29] I also included outcome measures such as disability using well defined scales.[44-47]

However, this study has a number of shortcomings. First, there is significant clinical heterogeneity between the stroke/TIA and the ACS group when developing a multivariate model of bleeding risk. Interventional strategies and dual antiplatelet therapy are used more frequently in the ACS group and a higher early risk of bleeding would be expected. However, the increased risk of bleeding with age remains when bleeds occuring on dual antiplatlet treatment (A+C) were excluded from the analysis. Second, an increased disability secondary to bleeding events, in particular following gastrointestinal bleeds could be caused by discontinuation of antiplatelet treatment. Bleeding may induce a prothrombotic state by causing platelet and coagulation activation, and this coupled with discontinuation of antiplatelet treatment is a likely cause of

recurrent ischaemic events. However, I am able to report the relationship between bleeding and recurrent vascular events as a cause of disability in our cases and discontinuation of antiplatelets was not a factor. Fourth, variations in the definitions of bleeding in various trials exist making comparisons between bleeding events among trials difficult.[27,28] I defined bleeding severity by using the CURE trial criteria which uses a combination of clinical and laboratory data rather than transfusion data alone and is independently associated with an increased risk of mortality.[48]

A difficult balance comes into play when treating elderly patients with antiplatelet agents. Aging increases the risk of adverse outcomes, most notably bleeding, but also increases ischaemic event risk for which treatment would be beneficial. However, rather than being excluded from randomised controlled trials, the elderly should be the focus of more intensive research so that absolute benefits of treatment can be assessed. Population data on the outcomes of haemorrhages associated with antiplatelet use among the older population are vital to improving how a clinician can decide on the overall benefit of such treatments. Modifiable measures such as maintaining anticoagulation intensity within therapeutic range can but will not completely remove the risk of bleeding associated with warfarin [26] Proton pump inhibitor use and screening and treatment of helicobacter pylori are potential modifiable measures to reduce gastrointestinal bleeds associated with antiplatelet use.[58,59]

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7.7 Appendix

Table 7.4 Aetiology of disability following extracranial bleeding events

Reasons	**n**
CCF/pulmonary oedema	6
Impairment in mobility and cognition	12
Recurrent MI within 30 days	2
Symptomatic anaemia- reduced mobility and falls	8
Recurrent stroke within 30 days	1
Introcular blindness	2
Unknown	2
Total	33

Table 7.5 Aetiology of gastrointestinal bleeding events

Upper Gastrointestinal bleeding n=161	**n**	**%**
Oesphago/gastro/duodenal ulcers	34	21
Gastritis/oesophagitis	48	30
Upper GI tumour	4	2.5
Mallory Weiss lesion	1	0.6
Other	15	9
Unknown aetiology	42	26
Lower gastrointestinal bleeding n=13		
Lower GI tumour	3	23
Diverticular disease	4	30
Angiodysplasia	2	15
Colonic Polyp	2	15
Unknown	2	15

CHAPTER 8

Long-Term Prognosis of TIA and Stroke

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8.1 Abstract

Background: The early risk of recurrence following TIA and minor stroke is high. Early use of existing secondary preventative therapies has been shown to reduce this risk. However, long - term prognosis after TIA and minor stroke within the modern era is less certain. Data on the time course of recurrent stroke risk could help to target secondary prevention.

Methods: I prospectively ascertained and assessed all incident and recurrent cerebrovascular events in a population based study in Oxfordshire, UK, from April 2002 to March 2010 (Oxford Vascular Study). The NIHSS (National Institutes of Health Stroke Scale) was performed at time of case ascertainment. The exact timing of all recurrent strokes, cardiac events and deaths up to July 2010 were recorded. Patients received best medical treatment and secondary prevention according to current guidelines.

Results: Of 2035 consecutive patients with cerebrovascular events, 1928 were ischaemic (832 TIA, 778 minor ischaemic stroke, NIHSS 0-5, 318 major ischaemic stroke NIHSS >5). There were 114 recurrent strokes at 7 days (6.0%, 95% CI 5.0-7.0), 197 at 90 days (10.7%, 9.3-12.1), 251 at 1 year (13.0%, 12.4-15.6) and 328 at 8 years (24.6%, 21.5-27.7). The risk of recurrent stroke after TIA was about double that after minor stroke at 7-days (8.9% vs 4.1%, OR 2.02, 95% CI 1.25-.3.26, p=0.005), but the recurrence risk after minor stroke was higher at 8-90 days (4.2% vs 2.1%, p=0.04). After major stroke, the pattern of risk was similar to minor stroke, 2.7% (0.7-4.7) at 7 days and 7.6% (4.1-11.1) at 90 days. In all patients, the 8 year risk of a cardiac event was half the risk of a recurrent stroke (10.4% (6.7-14.2) vs 24.6% (21.5-27.7)). Secondary prevention measures at one year were similar in patients with TIA and minor stroke, with 90% on antiplatelets or anticoagulants, 77% on statins and 74% on one or more blood pressure lowering drug.

Conclusions: Stroke recurrence risk after minor stroke is delayed compared with TIA, and remains high during the late phase despite current best medical treatment. There is a major

unmet need for more effective prevention of recurrence in the late phase after minor ischaemic stroke. The long-term cardiac risk after TIA and ischaemic stroke is low.

8.2 Introduction

The high early risk of stroke after TIA has been established in population based and hospital-based studies.[1-7] In a recent systematic review including 18 independent cohorts, which reported stroke risk in 10 126 TIA patients, the pooled stroke risk was 5.2% (95% CI 3.9-6.5) at seven days.[8] Furthermore, the very early stroke risk after TIA has been shown to be particularly high, with 42% of all strokes during the 30 days after a first TIA occurring within the first 24 hours.[9] Population based studies have shown the recurrence risk depends on the clinical characteristics, vascular territory and aetiology of the event.[10-14] In addition, urgent intervention after TIA has been shown to be highly effective in reducing the early recurrent stroke risk.[15-17] However, whilst much is known about prognosis and predictors of risk early after TIA, there is less published data on the risk after minor stroke, particularly in the medium and long-term.[18] Furthermore, whether there are differences between TIA and minor stroke in the time course of recurrent stroke risk is not known. The improvements in secondary prevention measures may also reduce cardiac risk as well as stroke risk. A metanalysis has shown the risk of MI after TIA or stroke to be approximately 2% per year, however, whether there has been any reduction in risk in light of improvements in secondary prevention is not known.[19,20] Data on any differences in the timing of recurrent events could help to target secondary prevention. The aim of our study was to determine the time course of recurrent stroke risk and cardiovascular risk after TIA and ischaemic stroke beyond the acute phase and whether the quality of secondary prevention is a factor determining late recurrence. We addressed this issue in a prospective population based study of all incident and recurrent TIA and stroke in Oxfordshire, UK (Oxford Vascular Study), from the 1st April 2002 to 31st March 2010 with follow-up until 31st July 2010.

8.3 Methods

The Oxford Vascular Study (OXVASC) is a population based study of all stroke, TIA and acute cardiac events in 91,105 individuals of all ages registered with 63 general practitioners in Oxfordshire, UK. OXVASC is approved by our local ethics committee. The study methods have been described elsewhere.[21,22]

8.3.1 Case Ascertainment

Briefly, multiple overlapping methods of "hot" and "cold" pursuit were used to achieve near complete ascertainment of all individuals presenting to medical attention with TIA or stroke. [21-23] These include, a daily (weekdays only), urgent open-access "TIA clinic" to which participating general practitioners (GPs) and the local accident and emergency department (A&E) refer all individuals with suspected TIA or stroke whom they would not normally admit to hospital, daily searches of admissions to the medical, stroke, neurology and other relevant wards, daily searches of the local A&E attendance register, monthly computerized searches of GP diagnostic coding and hospital discharge codes, monthly searches of all cranial and carotid imaging studies performed in local hospitals and monthly searches of all death certificates and coroners reports.

All patients were consented and seen by study physicians as soon as possible after their initial presentation. Baseline characteristics were recorded in all patients and assessments were made for severity of event (using National institute of health stroke scale NIHSS[24]) and clinical features. Events were classified as minor stroke if there was a focal neurological deficit lasting greater than 24 hours and an NIHSS score ≤5 at time of assessment by a study physician. A cut off of NIHSS score ≤5 was chosen as this included the majority (96%) of patients with stroke seen in the outpatient setting[15]. Patients ascertained with a stroke but who had a preceding TIA that they had not brought to medical attention were included.

Event characteristics and risk factors were recorded and all patients underwent brain imaging, with CT or MRI as appropriate. All cases were subsequently reviewed by the study senior neurologist (PMR) and classified as TIA or stroke or other condition using standard definitions.[21,22] All patients with recurrent events were reassessed by a study physician and then case reviewed by PMR. I excluded patients in whom it was impossible to obtain a definite history of TIA or stroke because they were aphasic, confused, or unconscious. Patients with primary intracerebral haemorrhage and those who presented as a stroke death were excluded. All patients received best medical treatment and secondary prevention according to current guidelines.

Patients were followed up face-to-face at 30, 90 days, 6 months, 1 year and 5 years by a study nurse or physician. For patients who had moved out of the study area, telephone follow-up was performed. Follow-up was conducted via a carer if the patient was unable to participate, for example due to dementia. The timing of all recurrent strokes and cardiac events (including ST elevation myocardial infarction (STEMI), non-ST elevation myocardial infarction (NSTEMI) and sudden cardiac deaths) up to 8 years after the first event was recorded. All recurrent strokes and cardiac events that presented to medical attention would also be identified acutely by ongoing daily case-ascertainment within OXVASC. Aetiological classification of cerebrovascular events was performed according to the TOAST classification once investigations were complete. All deaths during follow-up were recorded with cause of death. The cause of death was determined from death certificates, coroners reports and coding from the Office for National Statistics National Health Service Central Register and then categorized into

- fatal stroke, in patients who died as a direct result or complication of stroke within 6 months of the event
- myocardial infarction or sudden cardiac death

- non-vascular death
- peripheral vascular disease death, in patients who died due to an acute peripheral vascular event such as an abdominal aortic aneurysm rupture or a complication of limb ischemia.

8.3.2 Analysis

I restricted analysis to the risk of recurrent events after the first TIA or ischaemic stroke in the study period (index event). The risks of recurrent ischaemic stroke, cardiac events and deaths within 8 years of TIA and ischaemic stroke were censored for deaths and follow-up until 31st July 2010. Recurrent stroke risks were analysed from the time of index event and from time of first seeking seek medical attention. A recurrent stroke was defined as a new or persistent neurological symptom in a patient in whom the initial symptoms were stable or had already substantially or fully recovered. In patients who had multiple recurrent cerebrovascular events the end point was classified as the first recurrence following the index event. Kaplan-Meier survival analysis was used to calculate recurrence risks.

8.4 Results

Of 2035 consecutive, first cerebrovascular events within the study period from 1st April 2002 to 31st March 2010, there were 1928 patients with ischaemic events, 100 with primary intracerebral haemorrhage and 7 acute stroke deaths of uncertain cause. Complete baseline data were available and face to face or telephone follow-up data were available on 1811/1928 first ischaemic events. (106 refused participation in the follow-up study and 11 moved out of area and were not available for follow up, however death certificates and Hospital Episode Statisitics(HES) were available for all patients).The mean (range) age at first TIA was 71.8 (24-99) years and at first stroke 75.2 (26-99) years (Table 8.1). 39.6% of cases (763/1928) were

aged over 80 years. Patients with minor ischaemic stroke were more likely to be male (p<0.01). Increasing event severity was associated with age (p<0.0001), atrial fibrillation (p<0.0001), hypertension (p=0.002), peripheral vascular disease (p=0.004), previous stroke (p=0.004), previous anti-platelet (p=0.001) and anti-hypertensive (p=0.03) use.

There were 328 recurrent strokes within 8 years of follow-up. Table 8.2 shows the stroke risks up to 8 years after TIA, minor stroke and major ischaemic stroke from time of event onset and time of first seeking medical attention. Of the 328 cases of recurrent stroke at 8 years, 114 occurred within 7 days (35%), the majority of these (74, 65%) following a TIA. Of the 197 recurrent events within 90 days, 107 (54%) were preceded by a TIA, 72 (37%) by minor stroke and 18 (9.1%) by major ischaemic stroke. The 90-day stroke risks from event onset were 12.9% (95% CI 10.5-15.3) after TIA, 9.4% (7.2-11.6) after minor stroke and 7.6% (4.1-11.1) after major stroke.

By 8 years from event onset, the recurrent stroke risks after TIA, minor and major stroke were similar (22.5% vs 26.6% vs 29.7%, p=0.77, Figure 8.1a). However, the timing of recurrence risk varied according to initial event type and time of seeking medical attention. Up to 7 days after event onset, stroke risk following TIA was double that after minor (8.9%, 74/832 vs 4.1% 21/778, OR 2.28, 95% CI 1.49-.3.48, p<0.001). 72 patients (54 TIA, 15 minor and 3 major strokes) did not seek medical attention at the time of their event but sought medical attention after the recurrent event. When cases that did not seek medical attention at the time of the first event were excluded, the risks of recurrence after TIA and minor stroke were more similar up to 7 days (5.1%, 40/778 vs 3.5%, 27/763, p=0.14, Figure 8.1b), however, between 8-90 days the risk after minor stroke remained high, (4.2%, 31/736 vs 2.2%, 16/738, OR 1.94, 1.06-3.55, p=0.04, Figure 8.1b). The higher recurrent stroke risk after minor stroke persisted beyond 90 days up to 8 years from seeking medical attention (18.8% (13.7-23.9) vs 10.7% (6.2-15.2), p<0.0001, Figures 8.2 and 8.3).

The median time to recurrent stroke up to 8 years after event onset was 8.6 days for TIA vs 105.9 days for minor stroke (p<0.0001). The number of recurrences after major stroke were small (35/318), however the median time to recurrent event was similarly delayed when compared to TIA (75.1 days vs 8.6 days, Table 8.3).

Table 8.4 shows the cardiac risks up to 8 years after TIA and ischaemic stroke. When all cardiac events (STEMI, NSTEMI and sudden cardiac death) were combined, the 8 year risk of a cardiac outcome was half the risk of a recurrent stroke (10.4% (6.7-14.1) vs 24.6% (21.5-27.7)). The cardiac risk after TIA was just as high as the risk after minor stroke (12% (5.3-18.7) vs 9.3 (6.4-12.2) p=0.73, Figure 8.4), with most of the risk accounted for by NSTEMI. After all event types, the 8 year risks of STEMI and sudden cardiac death were low (1.5% and 2.1% respectively). The cardiac risk after major stroke was limited to the first year (Figure 8.4).

There were 667 deaths during the study period (Table 8.5). Mortality was highest after major stroke within the first 90 days (46.9%, 41.4-52.4). Time to death was related to initial event severity, with 87% (68/78) of all deaths within 7 days occurring after major stroke. Mortality risks after TIA and minor stroke were similar up to 7 days (0.5% vs 0.8%, p=0.54), however, between 8 to 90 days, mortality risk after minor stroke was 3 times the risk after TIA (5.8% vs 1.8%, OR 3.36, 95% CI 1.87- 6.0, p<0.001). By 8 years, the mortality risk after minor stroke remained higher than the risk after TIA but the difference was less pronounced (48.5% vs 37.8%, p<0.001, Figure 8.5). The 8 year risk of fatal stroke was six times the risk of fatal MI or sudden cardiac death (13.3 % vs 2.2%, Figure 8.6). Beyond 2 years, the risk of non-vascular death remained high and continued to rise, whilst risk of fatal stroke fell. The risk of death due to peripheral vascular disease remained low throughout the study period.

Secondary prevention measures and blood pressures were similar in patients with TIA and minor stroke at 1 month, although patients with TIA were more likely to be taking an antiplatelet or anticoagulant (p=0.02) (Table 8.6). However, by 1 year, there were no differences in secondary prevention measures between patients with TIA and minor stroke. Patients with major stroke were less likely than patients with TIA and minor stroke to be on an antiplatelet or anticoagulant at 1 month (86% vs 93%, p=0.001) and less likely to be taking 2 or more antihypertensives at 1 year (39% vs 51%, p=0.03) although there was no difference in blood pressure when compared to patients with TIA and minor stroke.

The recurrent stroke risks pre and post 90 days from seeking medical attention are shown in Table 8.7. Following minor stroke, the risk of recurrent stroke post 90 days was more than double the pre-90 day risk (18.8% vs 7.7%). The aetiology of recurrent strokes pre and post 90 days were also different. Table 8.8 shows the aetiology of all first and recurrent ischaemic events seeking medical attention. Recurrent events within 90 days were generally of the same aetiology as the initial event. However, beyond 90 days, there were a higher proportion of recurrent events of different aetiology to the initial event (Table 8.9). Of 127 recurrent strokes post 90 days, aetiology could be determined in 55% (70/127). Of these, 77% (54/70) were of cardioembolic aetiology, despite constituting only 21% (390/1856) of all first events.

8.5 Discussion

In this study, the recurrent stroke risks after TIA and minor stroke remained similar up to 90 days, however beyond 90 days, recurrence risk after minor stroke remained high. The time course of recurrent stroke risk differed according to initial event type. Recurrence after minor stroke occurred later than after TIA. The 90 day recurrent event rates in our study are similar to those in a hospital based cohort of TIA and minor stroke which found the risk after TIA to be 19% and after minor stroke to be 14.7%.[25]

Clinical factors (age, BP, duration of event and diabetes), vascular territory, aetiology and appearances on brain imaging have been associated with recurrence risk after TIA and minor stroke.[13,26] Similar factors may affect timing to recurrent event. There may also be additional reasons accounting for the difference in timing to recurrent events. Firstly, differences in patient delays to presentation after TIA and minor stroke. A longer delay to seeking medical attention after the presenting event may delay access to secondary prevention which could result in earlier recurrent events. However, in OXVASC, similar proportions of TIA and minor stroke patients sought medical attention within 24 hours of the event.[27] Secondly, different treatment settings for TIA and minor stroke could lead to differing access to secondary prevention. If patients with TIA were generally seen in the outpatient setting with secondary prevention being started after the clinic appointment by their GP and patients with minor stroke were seen as inpatients, then a higher earlier recurrence rate after TIA may be expected. However, in our study 97% of patients with minor stroke were seen in the urgent outpatient setting and therefore had similar access to preventative treatments to patients with TIA. Our cases also included patients who received the intervention of the EXPRESS clinic in which secondary prevention was initiated at the time of clinic assessment. Therefore it is unlikely that treatment setting has affected the time to recurrence. Thirdly, the intensity of secondary prevention may have varied between the TIA and minor stroke cases causing a difference in the timing of recurrent events.

However in OXVASC, the rates of prescription of aspirin, statin and anti-hypertensive medication after presentation to medical attention were similar in TIA and minor stroke.[15] Furthermore, regular face-to-face or telephone follow-up ensured high rates of compliance. Poor compliance and prescribing is common after TIA and stroke therefore it is usually difficult to know how effective secondary prevention actually is. [28] The high delayed recurrence risk after minor stroke in our study highlights the need for better secondary prevention in the subacute and late phase after minor stroke.

Our study had some potential limitations. Firstly, the risk of stroke in the acute phase may not be completely precise because an unknown proportion of patients with minor stroke will never seek medical attention. Secondly, I may have underestimated the risk of TIA and minor stroke as some patients with a major stroke with preceding events may not have been identified if it was impossible to obtain a history of events because they were aphasic, confused or unconscious. Thirdly, our study included patients recruited into the EXPRESS study,[15] Phase 2 of which involved more urgent investigation and treatment, which will have reduced the absolute risk of events and possibly influenced the timing of recurrent events. Stroke prevention efforts increased over the period of the study due to EXPRESS which may have reduced the number of recurrent events in the early phase but have not prevented events in the late phase. The high later risk may be secondary to undetected cardioembolism at the time of assessment after TIA and minor stroke. Although it has previously been shown that it is possible to reduce the high early risk of stroke by early initiation of secondary prevention after TIA and minor stroke, I have shown there is a high later stroke risk after minor stroke which has not been reduced by current secondary prevention methods. Since the long-term cardiac risk is low, it may be that another, non-atheromatous mechanism is responsible for later recurrent stroke which is not being addressed by current secondary prevention. The high number of cardioembolic recurrent strokes identified post 90-days in our study which occurred after events of a different aetiology suggests cardioembolism as a potential risk factor with current sub-optimal management. It remains, that

in spite of the known increased stroke risk associated with atrial fibrillation and the benefit of oral anticoagulation in reducing stroke risk, AF patients are not on adequate treatment. This can result from a variety of reasons such as patients preferences, reduced awareness of stroke risk among physicians and difficulties detecting AF. The ongoing focus in the development of non invasive and invasive devices with longer term monitoring should lead to improved detection of occult atrial fibrillation thereby reducing this risk further.[29,30]

The potential benefits of long term secondary prevention in reduction of non fatal vascular deaths looks promising. Daily aspirin reduced the incidence of colorectal cancers and more importantly, deaths due to several common cancers.[31,32] The role of aspirin and its reduction in the risks of infection by inhibition of thromboxane dependent platelet activation continues to be explored.[33]

The cumulative risk of long term stroke in the South London Registry (up to 25% at 10 years) and up to 30% in 5 years in OCSP highlight the substantial risk of long term stroke recurrences.[34,35] Although, differing rates of risk may be explained by different definitions of stroke recurrence, a comparison between our data on stroke recurrence would be helpful in defining prognosis for TIA and stroke patients and highlighting the long term commitment needed to control risk factors to protect patients from further recurrence. Furthermore, I aim to review how disabling long term recurrent strokes are as an outcome measure and whether increased use of secondary prevention has any effect in reducing disability related to stroke recurrences.

In summary, timing to recurrent events varies according to event type. Recurrent stroke occurs early after TIA and is delayed after minor stroke. There is a major unmet need for more effective prevention of recurrence in the late phase after minor ischaemic stroke.

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Table 8.1. Baseline characteristics, vascular risk factors and premorbid medication of patients presenting with TIA or ischaemic stroke, n=1928

	TIA (n=832)	Minor ischaemic stroke (n=778)	Major ischaemic stroke (n=318)	p-value
Age (mean (SD))	71.8 (13.4)	73.5 (12.7)	79.5 (10.8)	<0.0001
Male Sex	381 (45.8)	395 (50.8)	130 (40.9)	0.008
Hypertension	438 (52.6)	445 (57.2)	203 (63.8)	0.002
Diabetes	100 (12.0)	98 (12.6)	32 (10.1)	0.511
Angina or myocardial infarction	153 (18.4)	157 (20.2)	70 (22.0)	0.348
Peripheral vascular disease	40 (4.8)	59 (7.6)	31 (9.7)	0.005
Previously diagnosed atrial fibrillation	129 (15.5)	131 (16.8)	93 (29.2)	<0.0001
Current Smoker	102 (12.3)	108 (13.9)	38 (11.9)	0.554
Previous TIA	106 (12.7)	57 (7.3)	26 (8.2)	0.001
Previous stroke	83 (10.0)	106 (13.6)	53 (16.7)	0.004
Prior antiplatelet	292 (35.1)	319 (41.0)	149 (46.9)	0.001
Prior statin	190 (22.8)	174 (22.4)	69 (21.7)	0.922
Prior antihypertensive	450 (54.1)	442 (56.8)	200 (62.9)	0.026

Table 8.2: Recurrent strokes (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke

		7 days		90 days		1 year		5 years		8 years	
	Patients	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk	Strokes	% risk
All TIA	832	74	8.9 (6.9 - 10.9)	107	12.9 (10.5 - 15.3)	123	14.9 (12.5 - 17.3)	145	19.7 (16.6 – 22.8)	148	22.5 (18.0 - 27)
TIA seeking medical attention	778	40	5.1 (3.5 – 6.7)	56	7.2 (5.4 -9.0)	69	9.0 (7.0 – 11.0)	91	14.1 (11.2 – 17.0)	94	17.1 (12.6 – 21.6)
Minor stroke	779	32	4.1 (2.7 - 5.5)	72	9.4 (7.2 - 11.6)	103	13.8 (11.3 – 16.3)	141	23.8 (19.9 – 27.7)	146	26.6 (21.7 – 31.5)
Minor stroke seeking medical attention	764	27	3.5 (2.1 – 4.9)	59	7.7 (5.7 – 9.7)	89	15.4 (12.7 – 18.1)	127	22.3 (18.4 – 26.2)	131	25.1 (20.0 – 30.2)
Major stroke	317	8	2.7 (0.7 - 4.7)	18	7.6 (4.1 – 11.1)	25	12.3 (7.6 – 17.0)	34	25.6 (16.2 - 35)	34	29.7 (17.9 – 41.5)
Major stroke seeking medical attention	314	6	2.1 (0.5 – 3.7)	15	6.5 (3.2 – 9.8)	22	11.2 (6.5 – 15.9)	31	24.6 (15.2 - 34)	31	28.8 (16.8 – 40.8)
All patients	1928	114	6.0 (5.0 – 7.0)	197	10.7 (9.3 - 12.1)	251	14.0 (12.4 – 15.6)	320	21.7 (19.3 – 24.1)	328	24.6 (21.5 – 27.7)
All seeking medical attention	1856	73	4.0 (3.0 – 5.0)	129	7.3 (6.1 – 8.5)	180	10.5 (9.1 – 11.9)	249	18.5 (16.1 – 20.9)	256	21.5 (18.4 – 24.6)

Table 8.3. Median time to recurrent event up to 8 years from event onset (n=1928) and time of seeking medical attention (n=1856) in the OXVASC cohort (72 cases did not seek medical attention at the time of the event but presented after a recurrent stroke)

	Recurrent stroke		Time to recurrence	
	From event onset	From time of seeking medical attention	From event onset (days, (IQR))	From time of seeking medical attention (days, (IQR))
TIA, n=832	148	90	8.64 (1.25-162.5)	33.8 (1.94-453.2)
Minor stroke, n=778	145	130	105.9 (8.78-447.4)	133.2 (9.18-605.3)
Major stroke, n=318	35	32	75.1 (8.10-672.6)	103.1 (8.22-710.8)

Table 8.4: Risk of cardiac events (% risk, 95% CI) with median time to event up to 8 years after TIA and ischaemic stroke, n=1928

	Patients	NSTEMI	8 year % risk	STEMI	8 year % risk	Sudden cardiac death	8 year % risk	All cardiac events	8 year % risk	Median time to cardiac event (days)
TIA	832	25	8.2 (1.5 – 14.9)	7	1.7 (0.1 – 3.3)	11	2.3 (0.9 – 3.7)	43	12 (5.3 – 18.7)	691
Minor stroke	778	30	6.3 (3.8 – 8.8)	8	1.4 (0.4 – 2.4)	7	1.7 (0.3 – 3.1)	45	9.3 (6.4 – 12.2)	418
Major stroke	318	2	1.5 (0 – 3.5)	1	0.4 (0 – 1.2)	5	2.8 (0.4 – 5.2)	8	4.6 (1.5 – 7.7)	691
All patients	1928	57	7.0 (3.3 – 10.7)	16	1.5 (0.5– 2.5)	23	2.1 (1.1 – 3.1)	96	10.4 (6.7 – 14.1)	478

Table 8.5: Mortality (% risk, 95% CI) up to 8 years after TIA and ischaemic stroke, n=1928.

		7 days		90 days		1 year		5 years		8 years	
	Patients	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk	Deaths	% risk
TIA	832	4	0.5 (0.1 – 0.9)	19	2.3 (1.3 – 3.3)	49	6.0 (4.4 - 7.6)	160	26.3 (22.6 - 30)	179	37.8 (31.7 – 43.9)
Minor stroke	778	6	0.8 (0.2 - 1.4)	51	9.7 (7.5 – 11.9)	105	13.7 (11.3 – 16.1)	227	37.8 (33.7 – 41.9)	249	48.5 (42.0 – 55.0)
Major stroke	318	68	21.4 (16.9 -25.9.)	149	46.9 (41.4 – 52.4)	192	60.8 (55.3 – 66.3)	232	78.7 (73.6– 83.8)	239	84.3 (79.0 – 89.6)
All patients	1928	78	4.0 (3.2 – 4.8)	219	11.4 (10 - 12.8)	346	18.1 (16.3 – 19.9)	619	39.8 (37.3 – 42.3)	667	50.1 (46.2 – 54.0)

Table 8.6: Secondary prevention measures assessed at 1 month and 1 year follow-up in all patients (n = 1769 at 1 month, n=1474 at 1 year)*

		TIA n (%)	Minor stroke n (%)	Major stroke n (%)	p
On an antiplatelet or anticoagulant	at 1 month[a]	773 (94.0)	676 (91.0)	160 (85.6)	0.001
	at 1 year[b]	644 (90.8)	551 (88.9)	93 (85.3)	0.15
On a statin	at 1 month[a]	595 (72.4)	543 (73.1)	129 (69.0)	0.53
	at 1 year[b]	539 (76.0)	481 (77.6)	86 (78.9)	0.71
On one or more antihypertensive	at 1 month[a]	587 (71.5)	557 (75.0)	126 (67.7)	0.09
	at 1 year[b]	514 (72.7)	476 (76.9)	79 (72.5)	0.19
On two or more antihypertensives	at 1 month[a]	587 (71.5)	557 (75.0)	126 (67.7)	0.09
	at 1 year[b]	343 (48.5)	325 (52.6)	43 (39.4)	0.03
Systolic blood pressure, mm Hg (mean, SD)					
	at 1 month[c]	136.2 (21.2)	137.8 (22.6)	133.3 (20.8)	0.05
	at 1 year[d]	135.5 (20.6)	135.9 (20.8)	134.7 (22.6)	0.83
Diastolic blood pressure, mm Hg (mean, SD)[b]					
	at 1 month[c]	75.5 (10.6)	76.6 (11.3)	74.2 (11.8)	0.02
	at 1 year[d]	75.1 (10.3)	75.8 (10.8)	76.0 (12.0)	0.46

* 159 patients died before 1 month follow-up, 346 patients died before 1 year follow-up and 108 patients have not yet reached 1 year post event

[a] 17 cases missing (7 minor stroke, 10 major stroke), [b] 36 cases missing (16 TIA, 13 minor stroke, 7 major stroke), [c] 241 cases missing (116 TIA, 96 minor stroke, 30 major stroke), [d] 119 cases missing (47 TIA, 54 minor stroke, 17 major stroke)

Table 8.7. Risk of recurrent ischaemic stroke pre and post 90 days from time of seeking medical attention after TIA and ischaemic stroke n=1856

Event type	Pre 90 days recurrent strokes	% risk	Post 90 days recurrent strokes	% risk	p
TIA, n= 778	56	7.2 (5.4 -9.0)	38	10.7 (6.2-15.2)	
Minor stroke, n= 764	59	7.7 (5.7 – 9.7)	72	18.8 (13.7-23.9)	
Major stroke, n= 315	15	6.5 (3.2 – 9.8)	17	23.9 (11.4-36.4)	

Table 8.8. TOAST classification of all recurrent events by first event seeking medical attention, n=1856.

		TOAST of recurrent stroke							
N (%)	TOAST of first event	CE	LAA	SVD	UND	UNK	Multiple	Other	Total
390 (21.0)	CE	72	0	0	1	1	0	1	75
199 (10.7)	LAA	3	20	0	1	0	0	1	25
236 (12.7)	SVD	6	1	27	6	1	1	0	42
699 (37.7)	UND	8	3	4	54	7	0	1	77
239 (12.9)	UNK	3	3	0	1	19	0	0	26
36 (1.9)	Multiple	1	0	0	0	0	5	0	6
57 (3.1)	Other	1	0	0	0	1	0	3	5
1856	Total	94	27	31	63	29	6	6	256

Table 8.9. Difference in TOAST classification of recurrent stroke from TOAST classification of first event from time of seeking medical attention.

TOAST subtype of recurrent stroke.	Patients	Pre 90 day strokes	Post 90 day strokes
		Recurrent stroke TOAST different to first event % (n/total)	Recurrent stroke TOAST different to first event % (n/total)
CE	94	9.8 (4/40)	33.3 (18/54)
LAA	27	21.1 (4/19)	37.5 (3/8)
SVD	31	4.3 (1/23)	37.5 (3/8)
UND	63	3.57 (1/28)	22.9 (8/35)
UNK	29	38.3 (1/12)	52.9 (9/17)
Multiple	6	0 (0/4)	50 (1/2)
Other	6	33.3 (1/3)	66.7 (2/3)
Total patients	256	9.3 (12/129)	34.6 (44/127)

a)

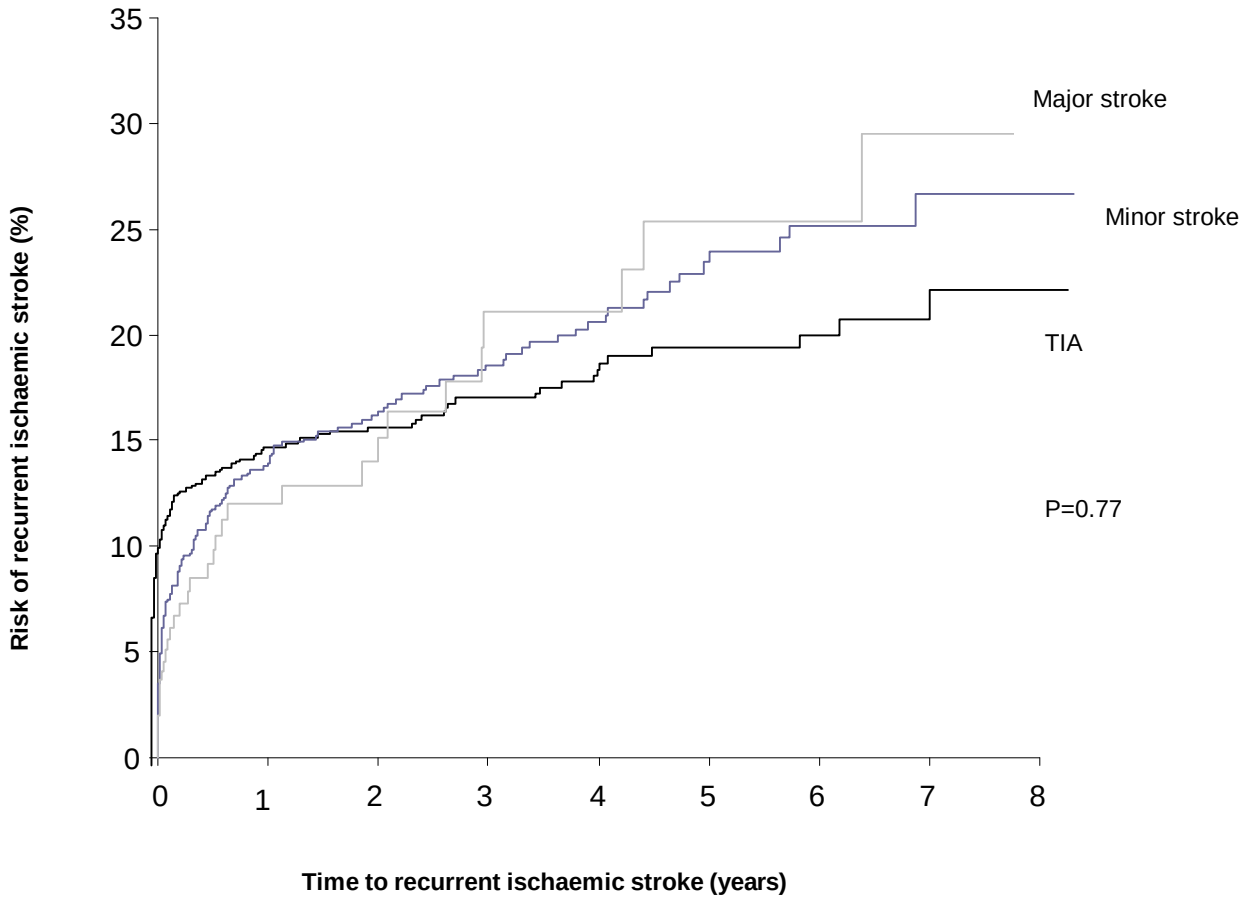
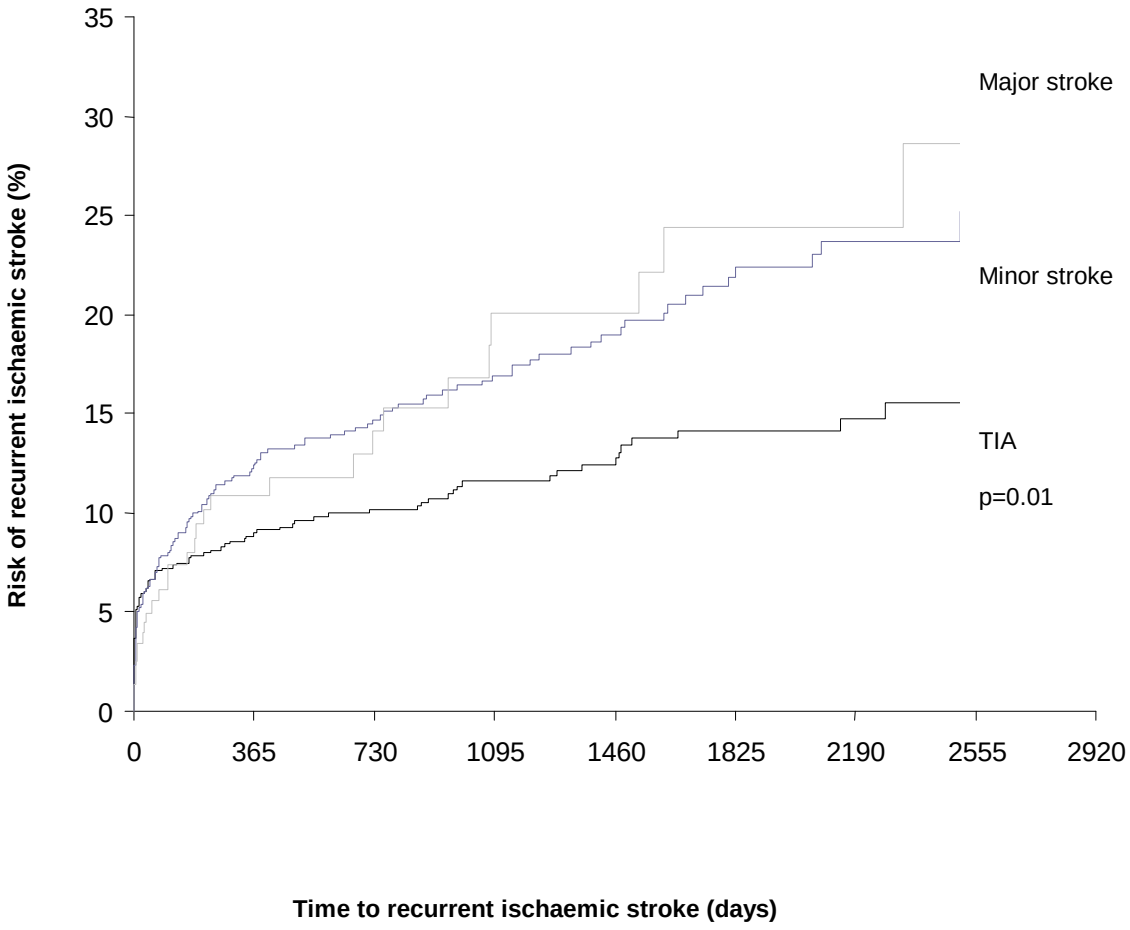


Figure 8.1a. Risk of recurrent stroke up to 8 years after TIA, minor ischaemic stroke and major ischaemic stroke: a) from event onset and b) from time of seeking medical attention

Figure 1b)


35
30
25
20
15
10
5
0
Risk of recurrent ischaemic stroke (%)
0
365
730
1095
1460
1825
2190
2555
2920
Time to recurrent ischaemic stroke (days)
Major stroke
Minor stroke
TIA
p=0.01

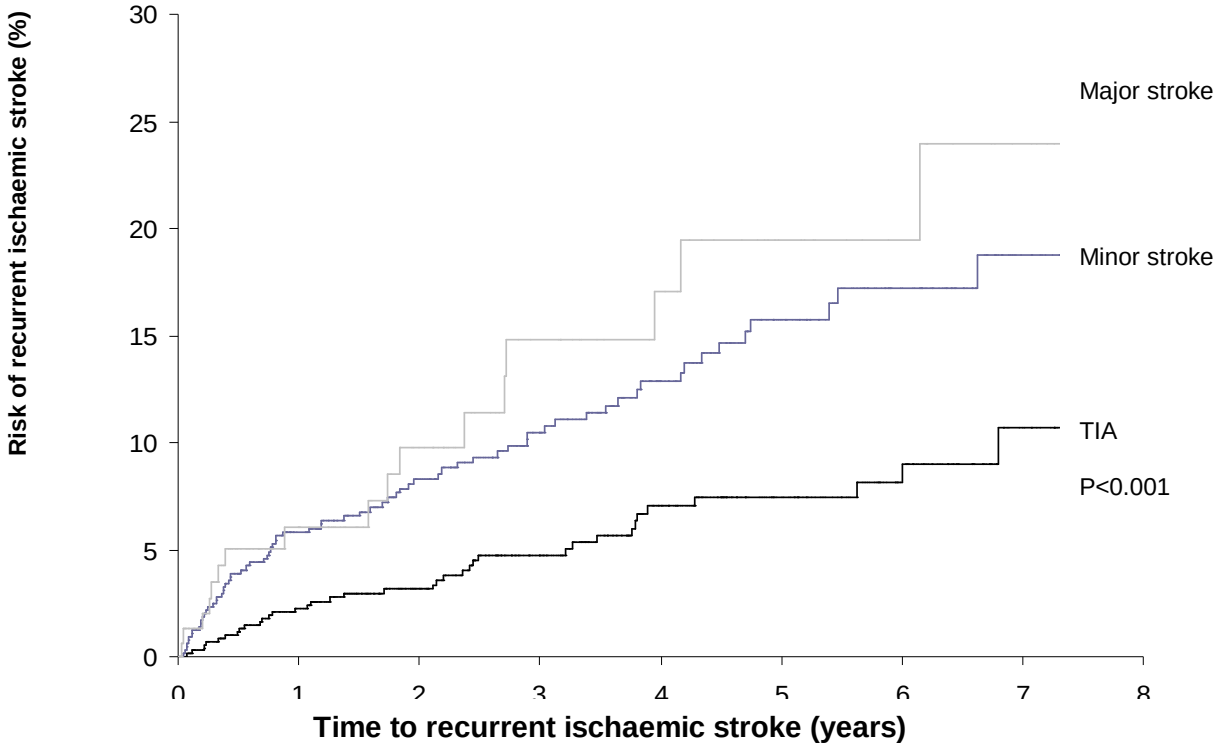


Figure 8.2 Post 90 day risk of recurrent stroke up to 8 years from time of first seeking medical attention after TIA or ischaemic stroke, (n=1856). 72 cases (54 TIA, 15 MIS and 3 major stroke) did not seek medical attention at the time of their event but presented after the recurrent stroke)

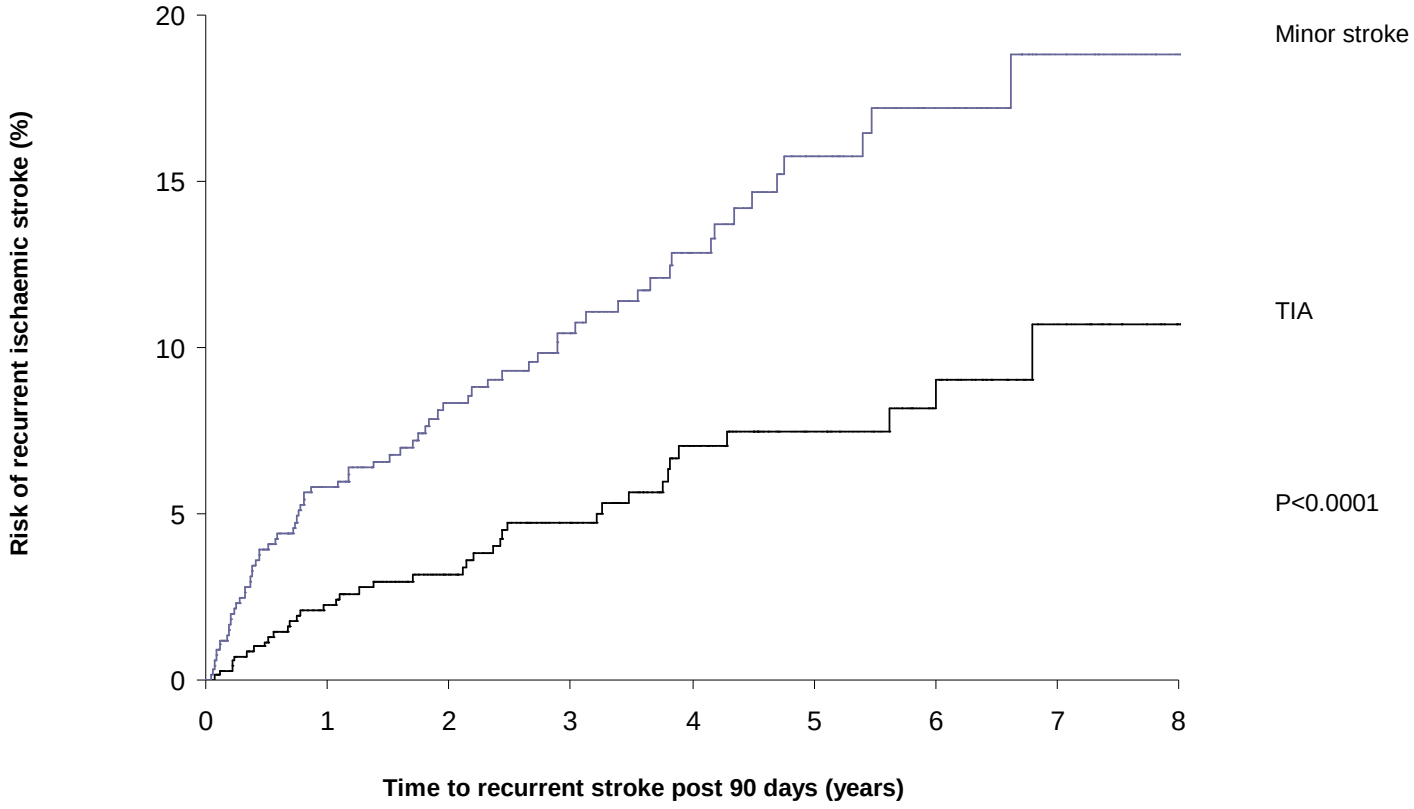


Figure 8.3 Risk of recurrent stroke up to 8 years post 90 days from time of first seeking medical attention after TIA or MIS, (n=1542).

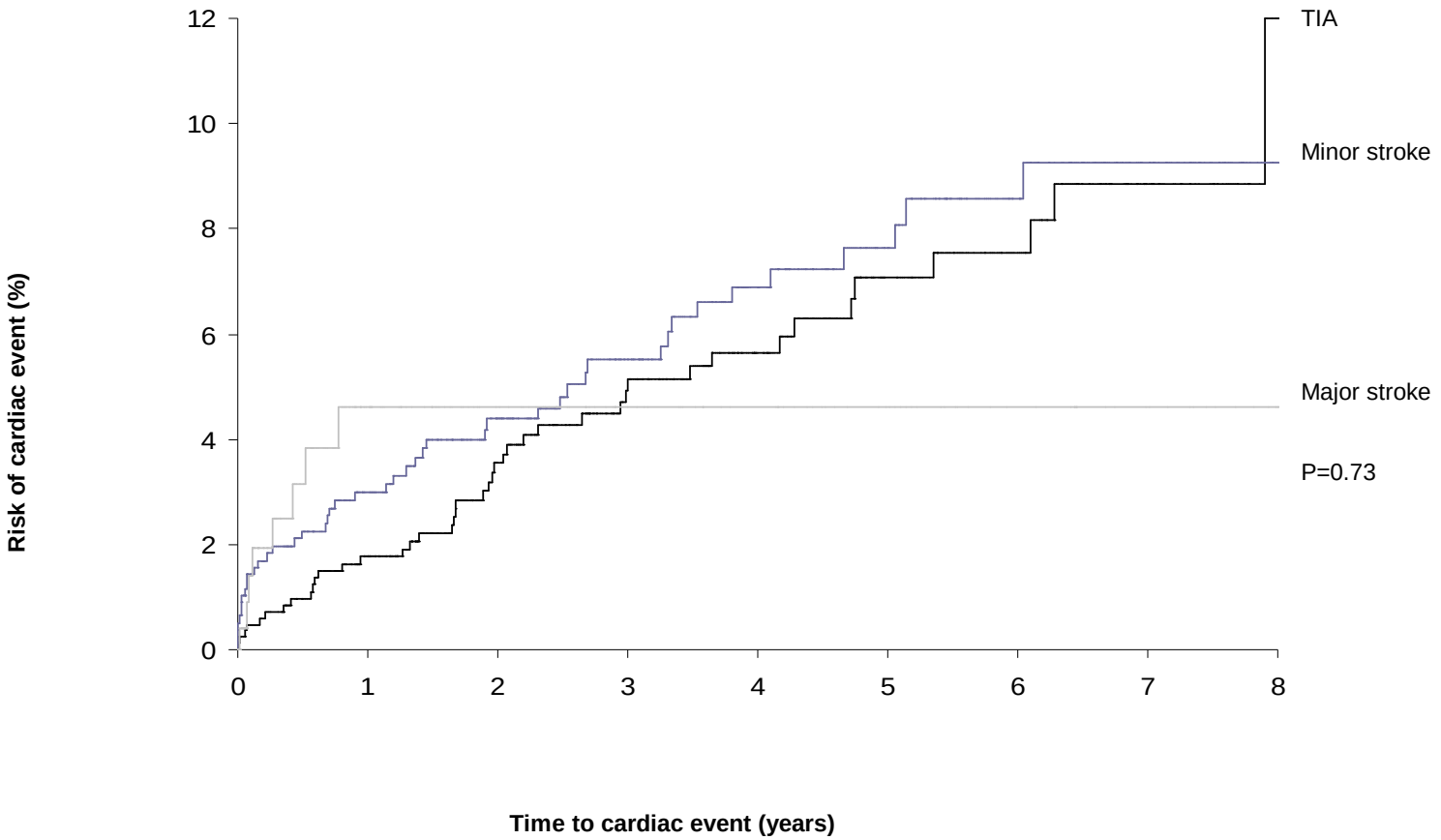


Figure 8.4 Risk of cardiac event (including NSTEMI, STEMI and sudden cardiac death) up to 8 years after TIA or ischaemic stroke

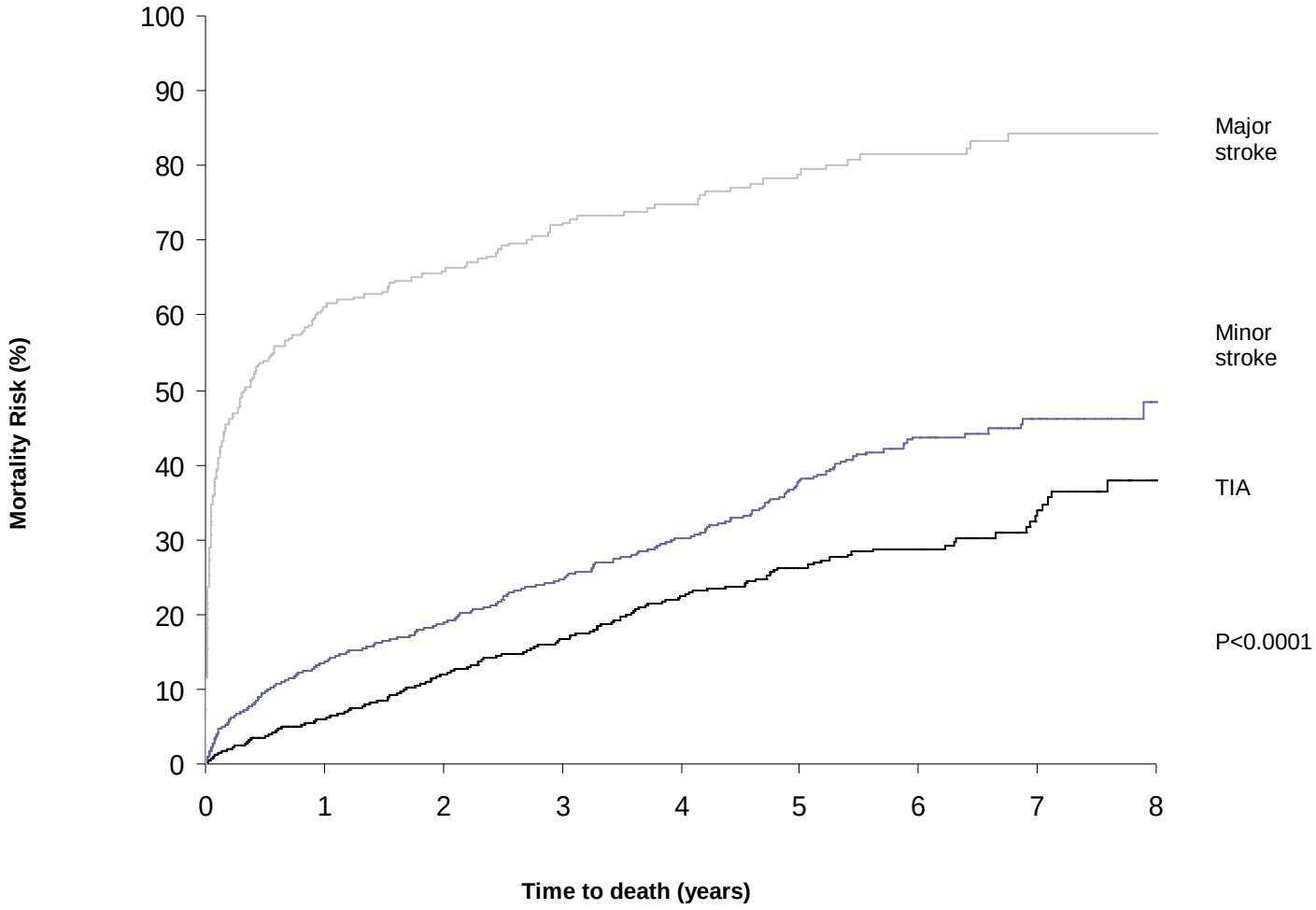


Figure 8.5 Mortality (% risk) up to 8 years after TIA and ischaemic stroke, n=1928.

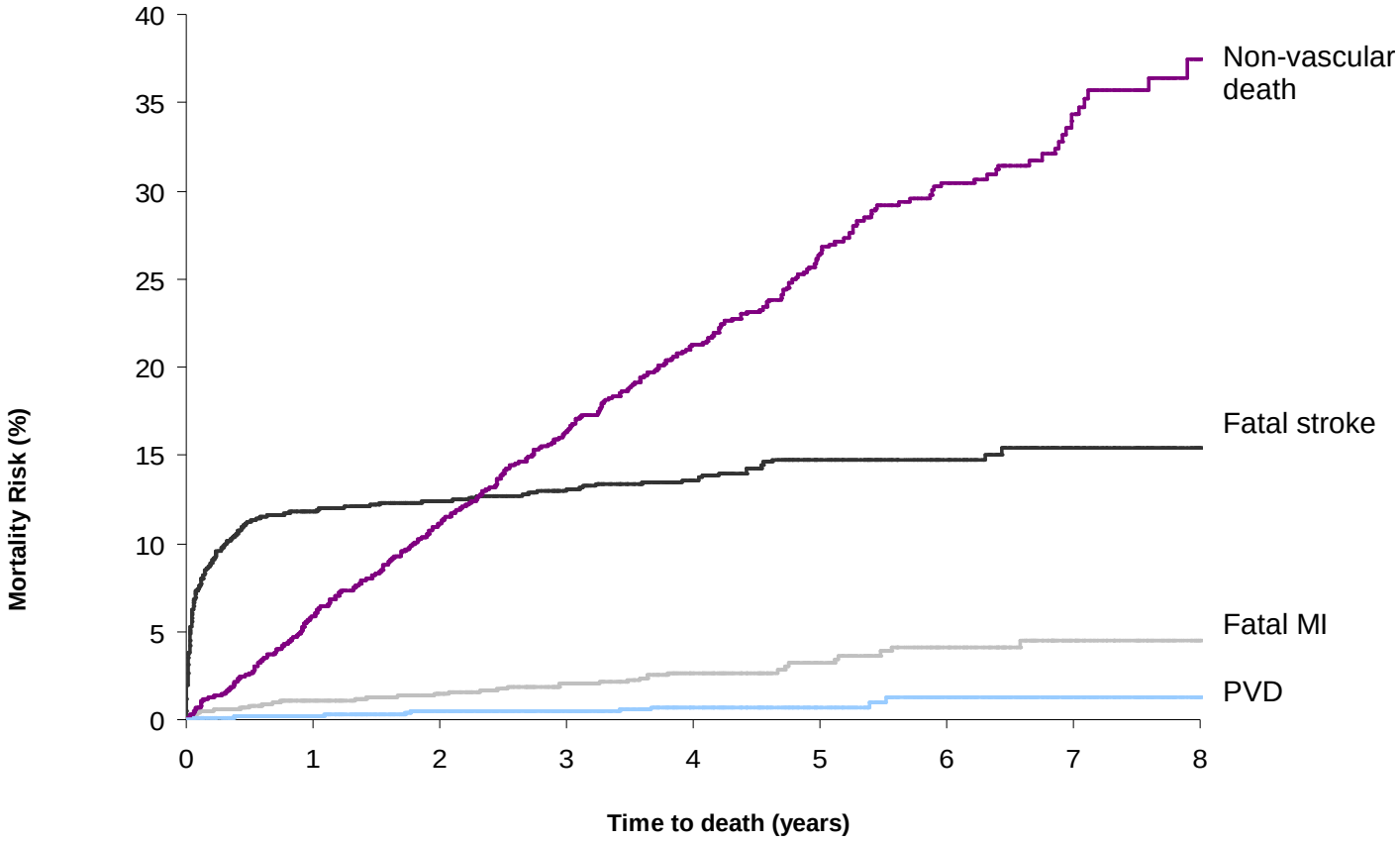


Figure 8.6 Mortality (%) risk by cause of death up to 8 years after TIA and stroke

CHAPTER 9

Risk factors for Early and Late recurrent ischaemic stroke in the Oxford Vascular Study

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9.1 Abstract

Introduction The risk of stroke after TIA is highest during the early phase and then declines over time but remains elevated for several years. Factors that increase the risk of a first ever TIA or stroke may not necessarily be as important in predicting a late recurrent stroke and risk factors might differ in patients presenting with a TIA versus stroke. It is also not clear whether the same risk factors are associated with early and late recurrence and to what extent late recurrence occurs because of suboptimal management of original risk factors**.**

Methods All early (≤90 days) and late (>90 days) recurrent ischaemic stroke events were identified in the OXVASC study TIA and stroke population with follow-up to 30/09/09. Univariate analysis was performed to detect variables associated with recurrence of a stroke. Statistical significance for differences in risk associated with early (≤90 day) versus late recurrence (>90-day) were assessed by Cox Regression analysis.

Results Of 1798 patients, 729(41%) had a TIA and 1069(59%) had a stroke as their presenting event. 124(6.8%) had an early (≤90 days) and 121(6.7%) had a late (>90 days) recurrent ischemic stroke. Symptomatic carotid stenosis was the main risk factor for early recurrence, while age, atrial fibrillation, cardioembolism as underlying aetiology, premorbid antiplatelet and antihypertensive use were the main risk factors for late recurrence. If TIA was the presenting event risk factors for recurrent stroke were frailty (HR 2.18, 95% CI 1.33-3.50) and prior hypertension (HR 2.15, 95% CI 1.38-3.34). If stroke was the presenting event risk factors for recurrent stroke were diabetes (HR 1.90, 95% CI 1.27-2.83).Increasing age, symptomatic carotid stenosis, cardioembolism and prior TIA were risk factors for recurrence if the presenting event was either TIA or stroke.

Conclusions I found that risk factors varied with timing of recurrence (early versus late) and type of presenting event (TIA or stroke). The risk of late recurrent ischaemic stroke is high. Further work is required, to reliably identify and treat the cause of late recurrent stroke.

9.2 Introduction

Our understanding of stroke recurrence and its prevention has significantly advanced over the last 10 years. Several treatments are effective in preventing stroke in the long-term after a TIA or minor ischaemic stroke, including aspirin, [1] other antiplatelet agents, [2-4] blood pressure lowering drugs, [5] statins, [6] anticoagulation for atrial fibrillation,[7] and endarterectomy for ≥50% symptomatic carotid stenosis.[8]

The risk of stroke after TIA is highest during the early phase and then declines over time but remains elevated for several years.[9,10] As a result, much of the recent attention in stroke and TIA has focused on early prognosis after TIA or minor stroke, risk factors for early recurrence and the effectiveness of treatment if started early.[11,12] Stroke recurrence adds significantly to stroke related disability thereby increasing burden in individuals and health care systems.[13,14] The opportunity for stroke prevention is greatest in the short term but secondary prevention measures should persist beyond the acute phase.[10]

A considerable variation exists in published long term recurrence rate of stroke, estimates ranging from 12-42%.[15,16] This variation may be caused by different definitions of stroke recurrence, differences in acute and preventative management, and different methodology, (ie hospital based, population based or clinical trial populations). Most randomised trials of interventions have follow up of only a few years and can define effectiveness of a treatment only over a certain time scale. Patients with TIA and minor stroke are a very heterogenous group in terms of symptoms, risk factors, underlying pathology and prognosis. Factors that

increase the risk of a first ever stroke may not necessarily be as important in predicting a late recurrent stroke. It is also not clear, to what extent late recurrence occurs because of suboptimal management of original risk factors.[17-25] If risk factors are different in early and late recurrence this might hold different therapeutic implications.[26] It is also worth noting that estimates of treatment effects in randomised trials may not always apply in the real world, especially if compliance is substantially lower in routine practice than in closely monitored and motivated trial populations.

My aim was to determine what risk factors are associated with early (≤90 days) and late stroke recurrences (>90 days) and whether aetiology differs from that of the presenting event i.e. TIA or stroke. I studied a population based cohort of stroke and TIA who had experienced an early (≤90 days) and late (>90 days) recurrent ischaemic stroke with a follow up period of 7 years.

9.3 Methods

The methods of OXVASC and details of the study population have been reported previously.[27,28] Briefly, the study population comprised all 91,000 individuals, irrespective of age, registered with 63 family physicians in nine general practices in Oxfordshire, UK. In the UK, almost all individuals register with a general practice, which provides their primary health care and holds a lifelong medical record. OXVASC was approved by our local research ethics committee and began on 01/04/02 after a 3-month pilot to ensure reliable case ascertainment.

9.3.1 Case Ascertainment

This report concerns all early (≤90 days) and late (>90 days) recurrent ischaemic stroke events identified in the study population in the first 7 years, with follow-up to 30/09/09. All patients presenting to medical attention with TIA or stroke in the study population were

ascertained. This was achieved as part of the OXVASC study by multiple overlapping methods of hot and cold pursuit, including prospective daily searches for acute events and retrospective searches of hospital and primary care administrative and diagnostic coding data. Details of the methods of ascertainment have been published previously, and direct assessment has shown it to be complete.[29] Patients were assessed by a study physician in a standardised manner. Detailed data were collected on premorbid baseline risk factors, premorbid blood pressure recordings, baseline cholesterol and lipids, glucose and HBA1c. Frailty was defined by Strawbridge criteria as having problems in 2 or more of the 4 domains (physical function, nutrition, cognition and sensory impairments).[30]

Atrial fibrillation (AF) was diagnosed on resting electrocardiograph or 24 hour electrocardiograph readings. A CT brain was performed at baseline and when indicated brain MRI and MRA were performed. Strokes were classified according to their aetiology, large artery, cardioembolic, small vessel, other, undetermined and unknown using TOAST criteria.[31] All cases were reviewed with the senior study neurologist (PMR) and classified as TIA, stroke, or other condition using standard definitions.[29]

All patients in OXVASC were followed-up by a research nurse or clinical research fellow after 1, 6, 12, and 60 months and asked about any new neurological symptoms. Current medication was recorded and two measurements of resting blood pressure (5 minutes apart) were made. If a recurrent vascular event was suspected at a follow-up visit or referred by their GP to clinic or admitted, the patient was re-assessed and investigated by a study physician. All blood pressure readings between events either at follow up clinic or general practice databases were recorded. Details of all potential recurrent strokes were reviewed by senior study neurologist (PMR). The definition of recurrent stroke used in OXVASC has been

reported previously, and required a sudden new symptomatic neurological deterioration on a background of stability or improvement following the presenting event. [27,28]

9.3.2 Analysis

I analyzed ischaemic stroke risk in all patients who sought medical attention with a TIA or stroke of any severity. The primary outcome was the ≤90, and > 90-day risk of recurrent stroke. Univariate analysis was performed to detect risk factors associated with recurrence of a stroke. Statistical significance for differences in risk factors between early (≤90 day) versus late recurrence (>90-day) were assessed by Cox Regression analysis.

9.4 Results

729(41%) patients presented with a TIA and 1069(59%) with a stroke. 849(47%) were male and the mean age was 74 years. During this period 1553(86%) had no recurrent stroke and 245(14%) had a recurrent ischaemic stroke (figure 9.1), 124(6.8%) had early recurrent ischaemic stroke defined as ≤90days (figure 9.2) and 121(6.7%) (Figure 8.3) had a late recurrent ischemic stroke defined as >90days with follow up to a period of 7 years.



Figure 9.1 Kaplan Meier curve of all recurrent ischaemic strokes over 2002-2009 in patients presenting with TIA or stroke

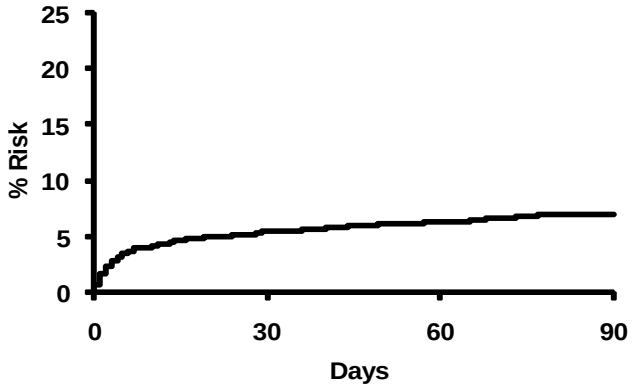


Figure 9.2: Kaplan Meier curve of recurrent ischaemic stroke at ≤90 days in patients presenting with TIA or stroke

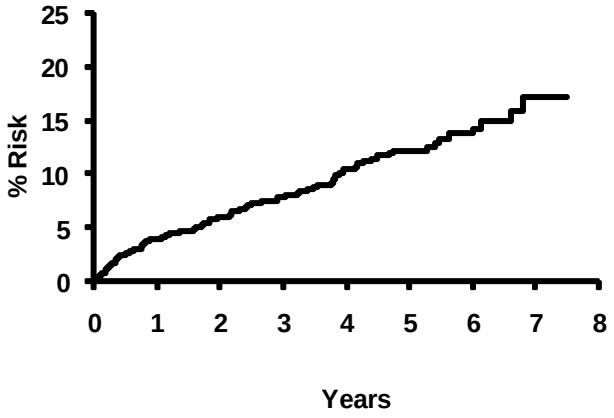


Figure 9.3 Kaplan Meier curve of recurrent ischaemic events > 90 days in patients presenting with TIA or stroke

Baseline risk factors for stroke recurrence on univariate analysis, (table 9.1) were increasing age (HR 1.025, 95% CI 1.01-1.036), symptomatic carotid stenosis (HR 2.82, 95% CI 1.98-4.02), atrial fibrillation (HR 2.17, 95% CI 1.6-2.8) history of TIA (HR 1.61, 95% CI 1.14-2.27), history of stroke (HR 1.46, 95% CI 1.05-2.05), frailty (HR 1.59, 95% CI 1.18-2.15), premorbid hypertension (HR 1.48, 95% CI 1.14-1.92), lower body weight (HR 0.97, 95% CI 0.96-0.98), premorbid antiplatelet treatment (HR 1.94, 95% CI 1.50-2.49), and premorbid antihypertensive treatment (HR 1.39, 95% CI 1.07-1.81).

Baseline risk factor differences for early (≤90 days) versus late recurrent stroke (>90 days) were tested by univariate analysis (Table 9.1) Risk factors specific to early recurrence were symptomatic carotid stenosis (HR 4.04, 95% CI 2.58-6.30,difference to late recurrence p=0.02). Increasing age (HR 1.054, 95% CI 1.035-1.073, difference to early recurrence p=0.002), atrial fibrillation (HR 3.45, 95% CI 2.38-5.00, difference to early recurrence p=0.0006), cardioembolism as underlying aetiology (p=0.0005), lower body weight (HR 0.96, 95% CI 0.95-.0.98, difference to early recurrence p=0.06), premorbid antihypertensive use (HR 3.22, 95% CI 2.20-4.70, difference to early recurrence p=0.0001) and premorbid antiplatelet use (HR 1.79, 95% CI 1.22-2.63 difference to early recurrence p=0.06) were risk factors for late recurrence.

I compared whether there were any differences in risk factors for stroke recurrence if the presenting event was either TIA or stroke (Table 9.2 and Table 9.3). If TIA was the presenting event specific risk factors for recurrence were frailty (HR 2.18, 95% CI 1.33-3.58 p=<0.0001) and premorbid hypertension (HR 2.15, 95% CI 1.38-3.34, p=0.0007). If stroke was the presenting event, diabetes (HR 1.84, 95% CI 1.27-2.83, p=0.001) was particularly important. Age, symptomatic carotid stenosis, atrial fibrillation, cardioembolism as underlying aetiology prior TIA, lower body weight and premorbid antihypertensive and antiplatelet use were predictive of recurrences if the presenting event was either TIA or stroke.(Table 9.2, 9.3).

From the multivariate analysis the factors independently associated with early recurrence included symptomatic carotid stenosis (HR 4.23, 95% CI 2.50-7.16, p=<0.0001), frailty (1.59, 95% CI 0.96-2.60, p=0.06), premorbid hypertension (HR 1.68, 95% CI 1.008-2.68, p=0.03), anterior territory as presenting event (2.20, 95% CI 1.12-4.30, p=0.02). Factors independently predictive of late recurrence were age (HR 1.04, 95% CI 1.014-1.068, p=0.002), atrial fibrillation (HR 2.52, 95% CI 1.25-5.05, p=0.009), symptomatic carotid stenosis (HR 7.94,

95% CI 2.94-21.44, p<0.0001), diabetes (2.07, 95% CI 1.13-3.81, p=0.01), lower body weight(kg) (HR 0.97, 95% CI 0.96-0.98, p<0.0001), premorbid antiplatelet use(HR 2.2, 95% CI 1.14-3.45, p=<0.0001) and cardioembolism as underlying aetiology p=0.008, body weight (HR 0.97,95% CI 0.96-0.99) and premorbid antiplatelet use (HR 2.23, 95% CI 1.39-3.59, p=0.001). Symptomatic carotid stenosis remained an independent predictor of late recurrences, however 6/12 of these cases did not proceed to either carotid endaterectomy or stenting as they opted for medical treatment. In the remaining 6 cases, 3/6 had a carotid endarterectomy prior to their late recurrence and 3 following their late recurrence.

9.4.2 Secondary prevention

Blood pressure control at one month follow up for non recurrences showed a mean systolic/ diastolic of 137/76mmHg, 136/76mmHg for early recurrence, and 142/79 for late recurrences. At 1 year follow up, mean systolic/diastolic blood pressure was 137/77mmHg for non recurrences, 136/78mmHg early recurrences and 142/85mmHg for late recurrence (p=0.008). Secondary prevention measures at 1 month were similar in early versus late stroke recurrences, however at 1 year a higher proportion of late recurrences were on antiplatelet treatment (80% vs 91% p=0.02). A higher proportion of recurrences (early and late) were on 2 and more antihypertensives at 1 year compared with non recurrences. If the presenting event was a TIA patients were more likely to be on an antiplatlelet/anticoagulant at 1 month (93.3% vs 86.6%, p =0.003) and at 1 year (83.5% vs 71.4%, p=0.06).

The aetiology of early versus late recurrences was also different. Recurrent events within 90 days were generally of the same aetiology as the initial event. However, beyond 90 days, there were a higher proportion of recurrent events of different aetiology to the initial event. Of 124 recurrent strokes post 90 days, aetiology could be determined in 49% (61/124). Of these,

80% (49/61) were of cardioembolic aetiology, despite constituting only 20% (356/1775) of all firstevents.

Table 9.1 Univariate analysis of risk factors of stroke recurrence in stroke and TIA in OXVASC population 2002-2009 n=1798

	≤90 Day Events/patients (%) HR (95% CI) **n=124 events**			**>90 Day** Events/patients (%) HR (95% CI) **n=121 events**			**p Difference <90 and ≥90 days**
			P			**p**	
Age		1.005(0.99-1.019)	0.50		1.054(1.035-1.073)	<0.0001	0.0004
Age bands							**0.002**
<65		1.00	0.76		1.00	<0.0001	
65-74	32/424(13) vs25/394(6)	1.20 (0.80-1.79)	0.49	22/373(6) vs17/360(5)	1.13 (0.60-2.13)	0.69	
75-84	40/618(6) vs 25/394(6)	1.05 (0.64-1.74)	0.82	48/516(9) vs 17/360(5)	2.10 (1.20-3.65)	0.008	
85+	27/362(7) vs25/394(6)	1.29 (0.75-2.22)	0.35	34/246(14) vs 17/360(5)	4.21 (2.34-7.57)	<0.0001	
Males	55/849(6) vs 69/949 (7)	0.87 (0.61-1.23)	0.44	53/728(7) vs 68/767(9)	0.85 (0.60-1.23)	0.36	0.90
Atrial fibrillation	26/318(8) vs 98/1480(7)	1.30 (0.85-2.01)	0.22	44/234 (19) vs77/1261(6)	3.45 (2.38-5.00)	<0.0001	0.0007
Symptomatic carotid stenosis (≥50%)	24/105(34) vs 100/1693(6)	4.04 (2.58-6.30)	<0.0001	12/80(15) vs109/1415(8)	1.76 (0.97-3.20)	0.063	0.024
Prior stroke	22/238(9) vs 102/1560(7)	1.45(0.91-2.29)	0.11	20/188(11) vs 101/1307(8)	1.50(0.92-2.42)	0.102	0.93
Prior TIA	19/187(10) vs 105/1611(7)	1.59(0.97-2.6)	0.06	20/155(13) vs101/1340(8)	1.64(1.015-2.6)	0.04	0.93
Prior PVD	10/108(9) vs 114/1655(7)	1.41(0.74-2.70)	0.29	6/78(8) vs 115/1384 (8)	1.01(0.44-2.29)	0.98	0.52
Frailty	35/377(9) vs 70/1119(6)	1.54(1.02-2.31)	0.03	27/286(9) vs 76/995 (8)	1.67(1.07-2.60)	0.02	0.79
Current smoker	17/238(7) vs107/1560(7)	1.02(0.61-1.70)	0.94	16/207(8)vs 105/1288(8)	0.89(0.52-1.51)	0.68	0.73
Prior MI	13/170(8) vs 111/1628(7)	1.18(0.66-2.10)	0.56	17/131(13) vs 104/1364(8)	1.54(0.93-2.58)	0.09	0.49
Hypertension	83/1006(8) vs 41/792(5)	1.64(1.13-2.39)	0.009	73/812(9) vs 48/683 (7)	1.33(0.93-1.92)	0.11	0.44
Hyperlipidaemia	28/468(14) vs 96/1330	0.80(0.53-1.22)	0.30	40/416 vs 81/1079()	1.19(0.82-1.74)	0.35	0.16

Territory							**0.34**
Anterior vs posterior	94/1060(9) vs 26/431(6)	1.51(0.97-2.33)	0.06	87/860(10) vs 30/382(8)	1.13 (0.74-1.71)	0.56	
TOAST in presenting event							**0.00009**
CE		1.00	<0.0001		1.00	0.0007	
LAA vs CE	26/173(15) vs 32/324(10)	1.35(0.80-2.26)	0.25	7/163(4) vs 38/208(18)	0.28(0.12-0.64)	0.002	
SMV vs CE	26/213(12) vs32/324(10)	1.12(0.66-1.87)	0.66	15/195(8) vs38/206 (18)	0.39(0.21-0.72)	0.002	
UND vs CE	25/638(4) vs32/324(10)	0.37(0.22-0.63)	0.0002	49/575(9) vs38/208 (18)	0.50(0.33-0.76)	0.001	
UNK vs CE	13/223(6) vs32/324(10)	0.63(0.33-1.20)	0.16	8/1148(5) vs 38/208 (18)	0.38(0.18-0.83)	0.01	
Angina	22/276(8) vs 102/1522(7)	1.22(0.77-1.94)	0.38	25/221(11) vs 96/1274)	1.45(0.93-2.26)	0.09	0.59
Diabetes	19/216(9) vs105/1582(7)	1.34(0.82-2.18)	0.23	17/177(11) vs 104/1318(8)	1.31(0.78-2.20)	0.29	0.96
Weight(Kg)		0.98(0.97-0.99)	0.007		0.96(0.95-0.98)	<0.0001	0.64
Premorbid Antiplatelet	54/707(8) vs 70/1091(6)	1.21(0.85-1.73)	0.28	81/572(14) vs 40/923(4)	3.22(2.20-4.70)	<0.0001	0.00018
Premorbid statin	24/401(6)vs 100/1397(7)	0.82(0.53-1.28)	0.38	28/350(8) vs 93/1145(8)	1.05(0.69-1.60)	0.82	0.42
Premorbid Antihypertensive	73/1023(15)vs 51/775(7)	1.10(0.77-1.57)	0.59	83/834(7) vs 38/661 (6)	1.79(1.22-2.63)	0.002	0.06

Table 9.2 Univariate analysis of risk factors for early versus late recurrent stroke in patients presenting with TIA in OXVASC population 2002-2009 n=729

	≤90 Day Events/patients (%) **n=54 events**			**>90 Day** Events/patients (%) **n=37 events**			**p Difference ≤90 and >90 days**
			P			**p**	
Age		1.02(0.998-1.043)	0.073		1.1(1.05-1.14)	<0.0001	0.0004
Age bands							**0.02**
<65		1.00	0.045		1.00	<0.0001	
65-74	15/193(8) vs9/183(5)	1.60 (0.70-3.66)	0.26	5/177(3) vs2/174(1)	2.30 (0.45-11.9)	0.31	
75-84	14/232(6) vs 9/183(3)	1.23 (0.53-2.86)	0.62	14/216(6) vs 2/174(1)	5.83 (1.32-25.65)	0.019	
85+	16/121(13) vs9/183(5)	2.83 (1.24-6.38)	0.012	16/104(15) vs 2/174(1)	17.63 (4.03-77.57)	0.0001	
Males	25/330(8) vs 29/399 (7)	1.05 (0.61-1.79)	0.85	14/302(5) vs 23/369(6)	0.79 (0.41-1.55)	0.50	0.52
Atrial fibrillation	15/115(13) vs 39/614(6)	2.13(1.17-3.87)	0.012	14/99 (14) vs23/572(4)	3.83 (1.97-7.45)	<0.0001	0.19
Symptomatic carotid stenosis (≥50%)	10/55(18) vs 44/674(7)	2.93(1.47-5.83)	0.0002	6/44(15) vs31/627(8)	2.54(1.06-6.10)	0.03	0.79
Prior stroke	7/76(9) vs 47/653(7)	1.28(0.58-2.84)	0.53	7/69(10) vs 30/602(5)	2.16(0.94-4.93)	0.06	0.37
Prior TIA	14/97(14) vs 40/632(6)	2.37(1.29-4.37)	0.005	5/83(6) vs 32/588(5)	0.98(0.38-2.52)	0.97	0.10
Prior PVD	6/32(18) vs 48/681(7)	2.76(1.18-6.45)	0.01	0/25(0) vs 37/630(6)	------	0.25	0.01
Frailty	12/108(11) vs 34/521(7)	1.72(0.89-3.33)	0.10	10/94(11) vs 22/486 (5)	3.09(1.45-6.57)	0.003	0.25
Current smoker	6/90(7) vs48/639(8)	0.87(0.37-2.03)	0.74	5/83(6)vs 32/588(5)	1.09(0.42-2.81)	0.84	0.72
Prior MI	6/62(10) vs 48/667(7)	1.36(0.58-3.19)	0.47	6/55(11) vs 31/616(5)	1.94(0.81-4.67)	0.13	0.56
Hypertension	38/376(10) vs 16/353(5)	2.29(1.27-4.10)	0.005	24/336(7) vs 13/335 (4)	1.97(1.003-3.86)	0.049	0.73
Hyperlipidaemia	14/216(6) vs 40/513 (8)	0.82(0.44-1.51)	0.53	12/200(6)vs 25/471(5)	1.04(0.52-2.08)	0.89	0.60
Presenting event							

Cerebral vs Ocular TIA	54/669(8) vs 0/60	------	----	31/612(5) vs6/59(10)	0.49(0.20-1.18)	0.11	0.0007
Territory							**0.73**
Anterior vs posterior	40/433(9) vs 11/178(6)	1.52(0.78-2.97)	0.21	28/389(7) vs 8/167(5)	1.24(0.58-2.79)	0.54	
TOAST in presenting event							**0.12**
CE		1.00	<0.0001		1.00	0.29	
LAA vs CE	11/79(14) vs 16/94(17)	0.82(0.38-1.76)	0.61	4/74(5) vs 10/82(12)	0.54(0.17-1.74)	0.30	
SMV vs CE	11/55(20) vs16/94(17)	1.17(0.54-2.53)	0.67	5/50(10) vs10/8(12)	0.85(0.29-2.51)	0.78	
UND vs CE	9/349(3) vs16/94(17)	0.16(0.07-0.36)	<0.0001	15/334(4) vs10/82(12)	0.45(0.20-1.01)	0.05	
UNK vs CE	6/59(10) vs16/94(17)	0.60(0.23-1.55)	0.29	2/56(4)vs 10/82(12)	0.36(0.08-1.67)	0.19	
Angina	11/111(10) vs 43/618(7)	1.44(0.74-2.80)	0.27	9/98(9) vs 28/573(5)	1.78(0.84-3.79)	0.12	0.67
Diabetes	3/85(4) vs 51/644(8)	0.43(0.13-1.40)	0.16	3/82(4) vs 34/589(6)	0.68(0.21-2.20)	0.53	0.59
Weight(Kg)		0.992(0.97-1.01)	0.39		0.96(0.94-0.98)	0.003	0.07
Premorbid Antiplatelet	24/267(9) vs 30/462(6)	1.40(0.82-2.39)	0.21	21/240(9) vs 16/431(4)	2.21(1.15-4.24)	0.01	0.28
Premorbid statin	10/172(6)vs 44/557(8)	0.72(0.36-1.44)	0.36	6/161(4) vs 31/510(6)	0.62(0.26-1.50)	0.29	0.79
Premorbid Antihypertensive	31/398(15)vs 23/331(7)	1.12(0.65-1.93)	0.66	27/363(7) vs 10/308 (6)	2.29(1.11-4.74)	0.02	0.11

Table 9.3 Univariate analysis of risk factors for early versus late recurrent stroke in patients presenting with stroke in OXVASC population 2002-2009 n=1069

	≤90 Day			>90 Day			
	Events/patients (%) HR (95% CI) n=70 events			Events/patients (%) HR (95% CI) n=84 events			p Difference ≤90 and >90 days
			P			p	
Age		0.994(0.977-1.012)	0.51		1.0.36(1.014-1.58)	0.001	0.003
Age bands							**0.03**
<65		1	0.77		1	0.77	
65-74	17/231(3) vs16/211(8)	0.97 (0.49-1.92)	0.26	17/196(9) vs15/186(8)	0.92 (0.46-1.80)	0.82	
75-84	26/386(7) vs 16/211(8)	0.93 (0.50-1.74)	0.83	34/300(11) vs 15/186(8)	1.50 (0.82-2.76)	0.18	
85+	11/241(13) vs16/211(5)	0.68 (0.31-1.47)	0.33	18/142(11) vs 15/186(8)	2.46 (1.23-4.91)	0.01	
Males	30/519(6) vs 40/550(7)	0.75 (0.46-1.20)	0.23	39/426(9) vs 45/398(11)	0.79 (0.51-1.22)	0.30	0.85
Atrial fibrillation	11/203(5) vs 59/866(7)	0.85(0.44-1.62)	0.63	30/135 (22) vs54/689(8)	3.23 (2.06-5.05)	<0.0001	0.0004
Symptomatic carotid stenosis (≥50%)	14/50(28) vs 56/1019(5)	5.30(2.95-9.52)	<0.0001	6/36(17) vs78/788(10)	1.49(0.65-3.43)	0.34	0.01
Prior stroke	15/162(9) vs 55/907(6)	1.57(0.88-2.78)	0.11	13/119(11) vs 71/705(10)	1.16(0.64-2.10)	0.61	0.47
Prior TIA	5/90(6) vs 65/979(7)	0.84(0.34-2.09)	0.71	15/72(21) vs 69/752(9)	2.35(1.34-4.10)	0.002	0.04
Prior PVD	4/76(5) vs 66/974(7)	0.81(0.29-2.23)	0.68	6/53(11) vs 78/754(10)	1.17(0.51-2.70)	0.70	0.57
Frailty	23/269(9) vs 36/598(6)	1.49(0.88-2.51)	0.13	17/192(9) vs 54/509(11)	0.65(0.65-1.96)	0.65	0.47
Current smoker	11/148(7) vs59/921(6)	1.12(0.59-2.14)	0.72	11/124(9)vs 73/700(10)	0.77(0.41-1.46)	0.43	0.42
Prior MI	7/108(6) vs 63/961(7)	1.07(0.49-2.34)	0.85	11/76(14) vs 73/748(10)	1.34(0.72-2.57)	0.33	0.64

Hypertension	45/630(7) vs 25/439(6)	1.28(0.78-2.09)	0.31	49/476(10) vs 35/348(10)	1.04(0.67-1.60)	0.85	0.52
Hyperlipidaemia	14/252(6) vs 56/608(7)	0.77(0.42-1.38)	0.38	28/216(13)vs 56/608(9)	1.32(0.84-2.08)	0.22	0.14
Presenting event							
Major stroke vs minor	22/413(5) vs 48/656 (7)	0.88(0.53-1.46)	0.62	22/244(9) vs62/580(10)	0.96(0.59-1.56)	0.87	0.80
Territory							**0.40**
Anterior vs posterior	54/627(9) vs 15/253(6)	1.50(0.85-2.66)	0.16	59/471(13) vs 22/215(10)	1.09(0.67-1.79)	0.71	
TOAST in presenting event							**0.0003**
CE		1.00	0.053		1.00	<0.0001	
LAA vs CE	15/94(16) vs 16/230(7)	1.89(0.93-3.83)	0.07	3/89(3) vs 28/126(22)	0.18(0.05-0.61)	0.005	
SMV vs CE	15/158(10) vs16/230(7)	1.15(0.57-2.33)	0.69	10/89(11) vs28/126 (22)	0.27(0.13-0.56)	0.0004	
UND vs CE	16/289(6) vs16/230(7)	0.70(0.35-1.40)	0.31	34/241(14) vs28/126(22)	0.61(0.37-1.01)	0.05	
UNK vs CE	7/164(4) vs16/230(7)	0.67(0.27-1.63)	0.38	6/92(7)vs 28/126(22)	0.38(0.16-0.94)	0.03	
Angina	11/165(7) vs 59/904(7)	1.06(0.55-2.02)	0.84	16/123(13) vs 68/701(10)	1.32(0.76-2.28)	0.31	0.60
Diabetes	16/131(12) vs 54/938(6)	2.19(1.25-3.84)	0.005	14/95(15) vs 70/729(10)	1.65(0.93-2.94)	0.53	0.48
Weight(Kg)		0.98(0.96-0.99)	0.005		0.97(0.95-0.98)	<0.0001	0.34
Premorbid Antiplatelet	30/440(7) vs 40/629(6)	1.09(0.68-1.75)	0.70	60/332(18) vs 24/492(5)	3.74(2.32-6.00)	<0.0001	0.0002
Premorbid statin	14/229(6)vs 56/840(7)	0.89(0.49-1.60)	0.70	22/189(12)vs 62/635(10)	1.32(0.81-2.54)	0.25	0.30
Premorbid Antihypertensive	42/625(7)vs 28/444(6)	1.09(0.67-1.76)	0.71	56/471(12)vs 28/353(8)	1.59(1.01-2.51)	0.04	0.26

Table 9.4 Multiivariate analysis of risk factors for early versus late recurrent stroke in OXVASC population 2002-2009 n=1798

	≤90 Day HR (95% CI) **n=124 events**	**p**	**>90 Day** (HR (95% CI) **n=121 events**	**p**
Age			1.04(1.014-1.068)	0.002
Symptomatic carotid stenosis (≥50%)	4.23 (2.50-7.16)	<0.0001	7.94 (2.94-21.44)	<0.0001
Hypertension	1.68(1.03-2.74)	0.006		
Atrial fibrillation			2.52 (1.25-5.05)	0.009
Diabetes			2.07(1.13-3.81)	0.019
Weight (kg)			0.97(0.96-0.99)	0.002
Premorbid AP			2.23(1.39-3.59)	0.001
TOAST				0.01
Cardioembolism			1.00	
LAA vs CE			0.18(0.04-0.72)	0.01
SMV vs CE			1.26(0.53-3.01)	0.59
UND vs CE			1.57(0.75-3.28)	0.22
UNK vs CE			0.92(0.31-2.70)	0.88
Territory				
Anterior vs posterior	2.20(1.12-4.30)	0.02		

		No Recurrence	Early recurrence	Late recurrence	P
		n/(%)	n/(%)	n(%)	
On an antiplatelet or anticoagulant	at 1 month[a]	1280(92)	105 (91)	115 (93)	0.77
	at 1 year[b]	1125 (90)	76(85)	103 (91)	0.02
On a statin	at 1 month[a]	1001 (72)	83 (72)	92 (74)	0.83
	at 1 year[b]	950 (77)	65(76)	88 (78)	0.96
On one or more antihypertensive	at 1 month[a]	1004 (72)	83 (72)	96 (77)	0.45
	at 1 year[b]	911 (74)	70 (79)	89 (79)	0.33
On two or more antihypertensives	at 1 month[a]	533(38)	49(42)	57(46)	0.17
	at 1 year[b]	592 (48)	52(58)	66 (58)	0.02
Systolic blood pressure, mm Hg (mean, SD)					
	at 1 month[c]	137(21.2)	136 (21.8.)	142 (21.8)	0.14
	at 1 year[d]	137 (20.4)	135.9 (21.8)	143 (21.6)	0.11
Diastolic blood pressure, mm Hg (mean, SD)[b]					
	at 1 month[c]	76.5 (10.4)	76.6 (12.1)	78.7 (10.4)	0.16
	at 1 year[d]	76.6 (10.1)	77.87(12.1)	85.1(65.0)	0.008

Table 9.5 Secondary prevention measures assessed at 1 month and 1 year follow up in all patients (n=1630 at 1 month, n=1440 at 1 year)* 68 patients died before 1 month follow up and 198 died before 1 year follow-up and 60 patients have not reached 1 year post event

5 Discussion:

In this population based cohort the rate of early recurrent stroke (≤90 days) was 6.5% and the rate of late recurrent stroke (>90 days was 6.6%). A wide variation in the relationship between risk factors and ischaemic stroke recurrence has been reported in previous studies, trials and registries and no independent risk factor has been associated with an increased or reduced risk of recurrence. I identified age [17,32] atrial fibrillation, [32,33] prior history of stroke or TIA, [34,34] angina, [35] symptomatic carotid stenosis, [37-39] hypertension [18, 21,32, 34-36,40] lower body weight and frailty as important risk factors for ischaemic stroke recurrence. Frailty, defined by Strawbridge criteria as having problems in 2 or more of the 4 domains (physical function, nutrition, cognition and sensory impairments) has not been associated with recurrent vascular events, although dementia has been reported as a risk factor for late recurrent stroke.[40] Lower body weight reported in this study, has not been reported as a risk factor for recurrent ischaemic stroke, and may be due to reduced adherence to medications as higher bleeding rates are reported with antiplatelet use and lower body weight.[41]

When I examined the factors associated with early versus late ischaemic stroke recurrence, I identified symptomatic carotid stenosis as a risk factor for early recurrence. Potential mechanisms are early cerebral embolism from plaque ulceration and lumen thrombosis. Two studies (NASCET [the North American Symptomatic Carotid Endarterectomy Trial], ECST [the European Carotid Surgery Trial], have clearly shown the benefits of carotid endaterectomy compared with medical treatment in recently symptomatic patients with severe carotid stenosis. [37,38] Evidence from observational and epidemiological studies further highlight that the risk of subsequent stroke in patients with carotid stenosis is highest in the first few weeks, necessitating the rapid identification of patients with carotid stenosis and initiation of medical treatment or

revascularisation procedures.[42-44] Symptomatic carotid stenosis remained a potential risk factor for late recurrence in this study, however a review of the cases identified that 8/12 did not proceed to carotid endarterectomy thereby contributing to risk of late recurrence.

I found an increased risk of late ischaemic stroke recurrence due to increasing age prior MI, angina and atrial fibrillation. Abnormalities in the atrial activity and contractility result in sluggish blood flow and an increased risk for thrombi that can embolise to the brain.[45] For patients with AF the ideal methods for reducing risk and optimising cardiac function is conversion to normal sinus rhythm. However, for older patients, underlying heart disease, or long standing AF conversion to sinus rhythm is difficult to achieve. For most, appropriate treatment is control of ventricular rate and antithrombotic therapy.[46] Warfarin reduced the risk of recurrent stroke by 61% compared with control in atrial fibrillation patients with recent TIA or ischaemic stroke.[47,48] Despite the efficacy and affordability of warfarin many patients with cardioembolic ischaemic stroke and TIA are not treated with warfarin because it is perceived to be hazardous or inconvenient. For those who are treated the long term efficacy and safety of warfarin depends on maintaining the INR between 2.0-3.0. In recent carefully monitored trials, patients treated with warfarin spent only 63-68% of the time in the therapeutic INR range.[49] In clinical practice, this proportion is likely to be lower and many patients discontinue treatment. Beyond factors of INR control, recurrent events may still occur within therapeutic INR ranges.

I found that risk factors associated with recurrence were broadly similar whether the presenting event was either TIA or stroke.[50] However, frailty and prior hypertension were identified as potential risk factor differences if the event was a TIA. Higher rates of diabetes were seen when stroke was the presenting event. Increasing age, symptomatic

carotid stenosis, atrial fibrillation and cardioembolism as an underlying aetiology were predictive of recurrences irrespective of whether the presenting event was TIA or stroke demonstrating the importance of cardiovascular risk factors in long term stroke management.

In addition to baseline risk factors identified on assessment, long term control of risk factors such as blood pressure and adherence to medication were assessed on regular follow up. Hypertension is a potent and yet most modifiable risk factor for stroke and use of antihypertensive treatment has been shown to reduce this risk substantially.[51,52] Although a greater number of stroke recurrences were on 2 or more antihypertensive agents, the average blood pressure readings among late recurrences were above target treatment guidelines.

This study was nested in a rigorous and well established population based study of all incident and recurrent TIA and stroke, with consistent methods of case ascertainment, diagnosis, investigation, and long term follow up. Another strength is that patient selection was not based on age (682,38%) of our population were >80 years) which means that our study is more representative of the general population than most studies with more restricted selection. This study provides a large number of blood pressure readings that allows us to observe the long term control of blood pressure and its relation to recurrent stroke. Observational studies tend to record history of blood pressure and do not take into account how effectively BP is controlled during the follow up period.

Our study does have some shortcomings. First, we do not know the effects of each treatment on the risk of recurrent stroke and the effect of combining multiple approaches for the secondary prevention in ischaemic stroke may only prove effective over a short term period. Second, I cannot account for the effects that an individual treatment might have had on stroke risk. If a risk factor can be altered by a treatment or intervention then it less likely to be predictive of long term stroke (i.e carotid endarterectomy for symptomatic carotid stenosis). Other risk factors such as AF may be undertreated or undetected and its effect on long term stroke recurrence may be more a measure of failure of detection.

Third, there may also be additional reasons accounting for the difference in timing to recurrent events. A longer delay to seeking medical attention after the presenting event may delay access to secondary prevention which could result in earlier recurrent events. However, in OXVASC, similar proportions of TIA and minor stroke patients sought medical attention within 24 hours of the event.[53] In addition different treatment settings for TIA and stroke could lead to differing access to secondary prevention. If patients with TIA were generally seen in the outpatient setting with secondary prevention being started after the clinic appointment by their GP and patients with stroke were seen as inpatients, then a higher earlier recurrence rate after TIA may be expected. However, in our study 97% of patients with minor stroke were seen in the urgent outpatient setting and therefore had similar access to preventative treatments to patients with TIA.

These results demonstrate the importance of cardiovascular risk factors present at the time of the initial event as predictors of stroke recurrence throughout the follow up period. The high number of cardioembolic recurrent strokes identified post 90-days in our study which occurred after events of a different aetiology suggests cardioembolism as a

potential risk factor with current sub-optimal management. It remains, that in spite of the known increased stroke risk associated with atrial fibrillation and the benefit of oral anticoagulation in reducing stroke risk, AF patients are not on adequate treatment. This can result from a variety of reasons such as patients preferences, reduced awareness of stroke risk among physicians and difficulties detecting AF. The ongoing focus in the development of non invasive and invasive devices with longer term monitoring should lead to improved detection of occult atrial fibrillation thereby reducing this risk further.[54,55]

Our results have several implications for clinical practice. Firstly, the knowledge of key factors associated with early and late recurrence helps therapeutic decision making. We need more reliable methods to detect atrial fibrillation given its increased risk with ageing and long term stroke. The risk of late recurrent ischaemic stroke is high and the role of secondary prevention, given the potential differences in aetiology requires further research. Further work, to reliably identify and treat the causes late recurrent stroke should reduce this risk.

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Chapter 10

Conclusions and further research

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10.5 Identification of risk factors for early and late ischaemic stroke recurrence **239**

10.1 Early use of existing secondary prevention and reduction in early risk of ischaemic stroke

I have shown that urgent assessment and early initiation of a combination of existing secondary preventive treatments can reduce the risk of early recurrent stroke after TIA or minor stroke by about 80% without increasing bleeding event rates. This study was not a randomised comparison, but it produced a reliable estimate of the effect of urgent treatment of TIA and stroke. This study was nested in a rigorous and well established population- based study of all incident and recurrent TIA and stroke, with identical methods of case ascertainment, diagnosis, investigation, and follow up in both phases, therefore I could reliably determine any clinically significant effect on outcome.

The observed reduction in risk of recurrent stroke was also consistent with that predicted to result from use of combination of treatments given. The low risk of stroke in phase 2 in patients with TIA who were referred to the study clinic is consistent with other studies in which patients with TIA are treated urgently and intensively. Moreover, there was no increased risk of bleeding (major and minor) in both phases in spite of earlier and more intensive use of secondary prevention.

More evidence from randomised trials is required to establish the effects of individual classes of drugs, in view of the substantial benefit of the combination of such treatments. Such trials should assess the effects of treatment in the acute phase of stroke and TIA. In particular, I await the results of the POINT trial evaluating the effects of combined antiplatelet therapy, aspirin and clopidogrel verus aspirin alone in the acute phase of TIA and minor stroke. In addition, more evidence on the effect of blood pressure lowering in the acute phase after TIA and minor stroke

is also required. Furthermore, long-term follow up studies are also required to determine the long term effect of treatment in the acute phase.

10.2 Risk of bleeding in aspirin naïve patients treated acutely with dual antiplatelet treatment- aspirin and clopidogrel

Given the high early risk of ischaemic stroke, a short course of treatment with aspirin plus clopidogrel (A+C) might be particularly beneficial. Although the MATCH trial of A+C versus clopidogrel alone showed no benefit of longer-term combination treatment, there was a beneficial trend in the subgroup of patients randomised within 7 days of a TIA or stroke. Most recently, the FASTER Pilot (Fast Assessment of Stroke and Transient Ischemic Attack to prevent Early Recurrence) reported a trend towards a reduced early risk of stroke with A+C versus AO in patients with TIA or minor ischaemic stroke in the previous 24 hours. In the EXPRESS Study, early preventive treatment after TIA and minor stroke, including the use of A+C in high-risk patients, reduced early recurrent stroke by 80% without increasing bleeding complications, but safety data were not reported separately for patients given A+C.

I therefore, performed a pooled analysis using data from the EXPRESS study and FASTER pilot study. The 90 day risk of major/life-threatening bleeding on A+C occurred in 4.8% of aspirin-naïve versus 0.5% in prior-aspirin patients (p=0.009).

Although based on relatively few outcomes, the high risk of major bleeding on A+C acutely after TIA or minor stroke in aspirin-naive patients is a cause for concern. The potential risk to patients is sufficient to mandate detailed monitoring of bleeding risk in ongoing trials and stratify results by whether patients were aspirin-naïve.

10.3 Rebound thrombotic events following discontinuation of a short course clopidogrel in TIA and minor stroke

The combination of aspirin and clopidogrel is indicated after acute coronary events and possibly for a short period after TIA or minor ischaemic stroke. Early discontinuation of clopidogrel results in a transient “rebound” increase in risk of recurrence in acute coronary syndromes. I have shown from this study that discontinuation of a short course of clopidogrel given for 30 days to high risk TIA or minor ischaemic stroke does not increase the risk of recurrent ischaemic events.

Although larger studies are required, my findings suggest there is unlikely to be a large rebound effect after discontinuation of a 30-day course of clopidogrel in acute TIA and minor ischaemic stroke. However, planned trials of aspirin and clopidogrel in the acute phase after TIA or stroke should still follow-up beyond the cessation of clopidogrel treatment.

10.4 Long term risks and predictors of bleeding on Antiplatelet treatment

Antiplatelet drugs are effective for preventing recurrent ischaemic events or death in patients with acute coronary syndromes (ACS), transient ischaemic attack (TIA) and ischaemic stroke. Against this benefit they increase the risk of major gastrointestinal or extracranial bleeds. As newer and more potent antiplatelet therapies and interventional methods are emerging it is important to consider the application of existing and new therapies and strategies of care in the real world setting.

Given the lack of data on long term bleeding risk among those treated with antiplatelets, and the potential limitations of existing bleed scores among ACS populations, I derived a bleed risk model in the stroke and TIA patients treated with antiplatelet agents, ascertained throughout the OXVASC study period (April 1, 2002 to March 31st 2008) and validated in a cohort of ACS patients ascertained in OXVASC throughout the same period.

Although this score appeared to validate well in the ACS population, I would like to externally validate it in other cohorts, and if possible develop a bleed risk score tool aiding physicians to quantify bleeding/ischaemic risk in patients treated with antiplatelet agents.

10.5 Bleeding risk and age

Antiplatelet drugs are effective for preventing recurrent ischaemic events however, against this benefit they increase the risk of major gastrointestinal or intracranial bleeds. As elderly patient are often excluded from clinical trials my aim was to determine rates and outcomes of bleeding events associated with antiplatelet therapy in elderly patients (>70 years old) with ACS, stroke or TIA.

I used a bleed risk model, derived in the stroke and TIA patients ascertained throughout the OXVASC study period (April 1, 2002 to March 31st 2008) and validated in a cohort of ACS patients ascertained in OXVASC throughout the same period. I have shown that the annual rate of major bleeding increased with age however, similarly the ischaemic risk increased with age. In addition to increased fatality following bleeding events, increasing rates of disability following bleeding events occurred in the older cohort.

Therefore, future trials should aim to include elderly patients as data cannot always be extrapolated from younger patients in terms of absolute risks and benefits of treatment in this cohort.

10.6 Long-Term Prognosis of TIA and Stroke

Several treatments are effective in preventing stroke in the long-term after a TIA or minor ischaemic stroke. The risk of stroke after TIA is highest during the early phase and then declines over time but remains elevated for several years. However, whilst much is known about

prognosis and predictors of risk early after TIA and ischaemic stroke, there is much less published data on the risk after minor stroke, particularly in the medium and long-term.

In this study, the recurrent stroke risks after TIA and minor stroke remained similar up to 90 days, however beyond 90 days, recurrence risk after minor stroke remained high. Although it has previously been shown that it is possible to reduce the high early risk of stroke by early initiation of secondary prevention after TIA and minor stroke, I have shown there is a high later stroke risk after minor stroke which has not been reduced by current secondary prevention methods.

Therefore in ongoing research, I hope to compare the findings from this study with data from OCSP(Oxford Community Stroke Project) in further defining prognosis of TIA and stroke and highlighting the long term commitment needed to control risk factors to protect patients from further recurrence. Furthermore, I aim to review how disabling long term recurrent strokes are as an outcome measure and whether increased use of secondary prevention has any effect in reducing disability related to stroke recurrences.

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10.7 Identification of risk factors for early and late ischaemic stroke recurrence

Factors that increase the risk of a first ever stroke may not necessarily be as important in predicting a late recurrent stroke.

In this study I found different predictors of early and late stroke recurrence. Symptomatic carotid stenosis, and premorbid hypertension were the main risk factors for early recurrence, while age and atrial fibrillation were the main risk factors for late recurrence. Predictors of recurrence were broadly similar whether the type of presenting event was TIA or stroke. If TIA was the presenting event specific risk factors for any recurrent stroke were frailty and prior hypertension. If stroke was the presenting event diabetes was a risk factor. Increasing age. cardioembolism as the

underlying aetiology were predictive of recurrences irrespective of whether the presenting event was TIA or stroke demonstrating the importance of cardiovascular risk factors in long term stroke management.

The ongoing focus in the development of non invasive and invasive devices with longer term monitoring should lead to improved detection of occult atrial fibrillation thereby reducing this risk further. Therefore in ongoing research, I hope to determine whether improved detection and treatment of risk factors of late recurrence can reduce this risk further.

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53.Chandratheva A, Lasserson DS, Geraghty OC, Rothwell PM. Patient behaviour immediately after TIA and minor stroke in 1000 consecutive patients. Stroke. 2010 Jun;41(6):1108-14

54.Liao J, Khali Z, Scallan C, Morillo C, O'Donnell M. Non invasive cardiac monitoring for detecting Paroxysmal Atrial fibrillation or flutter after acute ischaemic stroke: A systematic review. Stroke 2007;38;2935-40

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Appendix 1 ICD-10 diagnostic codes

ICD-10 Ischaemic Heart Disease

I200	Unstable angina
I201	Angina pectoris with documented spasm
I208	Other forms of angina pectoris
I209	Angina pectoris, unspecified
I210	Acute transmural myocardial infarction of anterior wall*
I211	Acute transmural myocardial infarction of inferior wall*
I212	Acute transmural myocardial infarction of other sites*
I213	Acute transmural myocardial infarction of unspecified site*
I214	Acute subendocardial myocardial infarction*
I219	Acute myocardial infarction, unspecified*
I220	Subsequent myocardial infarction of anterior wall
I221	Subsequent myocardial infarction of inferior wall
I228	Subsequent myocardial infarction of other sites
I229	Subsequent myocardial infarction of unspecified site
I230	Haemopericardium as curr comp folow acut myocard infarct
I231	Atral sept defect as curr comp folow acut myocardal infarct
I232	Ventric sep defect as curr comp fol acut myocardal infarc
I233	Rup cardac wal withou haemopercard as cur comp fol ac MI
I234	Rup chordae tendinae as curr comp fol acut myocard infarct
I235	Rup papilary muscle as curr comp fol acute myocard infarct
I236	Thromb atrium/auric append/vent as curr comp foll acute MI

I238	Oth current comp following acute myocardial infarction
I240	Coronary thrombosis not resulting in myocardial infarction
I241	Dressler's syndrome
	Other forms of acute
	ischaemic heart
I248	disease
I249	Acute ischaemic heart disease, unspecified
I250	Atherosclerotic cardiovascular disease, so described
I251	Atherosclerotic heart disease
I252	Old myocardial infarction
I253	Aneurysm of heart
I254	Coronary artery aneurysm
	Ischaemic
I255	cardiomyopathy
I256	Silent myocardial ischaemia
	Other forms of chronic ischaemic
I258	heart disease
	Chronic ischaemic heart disease,
I259	unspecified
I460	Cardiac arrest with successful resuscitation
I460	Successful resusitation
I461	Sudden cardiac death, so described
I469	Cardiac arrest, unspecified

ICD-10 Cerebrovascular disease

G450-G468	Vascular brain syndromes
H340-H432	Retinal artery occlusion
H348	Retinal artery occlusions
I600-I609	Subarachnoid Haemorrhage
I610-I619	Intracerebral Haemorrhage
I620-I629	Other intracranial haemorrhages
I630-I64X	Cerebral infarction-stroke non specified
I650-I670	Cerebral artery occlusion and dissection of cerebral arteries
I671- I698	Acute and chronic cerebrovascular diseases

ICD-10	**Haemorrhage**
I850	Oesophageal bleeding
K250-K922	Upper gastrointestinal bleeding
K55-K63	Lower gastrointestinal bleeding
N938-N939	Uterine bleeding
R040-R049	Respiratory bleeding

Appendix 2

DATA NOTIFICATION FORM TIA AND STROKE

SUBJECT ID NO:

Patient identification label

Was patient interviewed	**Y**	**N**	**U**

If NO why not?	Please tick
1	Refused interview
2	Aphasic and relatives could not be contacted
3	Too unwell/ multiple medical problems
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted
5	Late ascertainment and no reply to invitation to join study
6	Ascertainment after death
7	Diagnosis uncertain
9	Unknown

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
Email address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

OXVASC db:

11 digit OXCODE for notification event											

Consultant	

1 Physician	5 Vascular surgeon
2 Physician with stroke interest	6 Cardiologist
3 Neurologist	7 Neurosurgeon
4 General surgeon	9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name or Initials					

Summary Diagnosis		Specify:		
S= Stroke	R= Retinal artery Occlusion	B= Burden		
T= TIA		Z= Other (specify)		
A= Amaurosis fugax	M= MI			

Is this the first ever in a lifetime (incident) stroke? *	**Y**	**N**	**U**
Is this the first ever in a lifetime (incident) TIA? *	**Y**	**N**	**U**

* Please tick as appropriate

Date of notification event (DD-MM-YY)				
Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp	4 Outpatients 5 Home 6 Other (specify)		Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up	4 Other (specify) 6 No follow-up 7 Home visits		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records	5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital (specify) 4 Other referrals (specify)	5 Health authority search 6 Death 7 Troponin 9 Other (specify)		Specify:

Other sources of notification (select all appropriate)	1	2	3	4
	Specify:	Specify:	Specify:	Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by other	Y	N	U

source of ascertainment? (please circle)			

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 3+4**

Narrative history & examination

Did patient have PRANS events?	**Y**	**N**	**U**	**Date most recent**	**OXCODE for PRANS event:**
				U	

Details:

Notification event*		What did you think was wrong?
Date DD-MM-YY	**Time** 24 hr clock	
U	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?	U		
Who called for help?	U		
If you did not call for help at time of event, why not?	U		

Who did you 1st call for help?	1= Medical 2=Non-Medical 9= Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
			Please give date/time for any 1st call *	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st medical call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

* This could be the same date and time as the first call for medical help (please provide anyway)

Calls for medical attention	**Date** DD-MM-YY	**Time** 24 hr clock

GP by telephone	**Y / N**		:
GP in person	**Y / N**		:
Telephoned 999	**Y / N**		:
Went to A&E in person	**Y / N**		:
Telephoned NHS direct	**Y / N**		:
Went to OEH	**Y / N**		:
Other (Specify)	**Y / N**		:

Outcome of first call for medical assistance

				Date DD-MM-YY	**Time** 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		: U
If GP referred subject to OXVASC clinic: **Notification by GP to OXVASC**					: U
If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		: U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					: U
Assessment by OXVASC staff					: U

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All fields unknown on page 5+6**

Duration of symptoms Please leave blank for stroke	Hrs:	Mins:

Onset on wakening from sleep?			**Y**	**N**	**U**
Time awake (ignore if onset not on wakening from sleep) 24 hr clock			:	U
Activity at onset (within 2 hrs of onset)				1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?				
Drugs within previous hour			**Y**	**N**	**U**
Meal within previous hour			**Y**	**N**	**U**
Record exact activity				U
Location of event	1 Home 2 Work 3 Leisure (non-sport)	4 Sport 8 Other (specify) 9 Unknown		Specify:

ONSET ANGER SCALE		Anger level
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= **Unknown**

Was there a further event between notification event and assessment?	Y	N	U

If yes to above please indicate number of events between any of the following:	
	No. events
Between notification event and seeing GP/ other medical opinion (including notification event)	# U
Between seeing GP and notification by GP to OXVASC	# U
Between notification by GP and OXVASC assessment	# U

Were there any events in the month preceding the notification event?	Y	N	U
How many events were there in the month before notification event?	# U		

HISTORY OF NOTIFICATION EVENT

Event	History of events between notification event and assessment		
1	**Notification event itself**		
2		**Event date*:** U	**Time** : U
3		**Event date*:** U	**Time** : U
4		**Event date*:** U	**Time** : U
5		**Event date*:** U	**Time** : U

Use extra piece of paper for event 6 onwards. * DD-MM-YY 24 Hr clock

If admitted as a result of the notification event (use ambulance sheet)

Was subject admitted to hospital? as a direct result of the notification event	Y	N	U

If YES then please answer:

Was subject admitted by ambulance?	Y	N	U

If admitted by ambulance:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service with patient	U	: U
Arrival of emergency service in Hospital *	U	: U

* If not on ambulance sheet use blue admissions

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

ACS		Cerebral		
NSTEMI	**STEMI**	**TIA**	**CVA**	**Peripheral**

Prior acute events?	Y	N	U	Y	N	U	Y	N	U	Y	N	U	Y	N	U
	Possible*			Possible*			Possible*			Possible*					
# of events			U			U			U			U			U
Date of most recent			U			U			U			U			U

* Please circle if it is unclear what type of event it was

BACKGROUND MEDICAL HISTORY

OXVASC db: 4

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U	Age at diagnosis		
Please tick if:	**All No**	**All U**	**Tick if:**	**All ageU**
Angina			U	
Hypertension			U	
Myocardial infarction			U	
Diabetes Mellitus			U	
Valvular heart disease			U	
Intermittent Claudication			U	
Peripheral vascular intervention			U	
Atrial fibrillation			U	

Treatment

Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Nature: U

Age at 1st intervention:

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			Angioplasty			Bypass			Amputation		
Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

1 Current
2 Previous
9 Unknown

Choose from above:

TREATMENT
1=Cardioversion
2=Paroxysmal
3=Persistent
4=Permanent
9=Unknown

Choose from above:

Pace maker			Type pacemaker
Y	N	U	U

Hyper lipidaemia		U	**Treatment**								
			Diet			**Statin**			**Other**		
			Y	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Cardiac failure		U	**Treated** (loop diuretic)**?**						**Y**	**N**	**U**
	Y/N/U	**Age at diagnosis**									

OXVASC db: 6

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose	**Age at:**											
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**									
Migraine					**With Aura?**			**Prolonged aura (>1hr)**					
					Y	**N**	**U**	**Y**	**N**	**U**			
Epilepsy			**Age @ Diagnosis**										
			U										
Cardiac intervention			**Age @ 1st Intervention**		**Number**	**Angiogram**			**Angioplasty**			**Stent**			**Bypass**		
			U			**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
			Results of angiogram:			U											
Carotid: Endarterectomy			**Age @ 1st operation**		**Side**												
			U		**Left**			**Right**			**Both**						
Carotid: Stent			**Age @ 1st operation**		**Side**												
			U		**Left**			**Right**			**Both**						
Asthma																	
Liver disease																	
COAD																	

Peptic ulcer disease											
Previous venous thromboses			**Number**		**Details:** Please enter U if not known						
Any other past medical history		**Details:** Please enter U if not known									
SLE Look in notes		**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**			**Lupus anticoagulant (LA)**					
		U	**Y**	**N**	**U**	**Y**	**N**	**U**			

OXVASC db: 7

CONTINUING BACKGROUND MEDICAL HISTORY

PRIOR TO NOTIFICATION EVENT ONLY

	Y/N/U choose			
Please tick if:	**All No**	**All U**		
Autoimmune disease			**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter No or Unknown.			
Nosebleeds				
Bleeding after dental extraction				
Any cancer				
End stage renal failure/ dialysis				

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT					
Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you currently take any vitamin supplements?		Y	N	U
Vitamin B	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) current vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter “No other”.

OXVASC db: 8

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification Event			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2		3	4	5	
Previous stroke or TIA?		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?**		**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins)	
Y N U							**recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y	N	#			
	L		Y	N				
Hemi-spheric TIA carotid	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Vertebro-basilar stroke			Y	N				
Vertebro-basilar TIA			Y	N			Mins: U	Mins: U
Stroke unknown territory			Y	N				
TIA unknown territory			Y	N			Mins: U	Mins: U
Amau-rosis fugax	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y	N				
	L		Y	N				

Comments:

MEDICATION

OXVASC db: 9

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG					**Dose mg/day**	**Other unit?** Please specify
1	**Aspirin**	Y	N	U		U	U
2						U	U
3						U	U
4						U	U
5						U	U
6						U	U
7						U	U
8						U	U
9						U	U
10						U	U
11						U	U
12						U	U
13						U	U
14						U	U
15						U	U
16						U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter “No other” here.

OXVASC db: 9

BACKGROUND FAMILY HISTORY

Patient is adopted	**Y**	**N**	**U**	**Twin**	**Y**	**N**	**U**
Total number of siblings (inc)				**Any vascular history**	**Y**	**N**	**U**

Oldest →

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	**Y/N/U**														
	Age 1st*														
MI	**Y/N/U**														
	Age 1st*														
PVD	**Y/N/U**														
	Age 1st*														
BrainHaem	**Y/N/U**														
	Age 1st*														
Diabetes	**Y/N/U**														
	Age 1st*														
Hyperlip aedemia	**Y/N/U**														
	Age 1st*														
Hypertension	**Y/N/U**														
	Age 1st*														
	Sibling* is:														

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	**A**	**D**	**U**			U	U
Father	**A**	**D**	**U**			U	U
Sib1 oldest	**A**	**D**	**U**	**M**	**F**	U	U
Sib 2	**A**	**D**	**U**	**M**	**F**	U	U
Sib 3	**A**	**D**	**U**	**M**	**F**	U	U
Sib 4	**A**	**D**	**U**	**M**	**F**	U	U
Sib 5	**A**	**D**	**U**	**M**	**F**	U	U
Sib 6	**A**	**D**	**U**	**M**	**F**	U	U
Sib 7	**A**	**D**	**U**	**M**	**F**	U	U
Sib 8	**A**	**D**	**U**	**M**	**F**	U	U
Sib 9	**A**	**D**	**U**	**M**	**F**	U	U

Sib 10	**A**	**D**	**U**	**M**	**F**	U	U
Sib 11	**A**	**D**	**U**	**M**	**F**	U	U
Sib 12 youngest	**A**	**D**	**U**	**M**	**F**	U	U

Total number of ☐ **Male** ☐ **#** ☐ **Female**

subject's children
please fill in "U" if unknown

OXVASC db: 10

AUTOIMMUNE HISTORY- Personal			
Do you have an autoimmune disease?	***Y***	***N***	***U***
Thyroid	***Y***	***N***	***U***
Early onset diabetes	***Y***	***N***	***U***
Pernicious anaemia	***Y***	***N***	***U***
Rheumatoid arthritis	***Y***	***N***	***U***

SMOKING			
Have you ever smoked?	***Y***	***N***	***U***
Are you a lifetime non-smoker?	***Y***	***N***	***U***
Smoking oddities *(pipes etc)*			*U*
Are you an ex-smoker?	***Y***	***N***	***U***
If so at what age did you stop?	*Age:*		*U*
<u>If you have stopped</u>: ***How many years did you smoke?***	*# Years:*		*U*
Do you currently smoke?	***Y***	***N***	***U***
How many do you smoke per day?	*Number:*		*U*
<u>If you are still smoking</u>: ***How many years have you smoked?***	*# Years:*		*U*

Premorbid modified Rankin

Do you have any symptoms?	***Y***	***N***	***U***
Are you able to look after yourself and carry out normal activities?	***Y***	***N***	***U***
Does anyone else help pay the bills, do the shopping, cleaning etc?	***Y***	***N***	***U***
Do you need someone to help you walk?	***Y***	***N***	***U***
Do you need help to wash yourself?	***Y***	***N***	***U***
Do you need to be lifted in and out of bed?	***Y***	***N***	***U***

0 = no symptoms at all *1 = no significant disability despite symptoms: able to carry out all usual duties and activities* *2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance* *3 = moderate disability: requiring some help, but able to walk without assistance* *4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance* *5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention* *6 = death*	*Score*

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS <u>PRIOR</u> TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?	***Y***	***N***	***U***	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?	***Y***	***N***	***U***	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?	***Y***	***N***	***U***	
d) When you get any pain or discomfort in your chest what do you do? 1=stop 2=slow down 3= continue at same pace 9= unknown				
e) Does it go away when you stand still?	***Y***	***N***	***U***	
f) How soon? **1**=10 minutes or less **2**= > 10 minutes **9**= unknown				

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	***Y***	***N***	***U***

PART C

a) Do you get pain in either leg when you are walking?	***Y***	***N***	***U***
b) Does this pain ever begin when you are standing still or sitting?	***Y***	***N***	***U***
c) Do you get this pain in your calf (or calves)	***Y***	***N***	***U***
d) Do you get it when you walk up hill or hurry?	***Y***	***N***	***U***
e) Do you get it when you walk at an ordinary pace on the level?	***Y***	***N***	***U***

f) Does the pain ever disappear while you are still walking?		***Y***	***N***	***U***
g) What do you do if you get it when you are walking?	**1**=stop **2**=slow down **3**=continue at same pace **9=** *unknown*			
h) What happens if you stand still?	1=usually continues for more than 10 minutes **2**= usually disappears in 10 minutes or less **9**= unknown			

OXVASC db:

<u>Premorbid</u> Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent

Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres 3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

OXVASC db: 13-16

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average	4 Prone to stress 5 Highly stressed 9 Unknown	
In terms of stress what kind of person are you?				
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing	5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**SPOUSE or:**	
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility		
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer	4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow	3 Single 4 Separated	5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home	4 Unemployed 5 Unable to work	6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)				U

Socioeconomic class		1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known
Alcohol units per week*		* *Please use guidelines provided below*
Age left school	U	
Education		1 Basic 2 Further 3 Higher 9 Not known
Age left full-time education	U	

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% -units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% -units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

SLEEP

What is the likelihood of you dozing in the following <u>three</u> situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8 = I don't know 9 = Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION			
How is your appetite?		1= Good 2= Normal	3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U		
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week	3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U		
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed	4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week	4= 1 /day 5= 2-4 /day 6= > 4 /day 9= Unknown

OXVASC db: 18

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	**Y**	**N**	**U**	
DRIVING	Do you drive?	**Y**	**N**	**U**	
Handedness	Left/Right/Both/Unknown				R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)					1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?	**Y**	**N**	**U**	**How upset were you by these events?**
Death or serious illness of close friend or relative	**Y**	**N**	**U**	
Financial difficulty	**Y**	**N**	**U**	
Divorce or break up of close friend or relatives	**Y**	**N**	**U**	
Major conflict with children or grandchildren	**Y**	**N**	**U**	
Muggings, robberies, accidents	**Y**	**N**	**U**	

1= Very much
2= Moderately
3= Not too much
9= Unknown

OTHER

AMTS

Age	**0**	**1**
Time (nearest hour)	**0**	**1**
Year	**0**	**1**
Name or place	**0**	**1**
Recognition of 2 persons	**0**	**1**
Date and month of birth	**0**	**1**
Date of 1st World War	**0**	**1**
Queen's name	**0**	**1**
Count 20-1 backwards	**0**	**1**
5 mins recall full street address	**0**	**1**

0= Fail
1= Pass

If AMTS not done explain why not

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.

OXVASC db: 19

19

GENERAL EXAMINATION					
	cm*		**inches***		
Collar size					U
Waist measurement					U
Hip measurement					U
Height					U
	kg*		**stone***		
Weight					U
Arcus	Y	N	U		
Xanthelasma	Y	N	U		
Nicotine staining	Y	N	U		
Ear crease	Y	N	U		
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown	

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

For all patients: **1st HEART RATE and BLOOD PRESSURE post event**				
	Date DD-MM-YY		**Time** 24 hr clock	
	U		:	U
Blood pressure 1st BP post event	**Sys**		**Dias**	U
Heart rate 1st HR post event				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic O Other N Not recorded U Unknown			

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE at admission					
Temp on admission		ºC			U
Admission Heart rate					U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown				
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown				
BP on admission		Sys	Dias		U
Sats/air		**%**			U
BM					U

For all subjects: HEART RATE and BLOOD PRESSURE at assessment				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U

Any pre-existing neurological disability?	Y	N	U

OXVASC db:

STROKE	Normal exam		All Unknown	

Prestroke disability	U	**Predicted 30 day Rankin**	U

SYMPTOMS AT ONSET

	Weakness		**Sensory**			**Eyes/vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemianopia**			**Dysphasia**	
Arm					**Monocular**			**Dysarthria**	
Hand								**Vertigo**	
Leg					**Diplopia**			**Headache**	

FINDINGS ON EXAMINATION:

Glasgow Coma Scale			
Eyes	**/4**	1 – No eye opening 2 – Eye opening in response to pain	3- Eye opening in response to speech 4- Spontaneous eye opening
Motor	**/6**	1 – No response to pain 2 – Extensor posturing to pain 3 - Flexor response to pain	4 – Withdrawal to pain 5 - Localizing response to pain 6 – Obeys commands
verbal	**/5**	1 – No speech 2 – Incomprehensible speech 3 – Inappropriate speech	4 – Confused conversation 5 – Oriented

	Weakness		**Sensory**			**Eyes/ vision**		**Other**	
	Right	Left	Right	Left		Right	Left		
	Please fill in: Y / N / U					Y / N / U			Y / N / U
Face					**Hemianopia**			**Dysphasia**	
Arm					**Gaze palsy**			**Dysarthria**	
Hand					**Nystag mus**			**Ataxia**	
Leg								**Neglect**	

NIH STROKE SCALE For instructions see separate sheet						Tick if: NOT DONE	
LOC		LOC questions		LOC commands		Best gaze	
Best visual		Facial Palsy		Right arm		Left arm	
Right leg		Left leg		Limb ataxia		Sensory	
Language		Dysarthria		Neglect		**TOTAL**	

STROKE PROGNOSIS	
Date of prognostic markers DD-MM-YY	U

OXVASC db: 21

Please tick:	**All fields normal**	**All fields unknown**

Hemianopia	1= No deficit 2= Mild 3= Moderate 4= Severe 9= Unknown	
Inattention		
Dysarthria		
Swallowing		
Dysphasia		

Limb deficit (able to lift both arms to horizontal MRC≥3)	**Y**	**N**	**U**
Unable to sit independently	**Y**	**N**	**U**
Unable to stand independently	**Y**	**N**	**U**
Unable to walk independently (Cannot walk without help of another or aid)	**Y**	**N**	**U**
Urinary incontinence	**Y**	**N**	**U**

Catheterised	Y	N	U

ABCD^2 score

A (Age); 1 point for age ≥60 years ☐

B (Blood pressure) ≥ 140/90 mmHg); 1 point for hypertension at the acute evaluation ☐

C (Clinical features); 2 points for unilateral weakness, 1 for speech disturbance without weakness ☐

D (Symptom duration); 1 point for 10-59 minutes, 2 points for ≥60 minutes ☐

D (Diabetes); 1 point ☐

Total ☐

OXVASC db: 22

MANAGEMENT - DISCHARGE

MANAGEMENT			
Did you discuss the need to change diet with subject?	**Y**	**N**	**U**
Did you discuss the need to reduce weight with subject?	**Y**	**N**	**U**
Did you discuss the need to quit smoking with subject?	**Y**	**N**	**U**

DRUG MANAGEMENT

	New			**Continued**			**Contra-indicated**		
Aspirin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Appendix 3

DATA NOTIFICATION FORM NSTEMI AND STEMI

SUBJECT ID NO:

Patient identification label

Was patient interviewed	Y	N	U
If NO why not? Please tick			
1	Refused interview		
2	Aphasic and relatives could not be contacted		
3	Too unwell/ multiple medical problems		
4	Dementia (need to record MMSE or AMTS) and relatives could not be contacted		
5	Late ascertainment and no reply to invitation to join study		
6	Ascertainment after death		
7	Diagnosis uncertain		
8	Diagnosis changed after assessment from diagnosis not requiring interview (eg Trop>1) to diagnosis requiring interview (eg NSTEMI)		
9	Unknown		

Patient contact details	
Telephone (day)	
Telephone (evening)	
Mobile	
Fax number	
mail address 1	
Email address 2	

Next of kin details	
Relationship to patient	
First name	
Surname	
Address 1st line	
Address 2nd line	
City/town	
County	
Postcode	
Country	
Telephone (day)	
Telephone (evening)	
Mobile phone no	
Fax number	
Email addres	

11 digit OXCODE for notification event											

STEMI, NSTEMI

Consultant	

1 Physician	5 Vascular surgeon
2 Physician with stroke interest	6 Cardiologist
3 Neurologist	7 Neurosurgeon
4 General surgeon	9 Other

Name Examiner

GP DETAILS					
Surname					
Location		01 Beaumont Street 03 East Oxford 04 Berinsfield	05 Malthouse 06 Kidlington (Exeter) 07 Wantage	08 Marcham Road 09 Stert Street 10 Kidlington (KYMG) 99 Other (please provide)	Other:
First name:					
or Initials:					

Summary Diagnosis for: STEMI / NON-STEMI				
Non ST elevation MI (NSTEMI)	Y	N	U	*Data entry: if Y use NSTEMI*
ST elevation MI (STEMI)	Y	N	U	*Data entry: if Y use STEMI*
Lytic	Y	N	U	
Unstable angina	Y	N	U	*Data entry: if Y use ANGINA*

Is this the first ever in a lifetime (incident) NSTEMI?	Y	N	U
Is this the first ever in a lifetime (incident) STEMI?	Y	N	U

Date of notification event (DD-MM-YY)				
Location of interview	1 JRH inpatient 2 RI in patient 3 Community hosp	4 Outpatients 5 Home 6 Other (specify)		Specify:
Follow-up plan at 1 month	1 OXVASC TIA clinic 3 Refused follow-up	4 Other (specify) 6 No follow-up 7 Home visit		Specify:
Info on form obtained from	1 Patient 2 Relative 3 GP 4 hospital records	5 Death certificate 6 Other (specify)		Specify:
Source of 1st notification	1 GP 2 JRH admission 3 Other Hospital	5 Health authority search 6 Death 7 Troponin		Specify:
Other sources of notification			1	2 3 4

of notification (select all appropriate)	(specify) 9 Other (specify) 4 Other referrals (specify)	Specify:	Specify:	Specify:	Specify:

If one had not identified the patient via the route of 1st notification would patient have been identified by [illegible] source of ascertainment? (circle) **All: 1**	Y	N	U

STEMI and NON-STEMI

Narrative history & examination

SYMPTOMS					
Chest pain				**Y**	**N**	**U**
Radiation to arms & neck				**Y**	**N**	**U**
SOB	**Y**	**N**	**U**	Description:		
Duration of chest pain in minutes				Mins: U		

Any previous chest pain, SOB, diagnosis of angina or cardiac investigation/ intervention	Y	N	U

CHARACTERISTICS OF ANGINA (if known angina)			
More severe	Y	N	U
More prolonged	Y	N	U
More frequent	Y	N	U
Angina at rest	Y	N	U
Angina on minimal exertion (lower threshold)	Y	N	U
New onset angina within last 2 months with minimal exertion	Y	N	U
ECG changes compatible with ischaemia	Y	N	U
History of, or new, positive exercise test	Y	N	U

Prior or new percutaneous catherisation (≥ 50% stenosis)						Y	N	U
Prior or new coronary intervention or CABG						Y	N	U
Any potential secondary aetiology If YES please tick below						Y	N	U
Arrythmia	**Anaemia**	**Thyroid disease**	**Sepsis**	**Surgery**	**Other:**			

HISTORY OF NOTIFICATION EVENT	**Please tick if:**	**All STEMI: 2 NSTEMI: 2 shown on page 4+5**

STEMI and NON-STEMI

Notification event*		**What did you think was wrong?**
Date DD-MM-YY	**Time** 24 hr clock	
	: U	

* The event that led to first seeking medical attention

Did notification event occur during hospital stay (while admitted for other reason)?	**Y**	**N**	**U**
Were you alone?	**Y**	**N**	**U**
If you were with someone who was it?			U
Who called for help?			U
If you did not call for help at time of event, why not?			U

Who did you 1st call for help?	1= Medical 2=Non-Medical 9=Unknown		**Date** DD-MM-YY	**Time** 24 hr clock
			Please give date/time* for any 1st call	
1st call for ANY help non-medical or medical				: U
			Please give date/time for 1st medical call	
1st call for MEDICAL help GP/ A&E / 999/ NHS direct				: U

* This could be the same date and time as the first call for medical help

Outcome of first call for medical assistance

HISTORY OF NOTIFICATION

STEMI: 2
NSTEMI: 3
ANGINA: 3

STEMI and NON-STEMI

				Date DD-MM-YY	**Time** 24 hr clock
Seen by GP / A&E <u>in person</u>?	**Y**	**N**	**U**		**:** U

If subject was not referred to OXVASC: **Admitted to hospital?**	**Y**	**N**	**U**		**:** U
If admitted to hospital but not referred to OXVASC: **Ascertainment** by OXVASC staff					**:** U
Assessment by OXVASC staff					**:** U

HISTORY OF NOTIFICATION EVENT

STEMI

Onset on wakening from sleep?			**Y** **N** **U**	
Time awake (ignore if onset not on wakening from sleep) 24 hr clock			**:** U	
Activity at onset (within 2 hrs of onset)				1= Asleep 2= Sedentary 3= Mild-moderate 6= Strenuous 9= Unknown
What were you doing in the same 2 hrs on the day prior to the event?				
Drugs within previous hour			**Y** **N** **U**	
Meal within previous hour			**Y** **N** **U**	
Record exact activity			U	
Location of event	1 Home 2 Work 3 Leisure (non-sport)	4 Sport 8 Other (specify) 9 Unknown		Specify:

ONSET ANGER SCALE		**Anger level**
Onset NOT on wakening from sleep	In the **two hours prior to the event** what best describes your emotional state from the list provided?	
	In the **exact same two hours on the day prior to your event** which best describes your mood?	
OR:		
Onset ON wakening from sleep	If you had your event on wakening how were you in the **two hours before you went to bed**?	

1 = **Calm**
2 = **Busy** (but not hassled)
3 = **Mildly angry** (irritated and hassled, but does not show)
4 = **Moderately angry** (so hassled it shows in your face)
5 = **Very angry** (body tense, clenching fists or teeth)
6 = **Furious** (almost out of control, very angry, pound table, slam door)
7 = **Enraged** (lost control, throwing objects, hurting yourself or others)
9= unknown

STEMI and NON-STEMI

If admitted (use ambulance sheet)

Was subject admitted by ambulance?	**Y**	**N**	**U**

If admitted:	**Date** DD-MM-YY	**Time** 24 hr clock
Arrival of emergency service		**:**
Arrival in Hospital *		**:**

* If not on ambulance sheet use blue admissions

STEMI and NON-STEMI

Any previous acute vascular event (ACS – note STEMI or NSTEMI if known, TIA, CVA, Ischaemic limb, aneurysm) 'Have you been admitted to hospital with chest pain or a threatened heart attack?'

	ACS						**Cerebral**						**Peripheral**		
	NSTEMI			**STEMI**			**TIA**			**CVA**					
Prior acute events?	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
	Possible*			Possible*			Possible*			Possible*					
# of events			U			U			U			U			U
Date of most recent DD-MM-YY			U			U			U			U			U

STEMI: 4
NSTEMI: 4

BACKGROUND MEDICAL HISTORY

	Y/N/U	Age at diagnosis

Please tick if:	All No	All U	Tick if:	All ageU
Angina				U
Hypertension				U
Myocardial infarction				U

Diabetes Mellitus — U

Treatment									
Diet			Tablets			Insulin		
Y	N	U	Y	N	U	Y	N	U

Valvular heart disease — U

Nature: U

Intermittent Claudication — U

Peripheral vascular intervention — Age at 1st intervention: U

Site:

1 Arm
2 Leg
3 Bowel
4 Carotid
5 Abdo aneurysm
6 Thoracic aneurysm
7 Other
8 Uncertain

Type:

Angiogram			Angioplasty			Bypass			Amputation		
Y	N	U	Y	N	U	Y	N	U	Y	N	U

Result: U

Atrial fibrillation — U

1 Current
2 Previous
9 Unknown
↓
Choose from above:

1=Cardioversion
2=Paroxysmal
3=Persistent
4=Permanent
9=Unknown
↓
Choose from above:

Pace maker			Type pacemaker
Y	N	U	U

Hyper lipidaemia — U

Treatment								
Diet			Statin			Other		
Y	N	U	Y	N	U	Y	N	U

Cardiac failure — U

Treated (loop diuretic)**?** Y N U

Y/N/U	Age at diagnosis

STEMI: 5
NSTEMI: 5

CONTINUING BACKGROUND MEDIC ORY

	Y/N/U choose		Age at:	
Please tick if:	**All No**	**All U**	**Tick if:**	**All age U**

Migraine			With Aura?			Prolonged aura (>1hr)		
			Y	N	U	Y	N	U
Epilepsy		Age @ Diagnosis						
		U						
Cardiac intervention		Age @ 1st Intervention	Number	Angiogram		Angioplasty		Stent		Bypass		
		U		Y	N U	Y	N U	Y	N U	Y	N U	
		Results of angiogram:		U								
Carotid: Endarterectomy		Age @ 1st operation	Side									
		U	Left			Right			Both			
Carotid: Stent		Age @ 1st operation	Side									
		U	Left			Right			Both			
Asthma												
Liver disease												
COAD												
Peptic ulcer disease												
Previous venous thromboses			Number			**Details:** Please enter U if not known						
Any other past medical history		**Details:** Please enter U if not known										

SLE Look in notes		**Age @ Diagnosis**	**Anticardiolipin antibodies (aCL)**			**Lupus anticoagulant (LA)**		
		U	**Y**	**N**	**U**	**Y**	**N**	**U**

STEMI: 6
NSTEMI: 6

STEMI and NON-STEMI

CONTINUING BACKGROUND MEDICAL HISTORY

	Y/N/U choose			
Please tick if:	**All No**	**All U**		
Autoimmune disease			**Diagnosis**	U
Allergies	Please list all. If no allergies or unknown please enter N or U.			
Nosebleeds				
Bleeding after dental extraction				
Any cancer				
End stage renal failure/ dialysis				

LIST OF MEDICATION BEFORE ONSET OF NOTIFICATION EVENT

Aspirin	Y	N	U	**Dose** mg/day	U
Dipyridamole	Y	N	U		
Clopidogrel	Y	N	U		
Warfarin	Y	N	U	**INR**	U

Do you take any vitamin supplements?		Y	N	U
VitB	**B6?**	Y	N	U
	Folate?	Y	N	U
	B12?	Y	N	U

Names of (other) Vitamin supplements	Please list all. If no other vitamin supplements were taken at time of notification event please enter "No other".

STEMI: 7
NSTEMI: 7

STEMI and NON-STEMI

Was your BP measured at any time prior to the notification event?	**Y**	**N**	**U**
Date of most recent BP measurement prior to notification event [			U
How many times have you had your BP measured in the last year?			U

Have you ever been on OCP?	**Y**	**N**	**U**
Have you ever been on HRT?	**Y**	**N**	**U**
No of years in lifetime on HRT and/or OCP			U

		1	2		3	4	5	
Previous stroke or TIA?		**Date most recent event** DD-MM-YYYY Prior to notification event	**Any other previous ?**		**No. of previous events** ALL events prior to notif. Event	**Date 1st event** DD-MM-YY Provide date even if same as most recent (number previous events = 1)	**Duration** (mins)	
Y N U							**recent**	**longest**
Hemi-spheric stroke carotid	**R**		Y	N	#			
	L		Y	N				
Hemi-spheric TIA carotid	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Vertebro-basilar stroke			Y	N				
Vertebro-basilar TIA			Y	N			Mins: U	Mins: U
Stroke unknown territory			Y	N				
TIA unknown territory			Y	N			Mins: U	Mins: U

Amau-rosis fugax	**R**		Y	N			Mins: U	Mins: U
	L		Y	N			Mins: U	Mins: U
Retinal infarc-tion	**R**		Y	N				
	L		Y	N				

Comments:

STEMI: 8
NSTEMI:

STEMI and NON-STEMI

MEDICATION

Was subject taking medication <u>at the time of</u> the notification event? If YES provide names below	Y	N	U

	NAME DRUG					**Dose mg/day**	**Other unit?** Please specify
1	**Aspirin**	Y	N	U		U	U
2						U	U
3						U	U
4						U	U
5						U	U
6						U	U
7						U	U
8						U	U
9						U	U
10						U	U
11						U	U
12						U	U

13		U	U
14		U	U
15		U	U
16		U	U

Other additional medication + dose/unit	If all lines above have been used and subject is not taking other medication please enter “No other” here.

STEMI: 8
NSTEMI: 8
Angina: 8

BACKGROUND FAMILY HISTORY: STEMI, NON-STEMI

Patient is adopted	Y	N	U	Twin	Y	N	U
Total number of siblings (inc)				Any vascular history	Y	N	U

Oldest →

		Dad	Mum	Sib 1	Sib 2	Sib 3	Sib 4	Sib 5	Sib 6	Sib 7	Sib 8	Sib 9	Sib 10	Sib 11	Sib 12
Stroke	Y/N/U														
	Age*														
MI	Y/N/U														
	Age*														
PVD	Y/N/U														
	Age*														
Brain Haem	Y/N/U														
	Age*														
Diabetes	Y/N/U														
	Age*														
Hyperlip aedemia	Y/N/U														
	Age*														
Hyper tension	Y/N/U														
	Age*														
Sibling* is:															

T = Twin **M** = Half-sibling mother's side **S** = Sibling **F** = Half-sibling father's side

Age/Sibling: please fill in "U" if unknown

	Alive/ Dead			Sex		Age at death	Cause of death
Mother	A	D	U	[redacted]		U	U
Father	A	D	U	[redacted]		U	U
Sib1 oldest	A	D	U	M	F	U	U
Sib 2	A	D	U	M	F	U	U
Sib 3	A	D	U	M	F	U	U
Sib 4	A	D	U	M	F	U	U
Sib 5	A	D	U	M	F	U	U
Sib 6	A	D	U	M	F	U	U
Sib 7	A	D	U	M	F	U	U
Sib 8	A	D	U	M	F	U	U
Sib 9	A	D	U	M	F	U	U
Sib 10	A	D	U	M	F	U	U
Sib 11	A	D	U	M	F	U	U
Sib 12 youngest	A	D	U	M	F	U	U

STEMI and NON-STEMI

FAMILY TREE *(Number siblings and children)*

SMOKING			
Have you ever smoked?	*Y*	*N*	*U*
Are you a lifetime non-smoker?	*Y*	*N*	*U*
Smoking oddities *(pipes etc)*			*U*
Are you an ex-smoker?	*Y*	*N*	*U*
If so at what age did you stop?	*Age:*		*U*
<u>If you have stopped</u>: ***How many years did you smoke?***	*# Years:*		*U*
Do you currently smoke?	*Y*	*N*	*U*
How many do you smoke per day?	*Number:*		*U*
<u>If you are still smoking</u>: ***How many years have you smoked?***	*# Years:*		*U*

STEMI: 10
NSTEMI: 10

Premorbid modified Rankin *STEMI and NON-STEMI*

Do you have any symptoms?	***Y***	***N***	***U***
Are you able to look after yourself and carry out normal activities?	***Y***	***N***	***U***
Does anyone else help pay the bills, do the shopping, cleaning etc?	***Y***	***N***	***U***
Do you need someone to help you walk?	***Y***	***N***	***U***
Do you need help to wash yourself?	***Y***	***N***	***U***
Do you need to be lifted in and out of bed?	***Y***	***N***	***U***

0 = no symptoms at all *1 = no significant disability despite symptoms: able to carry out all usual duties and activities* *2 = slight disability: unable to carry out all previous activities but able to look after own affairs without assistance* *3 = moderate disability: requiring some help, but able to walk without assistance* *4 = moderately severe disability: unable to walk without assistance, and unable to attend to own bodily needs without assistance* *5 = severe disability: bedridden, incontinent, and requiring constant nursing care and attention* *6 = death*	*Score*

Rose PVD: IHD questionnaire

NOTE: ALL QUESTIONS RELATE TO SYMPTOMS <u>PRIOR</u> TO THE NOTIFICATION EVENT

PART A

a) Have you ever had any pain or discomfort in your chest?			***Y***	***N***	***U***	n: **go to part C**
b) Do you get the pain or discomfort when you walk up hill or hurry?			***Y***	***N***	***U***	n: **go to part B**
c) Do you get it when you walk at an ordinary pace on the level?			***Y***	***N***	***U***	
d) When you get any pain or discomfort in your chest what do you do?	1=Stop 2=Slow down	3= continue at same pace 9= Unknown				
e) Does it go away when you stand still?			***Y***	***N***	***U***	
f) How soon?	**1**=10 minutes or less **2**= > 10 minutes **9**= unknown					

PART B

Have you ever had severe pain across the front of your chest lasting half an hour or more?	***Y***	***N***	***U***

PART C

a) Do you get pain in either leg when you are walking?	***Y***	***N***	***U***
b) Does this pain ever begin when you are standing still or sitting?	***Y***	***N***	***U***
c) Do you get this pain in your calf (or calves)	***Y***	***N***	***U***
d) Do you get it when you walk up hill or hurry?	***Y***	***N***	***U***
e) Do you get it when you walk at an ordinary pace on the level?	***Y***	***N***	***U***
f) Does the pain ever disappear while you are still walking?	***Y***	***N***	***U***

g) What do you do if you get it when you are walking?	1=Stop 2=Slow down 3=Continue at same pace *9= Unknown*	
h) What happens if you stand still?	**1**=Usually continues for more than 10 minutes **2**= Usually disappears in 10 minutes or less **9**= Unknown	

STEMI: 11
NSTEMI: 11

Premorbid Barthel

	Score	Key
Feeding		0 = unable 1 = needs help cutting, spreading butter, etc, or requires modified diet 2 = independent
Bathing		0 = dependent 1 = independent (or in shower)
Grooming		0 = needs help with personal care 1 = independent face/hair/teeth/shaving (implements provided)
Dressing		0 = dependent 1 = needs help but can do about half unaided 2 = independent (including buttons, zips, laces, etc.)
Bowels		0 = incontinent (or needs to be given enemas) 1 = occasional accident 2 = continent
Bladder		0 = incontinent, or catheterised and unable to manage alone 1 = occasional accident 2 = continent
Toilet use		0 = dependent 1 = needs some help, but can do something alone 2 = independent (on and off, dressing, wiping)
Transfers (bed to chair and back)		0 = unable, no sitting balance 1 = major help (one or two people, physical), can sit 2 = minor help (verbal or physical) 3 = independent
Mobility (on level surfaces)		0 = immobile 1 = wheelchair independent, including corners, > 50 metres 2 = walks with help of one person (verbal or physical) > 50 metres

		3 = independent (but may use any aid; for example, stick) > 50 metres
Stairs		0 = unable 1 = needs help (verbal, physical, carrying aid) 2 = independent

BARTHEL SCORE	

STEMI: 12-15
NSTEMI: 12-13
Angina: 12-13

STEMI and NON-STEMI

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

Interviewer's perception of patient personality		1 Very relaxed 2 Fairly relaxed 3 Average	4 Prone to stress 5 Highly stressed 9 Unknown	
In terms of stress what kind of person are you?				
Place of residence		1 Home 2 Home of relative 3 Home of friend 4 Warden housing	5 Care home 8 Other (specify) 9 Not known	**8-Specify:**
Do you live alone? Y/N/U		**If NO with whom?**	**Spouse**	Or:
Are you a carer*? Y/N/U		*Physical assistance to wash/dress/mobility		
Does anyone assist you at home?		1 Spouse 2 Relative 3 Private carer	4 Community services (specify) 5 No assistance needed 9 Not known	**4-Specify:**
Marital status		1 Married 2 Widow	3 Single 4 Separated	5 Partner 9 Not known
Employment status		1 Working FT 2 Working PT 3 Caring for home	4 Unemployed 5 Unable to work	6 Retired 7 Student 9 Not known
Most recent occupation (spouse's occupation if not employed)				U

Socioeconomic class	U	1 **Professional** (Doctors, accountants, engineers) **2 Managerial/technical** (Marketing, sales managers, teachers, journalists 3N **Skilled non-manual** (Clerks, cashiers, retail staff) 3M **Skilled manual** (Carpenters, van/lorry drivers, Joiner) 4 **Partly skilled** (Warehousemen, security guards, machine/tool operators) 5 **Unskilled** (Building/civil engineering labourers, other labourers, cleaners) 6 **Armed forces** 9 **Unknown**
Ethnic origin		1 White 2 Black Carribean 3 Black African 4 Indian 5 Pakistani 6 Bangladeshi 7 Chinese 8 Other 9 Not known
Exercise (Clinician judgement on amount of physical activity –age corrected- per week)		1 None 2 Below average 3 Normal 4 Above average 9 Not known
Alcohol units per week*		* Please use guidelines provided below
Age left school	U	
Education		1 Basic 2 Further 3 Higher 9 Not known
Age left full-time education	U	

(Sparkling) wine and Champagne					
	ml		**10%-units**		**14% - units**
M glass	175		1.75		2.5
L glass	250		2.5		3.5
Bottle			7.5		10.5

Shots (Gin, Rum, Vodka, Whisky, Tequila, Sambuca)			
		ml	**Units**
Small		25	1
Large		35	1.3
Double		50	2
L double		70	2.8

Lager, Beer and Cider					
	ml		**4% - units**		**9%-units**
Bottle	330		1.3		3
Can	440		1.8		4
Pint	568		2.3		5.1

275 ml bottle Alcopops	
	1.4 units

50 ml glass Sherry/ Port	
	1 Unit

STEMI: 16
NSTEMI: 14

STEMI and NON-STEMI

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

SLEEP

What is the likelihood of you dozing in the following <u>three</u> situations:

1) Sitting and reading		0= No chance of dozing 1= Slight chance of dozing 2= Moderate chance of dozing 3= High chance of dozing 9= Unknown
2) Lying down to rest in the afternoon		
3) Sitting and talking to someone		
On average, how many hours of sleep do you get per night?	U	
Do you snore?	Y N U	
Have you been told that you stop breathing at night?	Y N U	
Do you take medications for high blood pressure?	Y N U	
People tell me that I snore		1= Never 2= Rarely (1-2x / year) 3= Occasionally (4-8x /year) 4= Sometimes (1-2x /month) 5= Often (1-2x /week) 6= Usually (3-5x /week) 7= Always (every night) 8= I don't know 9= Unknown
People tell me that I gasp, choke or snort while I am sleeping		

NUTRITION		
How is your appetite?		1= Good 2= Normal 3= Poor 4= Uncertain
Do you have a healthy diet?	Y N U	
On average, how many portions of fish do you eat per week? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= 2 /week 4= ≥ 3/week 9= Unkown
Do you add salt to your food?	Y N U	
Do you drink full fat or low fat dairy milk (cow/goat)?		1= Full fat 2= Low fat (skimmed/ semi-skimmed) 3= No milk consumed 4= No dairy milk consumed 9= Uncertain
On average, how many portions of fresh fruit and vegetables? Either note 1, 2 etc or circle correct answer		1= < 1 /week 2= 1 /week 3= several/ week 4= 1 /day 5= 2-4 /day 6= > 4 /day 9= unknown

STEMI: 17
NSTEMI: 15

STEMI and NON-STEMI

FUNCTIONAL AND PSYCHOLOGICAL BACKGROUND

MOOD	Do you often feel sad or depressed?	Y N U	
DRIVING	Do you drive?	Y N U	
Handedness	Left/Right/Both/Unknown		R= Right L= Left B= Both U= Unknown
Clinical impression of frailty (corrected for age)			1= Frail 2= Normal 9= Unknown

LIFE EVENTS

Have any of these events happened to you over the last year*?				**How upset were you by these events?**
Death or serious illness of close friend or relative	Y	N	U	
Financial difficulty	Y	N	U	
Divorce or break up of close friend or relatives	Y	N	U	
Major conflict with children or grandchildren	Y	N	U	
Muggings, robberies, accidents	Y	N	U	
OTHER life events				

*Data entry instructions: N should be changed to Y if any of the answers below are answered as Y or if OTHER has been filled in.

1= Very much
2= Moderately
3= Not too much
9= Unknown

		1= Very much 2= Moderately 3= Not too much 9= Unknown

STEMI: 18
NSTEMI:
16

19

STEMI

GENERAL EXAMINATION				
	cm*		**inches***	
Collar size				U
Waist measurement				U
Hip measurement				U
Height				U
	kg*		**stone***	
Weight				U
Arcus	Y	N	U	
Xanthelasma	Y	N	U	
Nicotine staining	Y	N	U	
Ear crease	Y	N	U	
Own teeth/ denture	O	D	U	O= own teeth D= denture U= unknown

*Data entry instructions: If it is obvious that "cm" measurements have been placed in the "inches" column and vice versa please ensure data is entered on the db in the correct field. A note with initials is required on this form to make a note of this data change. The same is valid for incorrect kg/stone entries.

STEMI and NON-STEMI

New

FIRST POST-EVENT RECORDS				
		Date DD-MM-YY	**Time** 24 hr clock	
		U	: U	
Blood pressure		**Sys**	**Dias**	U
Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Recorded by	P Paramedic G GP A A&E C Clinic			

New

	O Other N Not recorded U Unknown	

STEMI: 19
NSTEMI:

STEMI

For admitted patients only: TEMP, HEART RATE and BLOOD PRESSURE				
Temp on admission		ºC		U
Admission Heart rate				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
BP on admission		Sys	Dias	U
Sats/air		**%**		U
BM				U

For all subjects				
BP on assessment		Sys	Dias	U
Heart rate on assessment				U
Heart rate type	1= Bradycardia <60 2= Normal 60-99 3= Tachycardia 100+ 9= Unknown			
Cardiac rhythm	1= Sinus 2= Atrial fibrillation 3= Other 9= Unknown			
Cardiac murmur?		Y	N	U
Cardiac failure?		Y	N	U

Any pre-existing neurological disability?	Y	N	U

STEMI: 19

STEMI			
MYOCARDIAL INFARCTION			
		Date DD-MM-YY	**Time** 24Hr clock
Reperfusion treatment?	Tick if: **No reperfusion**	U	: U
Delay from arrival in hospital to reperfusion treatment Leave blank if no reperfusion		Hrs:	Mins:
First cardiac arrest	Tick if: **No cardiac arrest**	U	: U

If cardiac arrest: please fill in below. If no cardiac arrest: leave blank

Territory	1 Anterior 2 LBBB	3 Inferior	4 Other	
Cardiac arrest	1 No arrest 2 Before ambulance 3 After ambulance	4 A&E 5 CCU	6 Medical ward 7 Elsewhere in hospital	
Presenting rhythm	1 No arrest 2 Asystole	3 VF/ pulseless VT 4 EMD	9 N/A or Unknown	
Outcome	1 No return circulation 2 Return spontaneous circulation, died in hosp	3 Discharged from hosp with neuro deficit 4 Discharged, no neuro deficit 5 Resuscitation not attempted	5 Resuscitation not attempted 6 No arrest 9 Not applicable/ Unknown	
Admission diagnosis	1 Definite MI 2 Probable MI	3 Unstable angina 4 Chest pain	5 Other initial diagnosis 6 Already in hospital	
ECG determining treatment	1 ST elevation 2 LBBB 3 ST depression	4 T wave change 5 Other	6 Normal 9 Unknown	

STEMI investigations				
Reperfusion attempted	1 Thrombolysis 2 PTCA	3 Rescue PTCA 4 Ci to reperfusion	5 Not attempted 9 Unknown	
Did patient receive aspirin	1 Already on 2 Given out of hosp 3 After arrival	4 Ci to aspirin 5 Other antiplatelet 6 None	7 On Warfarin 8 Not known	
Admission unit	1 CCU 2 AMAU 3 Gen med ward	4 ITU 5 Other 6 Died A&E	7 Cardiac ward 8 Stepdown	
Killip	1= Class I No clinical signs of heart failure 2= II/ III/ IV 3= Class II Rales or crackles in the lungs, an S_3 gallop and elevated jugular venous pressure 4= Class III Frank acute pulmonary edema 5= Class IV Cardiogenic shock or hypertension (measured as systolic blood pressure < 90mmHg) and evidence of peripheral vasoconstriction (oliguria, cyanosis or sweating) 9= Unknown			

Diuretic initiated or increased for heart failure?		Y	N	U

STEMI: 20

STEMI and NON-STEMI

INVESTIGATIONS: CARDIAC ENZYMES

	Date	CK	AST	troponin
Admission day				
Day 1				
Day 2				
Day 3				

Coded ECG	1 AF 2 BBB 3 ST Segment change 4 LVH	5 Acute MI 6 Old MI 7 Normal 9 Other (specify)		Specify:

NON-STEMI

TIMI – NSTEMI SCORE		
Age ≥65		0 no 1 yes
≥3 CAD risk factors =1, (FHx HBP Raised chol, DM)		0 no 1 yes
Known CAD, Stenosis ≥ 50%		0 no 1 yes
ASA use in past 7 days		0 no 1 yes
Recent (≤24 hrs) angina		0 no 1 yes
Raised cardiac markers		0 no 1 yes
ST deviation ≥ 0.5 mm		0 no 1 yes

TIMI-NSTEMI Total	

Notes

STEMI

TIMI – STEMI SCORE		
Age		0 < 65 2 65-74 3 ≥ 75
DM or HBP or angina		0 no 1 yes
SBP <100		0 no 3 yes
HR> 100		0 no 2 yes
Killip II-IV See p23		0 no 2 yes
Weight < 67kg		0 no 1 yes
Anterior STE/LBBB		0 no 1 yes
Time to Tx > 4		0 no 1 yes

TIMI – STEMI Total	

Notes

STEMI: 21
NSTEMI: 18

STEMI and NON-STEMI

MANAGEMENT – DISCHARGE

MANAGEMENT			
Did you instruct subject to change diet?	**Y**	**N**	**U**
Did you instruct subject to reduce weight?	**Y**	**N**	**U**
Did you instruct subject to quit smoking?	**Y**	**N**	**U**

	DRUG MANAGEMENT								
	New			**Continued**			**Contra-indicated**		
Aspirin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Dipyridamole	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Clopidrogel	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Warfarin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Low molecular weight heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
GPIIIa/IIb	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Unfractionated heparin	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Lipid lowering	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Ace inhibitors	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Thiazide diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Loop diuretics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Beta blockers	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Other antihypertensive	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**
Antiarrythmics	**Y**	**N**	**U**	**Y**	**N**	**U**	**Y**	**N**	**U**

Appendix 4

OXFORD VASCULAR STUDY FOLLOW UP

OREC A:05/Q1604/70

MONTH 1 6 12 24 60*

***Please circle one**

SUBJECT ID NO:

DATE DD/MM/YYYY**:**

Smoking		**Y**	**N**	**U**	**Driving**	**Y**	**N**	**U**
BP					**Working**	**Y**	**N**	**U**
Heart rate					**Being treated for depression?**	**Y**	**N**	**U**
Cardiac rhythm	1= Sinus 2= Atrial Fibrillation 3= Other 4= Regular 5= Irregular				**Barthel (/20)**			
Rankin (0-6)					**Euroquol**			
MMSE (/30)					**MOCA (/30)**			
Falls/presyncope		**Y**	**N**	**U**	**If 'yes' please give details**			

Type of contact		1 Phone call 2 Hospital visit 3 Home visit		
Location		1 Home 2 Acute hospital 3 Residential home 4 Clinic/ OPD	5 In a residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:
Living arrangements		1 In own home (rented or owned) 2 In relative's home 3 In nursing home 4 In hospital	5 In residential home 6 In intermediate care 7 In sheltered accommodation 8 Other (specify)	Other:

RECURRENT EVENTS				
Event	**Y/N/U**	**No. events**	**Date of event DD/MM/YYYY**	**Comments**
Chest pain (requiring admission)			1	
			2	
			3	
TIA (<24h sudden onset focal neurological disturbance)			1	
			2	
			3	
Stroke (>24h)			1	
			2	
Acute PVD event embolus, aneurysm			1	
			2	
CARDIAC PROCEDURE				
Angiogram				
Angioplasty				
Stent				
CABG				
CAROTID PROCEDURE				
Carotid endarterectomy				
PERIPHERAL PROCEDURE				
Angiogram				
Angioplasty				
Stent				
Bypass				
Amputation				
Surgery				
OTHER				
Other procedures			1	
			2	
Other admissions			1	
			2	

			3	
Bleeding req. med attention				

UNIVERSITY OF OXFORD

Department of Primary Health Care
Institute of Health Sciences
Old Road
Headington
Oxford OX3 7LF

OREC A: 05/Q1604/70

Appendix 5

The Stroke Prevention Research Unit

Department of Clinical Neurology

1st June 20

Study title: The Oxford Vascular Study (OXVASC)

You are being invited to take part in a research study. Before you decide it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part.

What is the purpose of the study?

The purpose of this study is to find out how common vascular disease (e.g. heart attacks, strokes, transient ischaemic attacks and other circulatory problems) is in Oxfordshire and how it affects people's lives. This has never been done before for different types of vascular disease at the same time and in the same population. We hope the study will provide us with useful information on the best way of providing a service for those who suffer from these common problems. We hope we can build up a detailed picture of the way that people recover and the subsequent changes in health over several years.

Why have I been chosen?
You have been chosen because you are registered with one of the nine GP practices in Oxfordshire which are collaborating in the study.

Do I have to take part?
It is up to you to decide whether or not to take part. If you do decide to take part you will be given this information sheet to read and be asked to sign a consent form. You will be given a copy of the information sheet and signed consent form to keep. If you decide to take part you are still free to withdraw at any time and without giving a reason. A decision to withdraw at any time, or a decision not to take part, will not affect the standard of care you receive.

What will happen to me if I take part?
If you decide to take part you would agree to an interview and a clinical examination by the researcher. It would also involve taking an extra sample of blood in the hospital or clinic. We would also like to gather some information on risk factors for vascular disease from both your hospital and GP notes. The study would also involve being followed up by telephone or at home by a researcher in thirty days time, in six months, at one year, two years and five years. All the information collected will be completely confidential.

What do I have to do?
This is an observational study and taking part in the study will not affect your current or future care. No investigations, new drugs or other treatments will be tested.

What are the possible disadvantages and risks to taking part?
You will be required to give a blood sample which will cause mild discomfort. Where possible this will be taken at the same time as those collected in the course of your normal medical care. There are no additional risks involved.

What are the possible benefits of taking part?
We hope the information we get from this study may help us to treat future patients with vascular disease better.

What if something goes wrong?
If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms should be available to you.

Will my taking part in this study be kept confidential?
All information which is collected about you during the course of the research will be kept strictly confidential. Any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised from it.

What will happen to the results of the research study?
It is likely that the results of this study will be published in medical journals after completion of the research. If you decide to take part in the study you will not be identified in any report.

Who is organising and funding the research?
This research is being organised by Professor Rothwell at The Stroke Prevention Research Unit, University of Oxford in collaboration with the Department of Primary Health Care, the Department of Cardiology and your participating General Practice. The study is funded by the Stroke Association and the Medical Research Council.

Who has reviewed the study?
The Oxfordshire Research Ethics Committee has approved the study.

Contact for Further Information

If you would like any further information please ask the researcher who is discussing this information sheet with you or by contacting the Oxford Vascular Study Office on 01865 231601.

Thank you for reading this.

Professor Peter Rothwell - Consultant Neurologist, Dr Adrian Banning - Consultant Cardiologist, Professor David Mant - Professor of General Practice
Dr Sarah Pendlebury – Senior Research Fellow, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva,
Dr Olivia Geraghty, Dr Lars Marquardt, Dr Nicola Paul and Dr Michela Simoni - Clinical Research Fellows
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28th December 2006

CONSENT FORM

Title of Project: **OXFORD VASCULAR STUDY (OXVASC)**

Name of Researchers: Professor Peter Rothwell, Dr Ami Banerjee, Dr Lucy Binney, Dr Arvind Chandratheva, Dr Olivia Geraghty, Dr Lars M Dr Michela Simoni, Louise Silver, Linda Bull, Sarah Welch, Fiona Cuthbertson.

	Please tick the relevant box	Yes	No
1.	I confirm that I have read and understand the information sheet dated 1st June 2005 for the above study and have had the opportunity to ask questions.	☐	☐
2.	**I agree to take part in the above study.**	☐	☐
3.	I understand that sections of any of my medical notes may be looked at by responsible individuals where it is relevant to my taking part in research. I give permission for these individuals to have access to my records. I understand that information held by the NHS and records maintained by the General Register Office may be used to keep in touch with me and follow up my health status.	☐	☐
4.	I understand future research using the blood sample I give may include genetic research aimed at understanding the genetic influences on vascular disease, but that the results of these investigations are unlikely to have any implications for me personally.	☐	☐
5.	**I agree to take part in the follow up study that involves being interviewed at home** or a place of my choice, by telephone or in person at 1, 6 , 12 , 24 and 60 months.	☐	☐
6.	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason and without my medical care or legal rights being affected.	☐	☐

_____	_____	_____
Name of Patient	Date	Signature
_____	_____	_____
Name of Witness	Date	Signature
_____	_____	_____
Researcher	Date	Signature

Copies: 1 for patient; 1 for researcher; 1 to be kept with hospital notes

	GRACE[16]	CRUSADE[28]	ACUITY[14]	Nikolsky[17]	Lenderlink[20]	Macie[21]	O'Donnell [29]	Sorensen [19]	Ziegelstein[37]	Stenestrand[23]
Age	√		√	√	√	√	√	√		√
Female	√	√	√	√	√			√		
Diabetes		√	√					√		
Anaemia		√	√	√						
Renal impairment	√	√	√	√				√		
History of bleeding	√	√					√	√		
Peptic ulcer disease							√			
Cancer							√	√		
PVD/stroke		√						√		√
Heart failure		√								
Lower body weight		√								
Invasive procedures	√	√	√		√					
ST changes	√		√							
Raised cardiac markers	√		√							
SSRI use									√	
Antiplatelet						√				

Appendix 7 Risk factors for bleeding events in ACS and Stroke/TIA published studies.

Abbreviations and Acronyms

GRACE= Global Registry of Acute Coronary Events

CRUSADE=Can rapid risk stratification of unstable angina patients suppress adverse outcoms with early implementation of the American college of Cardiology/American heart association guidelines

ACUITY= Acute catherisation and urgent intervention triage strategy

SSRI= selective serotonin reuptake inhibitors