ESC calls for greater awareness of potential for adverse events from bleeding as a result of PCI

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The European Society of Cardiology (ESC Working Group on Thrombosis) is calling for greater attention to be paid by health care staff to reducing bleeding in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary interventions (PCI), and for increased research in the field. The position paper, published online today in The *European Heart Journal*, summarises current knowledge regarding the epidemiology of bleeding in ACS and PCI, and provides a European perspective on management strategies to minimise the extent of bleeding and subsequent adverse consequences.

"Increasing progress in the treatment of ACS - due to the combination of antithrombotic therapy in the acute phase and wider use of revascularisation techniques- has meant bleeding (previously a footnote in the therapeutic armamentarium) has come to play a far more significant role in patient outcomes," says the first author of the consensus article Philippe Gabriel Steg, from the Centre Hospitalier Bichaut-Claude Bernard (Paris, France).

Bleeding associated with PCI is caused by a combination of factors. "It may be as a result of antithrombotic treatments, or due to co morbidities, such as gastric ulcers or renal dysfunction. Additionally there's the trauma that is created in the arteries from puncturing the vessels," says Kurt Huber, a former chairman of the Working Group, from Wilhelminenspital Hospital (Vienna, Austria).

Emerging evidence exists of a strong and potentially modifiable association between bleeding and adverse outcomes. In 2006 a study by John Eikelboom, which examined the association between bleeding and death or ischemic events in 34 146 patients with ACS enrolled in a clopidogrel study, found that patients who experienced major bleeds had a fivefold higher incidence of death during the first 30 days, and a 1.5 fold higher incidence of death between 30 days and 6 months. 2

Furthermore, in both the OASIS 5 and HORIZONS trials, subjects who showed a marked reduction in bleeding went on to show a subsequent reduction in mortality. "We're coming to appreciate that this may not be entirely coincidental," says Steg.

One explanation proposed to explain the relationship between bleeding and adverse outcomes is that recognised predictors of bleeding may overlap with predictors of ischemic events, with bleeding acting as a marker for increased ischemic risk. "But a second possibility that's being debated is that bleeding may have directly harmful consequences that set in motion a number of adaptive changes which themselves lead to adverse outcomes," says Huber.

Any form of bleeding can have a clinical consequence. "For example, people who have a minor nose bleed or even bleeding gums when brushing their teeth may discontinue antiplatelet therapy if they've been implanted with a stent. The train of events might lead to in-stent thrombosis or even death," says Steg.

Strategies clinicians can introduce to minimise bleeding, says the position paper, include using radial as opposed to femoral access for angiography and PCI, and adjusting the dose of anticoagulant agents, where ever possible, to body weight, age and renal function.

"One issue is that we're treating increasingly older populations who are

more likely to have decreased renal function making the possibility of anticoagulant overdoses greater," says Steg.

The Working Group on Thrombosis welcomes the recent efforts of the Bleeding Academic Research Consortium (BARC) to produce a consensus definition of bleeding for cardiovascular clinical trials. 3 The BARC definition, just published in Circulation, has been produced by an independent group of academics, research organisations (including the ESC), industry and regulator representatives:
"These definitions are based on consensus rather than data driven, making it important that they're validated in future clinical trials," says Huber.

The publication is nevertheless considered a major advance since until now there has been widespread confusion due to varying definitions of bleeding used in different clinical trials. "It's been well demonstrated that if the same study population is analyzed with different scales completely different rates of bleeding are likely to be recorded, with the rate of bleeding varying three fold according to the definition used," says Steg.

Bleeding, say the Thrombosis Working Group, should be reported using more than one bleeding scale, one of which should be the BARC bleeding definition. "Using more than one scale offers a way to minimise the potential for bias with selective reporting of bleeding events," says Steg.

For example, he says, investigators testing agents that have the potential to cause bleeding could minimise the reporting of adverse events by using a restrictive scale down playing bleeding; while investigators could over emphasis the safety of other agents by choosing sensitive scales.

Bleeding is an important subject for future research with gaps remaining in knowledge regarding the incidence of bleeding and the underlying

mechanisms, concludes the position paper. Important questions for investigation on including whether bleeding is truly causal in subsequent mortality or merely a marker of increases risk related to worse baseline characteristics; whether the outcomes for spontaneous bleeding differ from bleeding induced by percutaneous or surgical revascularization procedures; and what should be the optimal transfusion strategy for patients with ACS?

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