

The British Cardiovascular Society and clinical studies in ischaemic heart disease: from RITA to ORBITA, and beyond

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ABSTRACT

In this article, we provide a historical view of key aspects of British Cardiovascular Society (BCS) influence in clinical trials of ischaemic heart disease (IHD) followed by key research and developments, notable publications and future perspectives. We discuss the role of the BCS and its members. The scope of this article covers clinical trials in stable IHD and acute coronary syndromes, including interventions relating to diagnosis, treatment and management. We discuss the role of the BCS in supporting the original RITA trials. We highlight the changing face of angina and its management providing contemporary and future insights into microvascular disease, ischaemic symptoms with no obstructive coronary arteries and, relatedly, myocardial infarction with no obstructive coronary arteries. The article is presented as a brief overview of the BCS in IHD research, relationships with stakeholders, patient and public involvement and clinical trials from the perspective of past, present and future possibilities.

OVERVIEW

In this article, we provide an overview of the British Cardiovascular Society (BCS) in supporting research in ischaemic heart disease (IHD) and the impact its members have had in this area. The scope extends from cardiovascular pathology to clinical trials in stable IHD and acute coronary syndromes (ACS). BCS has directly supported seminal studies such as the original RITA trials. Also, its influence and association with linked societies and funding bodies have allowed BCS members to engage in clinical trials which have reshaped our perspectives on IHD and led to fundamental advances in the diagnosis, treatment and management of patients with stable and unstable coronary syndromes.

The BCS has been a leading supporter of clinical research in IHD since its inception as the Cardiac Club in 1922. Over the years, the BCS Annual Conference has provided an opportunity for members to present and learn about the results of the latest research and foster new research collaborations. To support this, BCS has championed research excellence through named lectures and prizes, including the Young Investigator Award, the Michael Davies Early Career Award, the Mackenzie Medal and best abstract awards. The prestigious BCS journals, including *Heart* and *Open Heart*, have provided a vehicle to prioritise publications of impactful IHD clinical research trials.

The Society continues to lead the development of clinical evidence in IHD through a spirit of altruism and by providing collegiate support for

clinical studies in daily practice. BCS members have made internationally leading research contributions which have substantially advanced medical knowledge in this field and continue to inform evidence-based practice and ongoing trials in IHD. A comprehensive review of every clinical study led by BCS members is beyond the scope of this article, but we have highlighted key IHD trials ([tables 1 and 2](#)) covering primary and secondary prevention, cardiac rehabilitation and clinical strategies (medical vs revascularisation) in ACS and chronic coronary syndromes (CCS).

Some of the key clinical trials, many of which significantly influenced clinical practice, merit further discussion and are covered in more detail in [tables 1 and 2](#).

LAYING THE FOUNDATIONS AND THE ISIS TRIALS

Many of the original members of the Cardiac Club remain influential role models in cardiovascular research. In the Club's early years, Sir James Mackenzie and A G Gibson introduced key concepts of the underlying disease process of coronary artery disease (CAD) and published case reports evidencing the association between CAD and ischaemic necrosis.^{1,2}

In the 1950s, Dr William Fulton developed the technique of stereo-arteriography to image the coronary microcirculation postmortem ([figure 1](#)).^{3,4} His extraordinary work was complimented by his publication of then futuristic images of his arteriographs using early three-dimensional glasses. Fulton's work passed largely unrecognised mainly because there was no firm association between cardiac small vessel disease and clinical outcomes, due to a lack of clinical diagnostic tests. This contrasts with the impact of clinical research undertaken by Michael Davies,⁵ Peter Sleight and many other BCS members, underpinned by the availability of coronary angiography to inform research and practice.

Seminal studies from the 1970s led by Professor Michael Davies identified CAD as being the causes for angina,⁶ myocardial infarction (MI)⁷ and premature death⁸ and demonstrated the relationship of occlusive thrombus with MI and necrosis ([figure 2](#)). These problems became established as targets for interventions in clinical trials. Starting in the late 1970s and based on Michael Davies pathological insights, Professor Peter Sleight led the International Studies of Infarct Survival (ISIS) trials. The ISIS trials introduced the concept of large scale, multicentre, multiarm, randomised, controlled



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Table 1 Multicentre clinical trials in acute coronary syndromes

| Name | Registration and funding | Population/objective | Sample size | Main finding and conclusion |
|-------------|---|---|-------------|--|
| CURE | Sanofi-Synthelabo Bristol-Myers Squibb | Acute coronary syndrome To assess the effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. | 12 562 | The primary endpoint, a composite of death from cardiovascular causes, non-fatal MI or stroke, occurred in 9.3% in the clopidogrel group and 11.4% in the placebo group (RR 0.80; 95% CI 0.72 to 0.90; $p < 0.001$). |
| CvLPRIT | ISRCTN70913605 BHF | STEMI with multivessel coronary artery disease To undertake an open-label randomised clinical trial comparing complete revascularisation at index admission with treatment of the IRA only. | 296 | The primary endpoint, a composite of all-cause death, recurrent MI, heart failure and ischaemia-driven revascularisation within 12 months, occurred in 10.0% of the complete revascularisation group vs 21.2% in the IRA-only revascularisation group (HR: 0.45; 95% CI 0.24 to 0.84; $p = 0.009$). In patients presenting for P-PCI with multivessel disease, inpatient total revascularisation may be considered. |
| ERIC-PPCI | NCT02342522 BHF | STEMI To investigate whether remote ischaemic conditioning could reduce the incidence of cardiac death and hospitalisation for heart failure at 12 months. | 5401 | At 12 months post-PPCI, the Kaplan-Meier-estimated frequencies of cardiac death or hospitalisation for heart failure (the primary endpoint) were 220 (8.6%) patients in the control group and 239 (9.4%) in the remote ischaemic conditioning group (HR 1.10 (95% CI 0.91 to 1.32), $p = 0.32$ for intervention vs control). Remote ischaemic conditioning does not improve clinical outcomes (cardiac death or hospitalisation for heart failure) at 12 months in patients with STEMI undergoing PPCI. |
| ISIS-1 | BHF ICI Pharmaceuticals Ltd | Acute MI To determine if intravenous atenolol followed by oral atenolol would reduce vascular mortality when compared with placebo. | 16 027 | Vascular mortality during the treatment period (days 0–7) was significantly lower ($p < 0.04$) in the treated group, 3.9% vs 4.6%, but this 15% difference has wide 95% confidence limits (about zero to about a 0.25) |
| ISIS-2 | BHF Sterling Drugs Behringwerke | Acute MI To determine if (1) intravenous streptokinase, (2) 1 month of aspirin, (3) both active treatments or (3) neither compared with placebo control would reduce vascular death. | 17 187 | Those allocated the combination of streptokinase and aspirin had significantly fewer reinfarctions (1.8% vs 2.9%), strokes (0.6% vs 1.1%) and deaths (8.0% vs 13.2%) than those allocated neither. The differences in vascular and in all-cause mortality produced by streptokinase and by aspirin remained highly significant ($p < 0.001$ for each) after the median of 15 months of follow-up. |
| ISIS-3 | BHF Sterling Drugs Behringwerke | Acute MI To determine the differences in bleeding, stroke, reinfarction and death between randomisation to intravenous SK or TPA or APSAC complex with aspirin given to all patients and randomisation to additional intravenous heparin. | 41 299 | Addition of heparin to aspirin was associated with excess of transfused or other major non-cerebral bleeds (1.0% aspirin plus heparin vs 0.8% aspirin alone; $p < 0.01$) and of definite or probable cerebral haemorrhage (0.56% vs 0.40%; $p < 0.05$), but with no significant differences in total stroke (1.28% vs 1.18%). Reinfarctions were slightly less common among those allocated aspirin plus heparin (3.16% vs 3.47%; $p = 0.09$). There was no significant difference in the prespecified endpoint of 35-day mortality (10.3% aspirin plus heparin vs 10.6% aspirin alone). There was no significant mortality difference during days 0–35, either among all randomised patients (10.6% SK vs 10.5% APSAC) or among the prespecified subset presenting within 0–6 hour of pain onset and with ST elevation on the ECG in whom fibrinolytic treatment may have most to offer. TPA was associated with significantly fewer reports of allergy causing persistent symptoms and of hypotension requiring drug treatment and with significantly more reports of non-cerebral bleeds, but not of transfused bleeds. There was a significant excess of strokes with TPA (1.04% SK vs 1.39% TPA; $p < 0.01$). |
| ISIS-4 | BHF Bristol-Myers-Squibb Astra-Hassle Artesan Pharma Casselamed | Acute MI To assess early oral captopril, oral mononitrate and intravenous magnesium sulphate on reduction in 5-week mortality rates. | 58 050 | There was a significant 7% proportional reduction in 5-week mortality with captopril. There was no significant reduction in 5-week mortality with mononitrate. There was no significant reduction in 5-week mortality with magnesium. |
| HEAT-PPCI | Liverpool Heart and Chest Hospital UK NIHR The Medicines Company AstraZeneca | ST-elevation MI To compare antithrombotic therapy with bivalirudin or unfractionated heparin during this procedure. | 1829 | The primary efficacy outcome occurred in 8.7% in the bivalirudin group and 5.7% in the heparin group (absolute risk difference 3.0%; RR 1.52, 95% CI 1.09 to 2.13, $p = 0.01$). The primary safety outcome occurred in 3.5% in the bivalirudin group and 3.1% in the heparin group (0.4%; 1.15, 0.70–1.89, $p = 0.59$). |
| High-STEACS | NCT01852123 BHF | Acute coronary syndromes To determine whether the introduction of a high-sensitivity cardiac troponin I (hs-cTnI) assay with a sex-specific 99th centile diagnostic threshold would reduce subsequent MI or cardiovascular death in patients with suspected acute coronary syndrome. | 48 282 | The high-sensitivity assay reclassified 1771 (17%) of 10 360 patients with myocardial injury or infarction who were not identified by the contemporary assay. In those reclassified, subsequent MI or cardiovascular death within 1 year occurred in 105 (15%) of 720 patients in the validation phase and 131 (12%) of 1051 patients in the implementation phase (adjusted OR for implementation vs validation phase 1.10, 95% CI 0.75 to 1.61; $p = 0.620$). |

Continued

Table 1 Continued

| Name | Registration and funding | Population/objective | Sample size | Main finding and conclusion |
|------------|------------------------------|---|-------------|--|
| PRAMI | Barts and the London Charity | ST-elevation MI To assess the value of PCI in non-infarct coronary arteries with major stenoses (preventive PCI). | 465 | The primary outcome of death from cardiovascular causes, nonfatal MI or refractory angina occurred in 9% in preventive PCI group and in 23% in no preventive PCI (infarct-artery-only PCI) group, (HR in the preventive-PCI group, 0.35; 95% CI 0.21 to 0.58; $p < 0.001$). |
| RAPID-CTCA | NIHR | Acute coronary syndromes To establish if the use of early CT coronary angiography improves 1 year clinical outcomes in patients presenting to the emergency department with acute chest pain. | 1748 | The primary endpoint of death or subsequent MI occurred in 5.8% participants randomised to CT coronary angiography and 6.1% participants who received standard of care only (adjusted HR 0.91 (95% CI 0.62 to 1.35), $p = 0.65$). |
| REACT | None BHF | STEMI with failed reperfusion To undertake a multicentre trial in the United Kingdom involving 427 patients with ST-segment elevation MI in whom reperfusion failed to occur (less than 50% ST-segment resolution) within 90 min after thrombolytic treatment. The patients were randomly assigned to repeated thrombolysis (142 patients), conservative treatment (141 patients), or rescue PCI (144 patients). | 427 | The adjusted HR for the occurrence of the primary end point for repeated thrombolysis vs conservative therapy was 1.09 (95% CI 0.71 to 1.67; $p = 0.69$), as compared with adjusted hazard ratios of 0.43 (95% CI 0.26 to 0.72; $p = 0.001$) for rescue PCI vs repeated thrombolysis and 0.47 (95% CI 0.28 to 0.79; $p = 0.004$) for rescue PCI vs conservative therapy. Rescue PCI should be considered for patients in whom reperfusion fails to occur after thrombolytic therapy. |
| RITA-3 | None BHF | Unstable angina or NSTEMI To test the hypothesis that an interventional strategy is better than a conservative strategy in such patients. | 1810 | At 4 months, 86 (9.6%) of 895 patients in the intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 patients in the conservative group (risk ratio 0.66, 95% CI 0.51 to 0.85, $p = 0.001$). In patients presenting with unstable coronary-artery disease, an interventional strategy is preferable to a conservative strategy, mainly because of the halving of refractory or severe angina and with no increased risk of death or MI. |

APSAC, anisoylated plasminogen-streptokinase activator; CTCA, CT coronary angiography; DAPT, dual antiplatelet therapy; FFR, fractional flow reserve; IRA, infarct-related artery; MI, myocardial infarction; PPCI, primary percutaneous coronary intervention; RR, relative risk; SK, streptokinase; TPA, tissue plasminogen activator.

clinical trials. These trials revolutionise the way clinical trials are designed and conducted and also transformed the treatment of acute MI worldwide. In 1988, the ISIS-2 trial demonstrated that systemic thrombolysis combined with aspirin was a highly effective treatment for acute MI that significantly reduced 30-day mortality.⁹

THE RITA TRIALS

In 1986, the BCS, then the British Cardiac Society, supported a small feasibility study to examine the possibility of conducting a randomised clinical trial to compare the effects of percutaneous transluminal coronary angioplasty (PTCA) and coronary artery bypass surgery (CABG). The pilot study assessed whether or not patients and doctors would accept randomisation between such widely different treatments and contributed to the development of the Randomised Intervention Treatment of Angina (RITA) trial.¹⁰ The Department of Health, the British Heart Foundation (BHF) and the BCS agreed to support the RITA trial, with the first patient randomised in March 1988. The trial was conceived by Edgar Sowton at Guy's Hospital with an Executive Committee including J R Hampton, S J Pocock, D G Julian, J Wallwork and R A Henderson. One thousand and eleven patients with CAD and a clinical indication for myocardial revascularisation were randomised to either PTCA ($n = 501$) or CABG ($n = 510$). The primary outcome was death or non-fatal MI at 5 years. The first interim report found that after 2.5 years, compared with PTCA, CABG reduced the risk of angina and need for additional diagnostic and therapeutic interventions, with no difference in the risk of death or MI, whereas healthcare costs were lower in the PTCA group.^{11 12} By 5 years, the primary endpoint occurred in 87 (17%) PTCA-group patients and 80 (16%) CABG-group patients ($p = 0.64$).¹³ The prevalence of angina and need for

reintervention were consistently higher in the PTCA group, and total health-service costs over 5 years were not different between the groups.

The RITA-1 trial set the scene for RITA-2 and RITA-3. RITA-2 was a randomised, controlled, multicentre trial comparing the long-term effects of PTCA and conservative (medical) care in 1018 patients with CAD considered suitable for either treatment option.¹⁴ The primary endpoint was the combined frequency of all-cause mortality and non-fatal MI. The median follow-up was 2.7 years. The primary endpoint occurred in 32 (6.3%) of 514 patients in the intervention group and in 17 (3.3%) of 504 patients in the conservative group ($p = 0.02$). Despite not having prognostic benefit, the results indicated that early intervention with PTCA was associated with greater symptomatic improvement, especially in patients with more severe angina. These results were maintained at 7 years.¹⁵ RITA-3 was a randomised trial of 1810 patients with non-ST-elevation ACS who were assigned an early intervention (angiography followed by revascularisation, if indicated) or conservative strategy (ischaemia-driven or symptom-driven angiography).¹⁶ The coprimary endpoints were a combined rate of death, non-fatal MI or refractory angina at 4 months and at 1 year. At 4 months, 86 (9.6%) of 895 patients in the intervention group had died or had a MI or refractory angina, compared with 133 (14.5%) of 915 patients in the conservative group (risk ratio 0.66, 95% CI 0.51 to 0.85, $p = 0.001$). This difference was mainly due to a halving of refractory angina in the routine invasive group. Death or non-fatal MI was similar in both treatment groups at 1 year; however, symptoms of angina were improved in the intervention group ($p < 0.0001$). At 5 years, 142 (16.6%) patients in the intervention group died or had non-fatal MI compared with 178 (20%) of patients in the conservative group (OR 0.78, 95% CI 0.61

Table 2 Multicentre clinical trials in stable ischaemic heart disease

| Name | Registration & funding | Objective | Sample size | Main finding and conclusion |
|------------|--|---|---------------------------|--|
| ART | ISRCTN46552265 BHF | To compare 10-year survival rates associated with bilateral and single internal-thoracic-artery grafting and secondary outcomes included clinical events, quality of life and health economic measures. | 1548 | Regarding the composite outcome of death, myocardial infarction or stroke, there were 385 patients (24.9%) with an event in the bilateral-graft group and 425 patients (27.3%) with an event in the single-graft group (HR, 0.90; 95% CI 0.79 to 1.03). |
| BCIS-1 | BCIS | To assess the utility of elective IABP use during high-risk PCI. | 301 | All-cause mortality at follow-up was 33% in the overall cohort, with significantly fewer deaths occurring in the elective IABP group (n=42) than in the group that underwent PCI without planned IABP support (n=58) (HR, 0.66; 95% CI 0.44 to 0.98; p=0.039). |
| CEMARC 2 | NCT01664858 BHF | To test the hypothesis that among patients with suspected CHD, CMR-guided care is superior to NICE guidelines-directed care and MPS-guided care in reducing unnecessary angiography. | 1202 | The number of patients with invasive coronary angiography after 12 months was 102 in the NICE guidelines group (42.5% (95% CI 36.2% to 49.0%)), 85 in the CMR group (17.7% (95% CI 14.4% to 21.4%)) and 78 in the MPS group (16.2% (95% CI 13.0% to 19.8%)). Study-defined unnecessary angiography occurred in 69 (28.8%) in the NICE guidelines group, 36 (7.5%) in the CMR group and 34 (7.1%) in the MPS group; adjusted OR of unnecessary angiography: CMR group vs NICE guidelines group, 0.21 (95% CI 0.12 to 0.34, p<0.001); CMR group vs the MPS group, 1.27 (95% CI 0.79 to 2.03, p=0.32). In patients with suspected angina, investigation by CMR resulted in a lower probability of unnecessary angiography within 12 months than NICE guideline-directed care, with no statistically significant difference between CMR and MPS strategies. |
| CorMicA | NCT03193294 BHF | To assess whether stratified medicine involving tests of coronary function changes the diagnosis and treatment and improves health and economic outcomes | Registry—391 Trial—151 | The intervention resulted in a mean improvement of 11.7 U in the Seattle Angina Questionnaire summary score at 6 months (95% CI 5.0 to 18.4; p=0.001). In addition, the intervention led to improvements in the mean quality-of-life score (EQ-5D index 0.10 U; 95% CI 0.01 to 0.18; p=0.024) and visual analogue score (14.5 U; 95% CI 7.8 to 21.3; p<0.001). Stratified medical therapy was routinely feasible and improved angina in patients with no obstructive CAD. |
| EUROPA | Servier | To assess whether the ACE inhibitor perindopril reduced cardiovascular risk in a low-risk population with stable coronary heart disease and no apparent heart failure. | 13 655 | 10% placebo and 8% perindopril patients experienced the primary endpoint, which yields a 20% relative risk reduction (95% CI 9 to 29, p=0.0003) with perindopril. |
| ORBITA | NIHR Imperial Biomedical Research Centre | To assess the placebo-controlled efficacy of PCI on symptoms in stable CAD | 200 | There was no significant difference in the primary endpoint of exercise time increment between groups (PCI minus placebo 16.6 s, 95% CI -8.9 to 42.0, p=0.200). |
| RITA | UK Department of Health BHF BCS | To compare the efficacy of CABG vs PTCA on the primary endpoint of death or non-fatal MI in stable CAD | 1011 | There was no difference in the predefined primary endpoint of death or non-fatal MI which occurred in 17% PTCA-group patients and 16% CABG-group patients (p=0.64). |
| RITA-2 | BHF MRC | To compare the long-term effects of PTCA and conservative (medical) care in patients with CAD considered suitable for either treatment option. | 1018 | Death or definite myocardial infarction occurred in 6.3% treated with PTCA and in 3.3% with medical care (absolute difference 3.0% (95% CI 0.4% to 5.7%), p=0.02). |
| SCOT-HEART | Chief Scientific Office of Scottish Government | To assess if the use of coronary computed tomographic angiography (CTA) improves diagnostic certainty in the assessment of patients with stable chest pain and improves 5 year clinical outcomes. | 4146 | The 5 year rate of the primary end point of death from coronary heart disease or nonfatal MI was lower in the CTA group than in the standard-care group (2.3% vs 3.9%; HR, 0.59; 95% CI, 0.41 to 0.84; p=0.004). |

BCS, British Cardiovascular Society; BHF, British Heart Foundation; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CMR, cardiovascular magnetic resonance; IABP, intra-aortic balloon pump; MPS, myocardial perfusion scintigraphy; NICE, National Institute for Health and Care Excellence; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal coronary angioplasty.

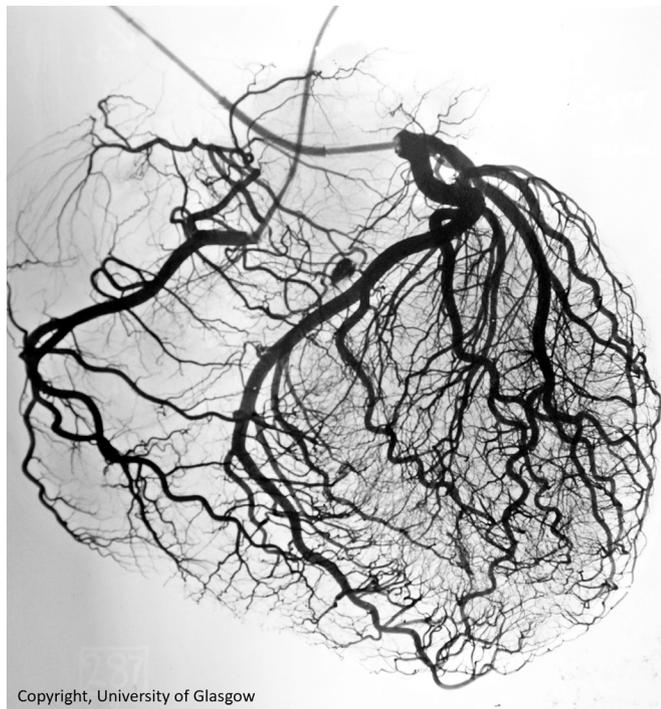
to 0.99, p=0.044). The benefit in the routine invasive group was largely driven by reduced mortality and events in high-risk patients with multiple morbidities. Findings on refractory angina were maintained at 5 years.¹⁷ The results from the RITA trials continue to underpin practice guidelines^{18 19} and were instrumental in laying the ground for the proliferation of future clinical research trials in IHD.

TRIALS THAT CHANGED CLINICAL PRACTICE

The late Anthony Gershlick, Professor of Interventional Cardiology at the University of Leicester, was the principal investigator for the REACT trial and an executive/steering committee member for the STREAM trial. In REACT, patients with STEMI and failed reperfusion therapy at 90 min were randomly assigned to receive repeat thrombolysis, rescue percutaneous coronary intervention (PCI) or medical management. Event-free survival, defined as death, reinfarction, stroke or severe heart failure within 6 months,

was significantly higher in the rescue PCI group as compared with the conservative group and the repeat thrombolysis group.²⁰ These results established rescue angioplasty as the evidence-based treatment for failed coronary reperfusion after systemic fibrinolysis.²¹ The STREAM trial demonstrated that prehospital fibrinolysis achieved effective reperfusion in patients presenting with STEMI who were unable to undergo primary PCI within 1 hour.²² A time-dependent reperfusion strategy was subsequently incorporated into NICE and ESC STEMI guidelines.^{21 23}

The Global Registry of Acute Coronary Events (GRACE) was co-chaired by Keith Fox, the then BHF Duke of Edinburgh Professor of Cardiology of the University of Edinburgh. The index of ACS management and prognosis yielded by GRACE (1999–2009) has impacted clinical practice worldwide.²⁴ Recommendations on coronary reperfusion therapy for high-risk NSTEMI defined by the GRACE risk scoring system are now endorsed by international guidelines.^{19 21 25}



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Figure 1 Stereoaerteriography of the human coronary arteries and microcirculation.

Keith Oldroyd, Honorary Professor of Cardiology at the University of Glasgow, led the interventional management of IHD in NHS Scotland and was a study investigator for the FAME trial. FAME demonstrated that FFR-guided PCI in patients with stable multivessel CAD significantly reduced major adverse cardiovascular events (MACE) at 1 year compared with a standard angiographic-guided approach.²⁶ FFR is now widely accepted as the gold standard assessment method of detecting flow-limiting epicardial lesions in stable CAD. More recently,

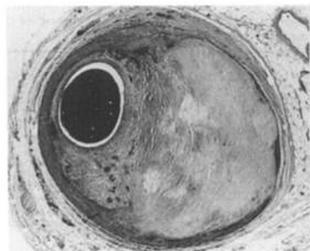


Fig 2 Photomicrograph of transverse section of stenosis caused by an eccentric fibrous plaque. There is an arc of normal media adjacent to the lumen. The plaque does not contain a pool of lipid. Elastic/haematoxylin and eosin stain.

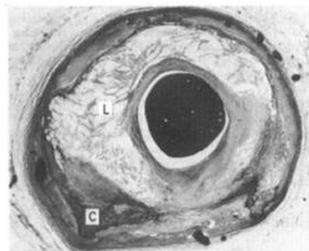


Fig 4 Photomicrograph showing stenosis caused by concentric lipid rich plaque. A pool of lipid (L) almost surrounds the residual lumen. Calcification (C) is also present. Elastic/haematoxylin and eosin stain.

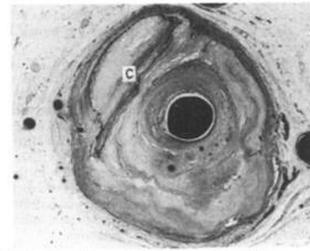


Fig 3 Photomicrograph showing stenosis caused by concentric fibrous thickening of the intima. The small central residual lumen contains angiographic medium. The intima does not contain a lipid pool but there is a plate of calcification (C). Elastic/haematoxylin and eosin stain.

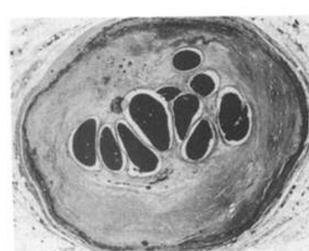


Fig 5 Photomicrograph showing recanalisation of a stenosis. The intima is replaced by connective tissue within which there are nine new vascular channels each containing angiographic medium. Elastic/haematoxylin and eosin stain.

Figure 2 Morphological characteristics of clinically significant coronary artery stenosis in stable angina.

Justin Davies, Senior Research Fellow and Honorary Consultant Cardiologist at the National Heart and Lung Institute, Imperial College London developed the proprietary instantaneous wave-free ratio (iFR).²⁷ The DEFINE-FLAIR and iFR-SWEDE-HEART trials led to guideline recommendations supporting the use of iFR to guide the invasive management of patients with CAD.²⁸

David Newby, the current BHF Duke of Edinburgh Chair of Cardiology at the University of Edinburgh, was the principal investigator for the SCOT-HEART trial. SCOT-HEART showed that the use of CT coronary angiography (CTCA) in patients with angina chest pain reduced risk of death from IHD and non-fatal MI at 5 years.²⁹ CTCA is now the first-line screening tool for CAD in patients with chest pain of suspected cardiac origin recommended by NICE.³⁰

There has been a plethora of important clinical trials into the role of antiplatelet therapies in both CCS and ACS. Robert Storey, Professor of Cardiology in the University of Sheffield, has been a lead investigator for many of these, most notably PLATO and COMPLETE. The PLATO trial demonstrated that, in combination with low-dose aspirin, ticagrelor decreased risk of MACE compared with clopidogrel without an associated increased risk of major bleeding at 12 months.³¹ This trial established ticagrelor as the first-line P2Y12 inhibitor in patients receiving DAPT for ACS as recommended by NICE.²¹ More recently, the COMPLETE trial showed that patients with STEMI and multivessel CAD receiving PCI for bystander disease alongside primary PCI reduced risk of MACE compared with patients with ‘culprit-lesion-only’ PCI at 3 years.³² NICE guidelines now recommend a complete revascularisation strategy in patients with acute STEMI without cardiogenic shock.²¹

The development and impact of cardiac biomarkers, especially in the identification and risk stratification of ACS, has been a major influence on routine clinical practice in recent years. Nicholas Mills, BHF Professor of Cardiology in the University of Edinburgh, led key research describing the clinical significance of a high-sensitivity troponin I assay in patients presenting with a suspected ACS.³³ He was the principal investigator for the High-STEACS trial, which concluded that the implementation of high-sensitivity troponin I had the potential to detect low-risk patients and thereby reduce hospital stay.³⁴ The use of high sensitivity troponin I assays for rapid rule out of NSTEMI is now supported by NICE and ESC guidelines.^{19 25}

Sir Nilesh Samani, Professor of Cardiology at the University of Leicester and Medical Director of the BHF, has been highly influential in researching the genetic basis of cardiac disease with major contributions identifying risk loci for CAD.^{35–38} These genomic discoveries have been instrumental in the development of novel therapeutic strategies for lipid disorders predisposing to premature CAD.³⁹

Finally, one of the authors of this article, Rasha Al-Lamee, Clinical Senior Lecturer at the National Heart and Lung Institute, has also contributed to one of the recent, important, and to some extent controversial IHD research trials. Dr Al-Lamee designed, conducted and led the ORBITA trial.⁴⁰ This was a multicentre, double-blind, randomised, placebo-controlled clinical trial of PCI in 200 patients with stable angina and severe single-vessel CAD treated with optimal medical therapy. What controversy existed at the time of this trial was around the inclusion of a ‘sham’ procedure limb at the time of angiography. The results demonstrated that PCI did not increase exercise time by more than the effect of a placebo procedure, nor did it significantly reduce angina frequency, although follow-up stress echocardiography identified a reduction in ischaemia. The trial

highlighted the need for placebo-controlled trials of interventional procedure.

THE BCS AND ITS AFFILIATED ORGANISATIONS

Currently, 21 organisations are affiliated to the BCS. Of these, the Cardiovascular Care Partnership UK (CCP UK) is a national charity which supports patients, carers and their families with cardiovascular disease and associated conditions. Importantly, the BCS supports women in academic cardiology and, most recently, the BCS has hosted the BHF Clinical Research Collaborative (BHF CRC), a new initiative designed to support the planning and delivery of clinical research in heart and circulatory disease. The working objective of the BHF CRC is to facilitate research collaborations across the wider research community to diversify and optimise research participation, engagement and efficiency.

The BCS works closely with the British Cardiovascular Intervention Society (BCIS) to support IHD research in the UK. Specific examples include the BCIS trials led by Professor Divaka Perera and colleagues in King's College London. The Elective Intra-aortic Balloon Pump Insertion during Percutaneous Coronary Intervention (BCIS-1) trial was a multicentre, randomised, controlled trial on 301 patients with severe left ventricular failure (LVF) and extensive CAD undergoing high risk, elective percutaneous coronary intervention (PCI). Patients were randomised to intra-aortic balloon pump insertion before PCI or PCI alone. Routine IABP insertion in the experimental group did not reduce MACE followings PCI at 28 days (OR=0.94, 95% CI 0.51 to 1.76, $p=0.85$).⁴¹ The Percutaneous Revascularization for Ischaemic Cardiomyopathy (BCIS-2) trial is an ongoing clinical trial on patients with moderate to severe ischaemic LVF, extensive CAD and demonstrable myocardial viability randomised to PCI or optimised medical therapy alone. The primary end point is all-cause mortality and hospitalisation for heart failure at follow-up (1 month to 5 years).⁴² The Percutaneous Left Ventricular Unloading in High-Risk Coronary Intervention (BCIS-3) trial started recruitment in 2021. This trial will also include patients with severe LVF and extensive CAD. Patients will be randomised to percutaneous left ventricular unloading device insertion prior to PCI or PCI alone. This clinical trial aims to determine whether the left ventricular unloading device strategy reduces MACE and disease burden in this high-risk patient population undergoing complex PCI.

THE CHANGING FACE OF IHD

Stable IHD is described in contemporary guidelines as being a chronic coronary syndrome (CCS).⁴³ ACS is a unifying hierarchical term with or without ST-segment elevation. MI is caused by myocardial ischaemia leading to elevation of cardiac biomarkers, whereas unstable angina represents an ischaemic syndrome without biomarker elevation. Traditional thinking has positioned these conditions as being mainly due to epicardial coronary disease. Widespread use of early coronary angiography in ACS has shown that the absence of a stenotic 'culprit' epicardial lesion is not uncommon in patients with NSTEMI. Similarly, many patients with CCS who undergo routine angiography have no evidence of obstructive epicardial disease. In the past 10 years, BCS members have led on pivotal studies providing new insights into the aetiology of IHD, demonstrating the importance of microvascular disease and vasomotor disorders in myocardial ischaemic symptoms with non-obstructive coronary arteries (INOCA) and, relatedly, MI with non-obstructive coronary arteries (MINOCA). Despite advances in the pathophysiology,

diagnosis and treatment of CAD over the last century, IHD remains a leading cause of death and disability worldwide.⁴⁴ One of the authors, Colin Berry, Professor of Cardiology in the University of Glasgow, has led several clinical trials in this area including the BHF Coronary Microvascular Angina (CorMicA) trial which introduced stratified medicine into the management of IHD,⁴⁵ identifying a new approach for patients with INOCA now supported in practice guidelines.⁴³

FUTURE DIRECTION OF IHD TRIALS

As we have seen in recent years, research into both CCS and ACS remains highly active and ever changing. There are several ongoing clinical trials to 'look out for' in the coming years. In ACS, these include DAPA-MI, SENIOR-RITA, StratMed-MINOCA and TARGET-CTCA. In stable IHD, notable trials are currently being led by BCIS-2, CE-MARC-3, iCorMicA, ORBITA-2 and SCOT-HEART-2 investigators. Organisational developments supported by the BHF Data Science Centre, NHS Digital and the BHF CRC, coordinated through the BCS, are supporting exciting developments for data-enabled trials. A new funding scheme from the BHF will support international trials led by BCS members. Throughout these developments, the patient voice has pivotal and increasing importance in the field of IHD research, including the patient based BCS affiliated group, Cardiac Care Partnership UK, as well as other key stakeholders such as INOCA International and International Heart Spasms Alliance. BCS will continue to play a significant role in supporting research in this exciting and evolving area through the next century, as it has done in its 100-year history to date.

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Competing interests CB is employed by the University of Glasgow which holds consultancy and research agreements for his work with Abbott Vascular, AstraZeneca, Auxilium Pharma, Boehringer Ingelheim, Causeway Therapeutics, Corovantis, Genentech, GSK, HeartFlow, Menarini, Neovasc, Siemens Healthcare and Valo Health. CB is named on a patent submitted by the University of Glasgow on the use of zibotentan for microvascular angina.

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