

Interventional Cardiology



NEWS

A novel anticoagulation system, REG1, shows promise for PCI procedures

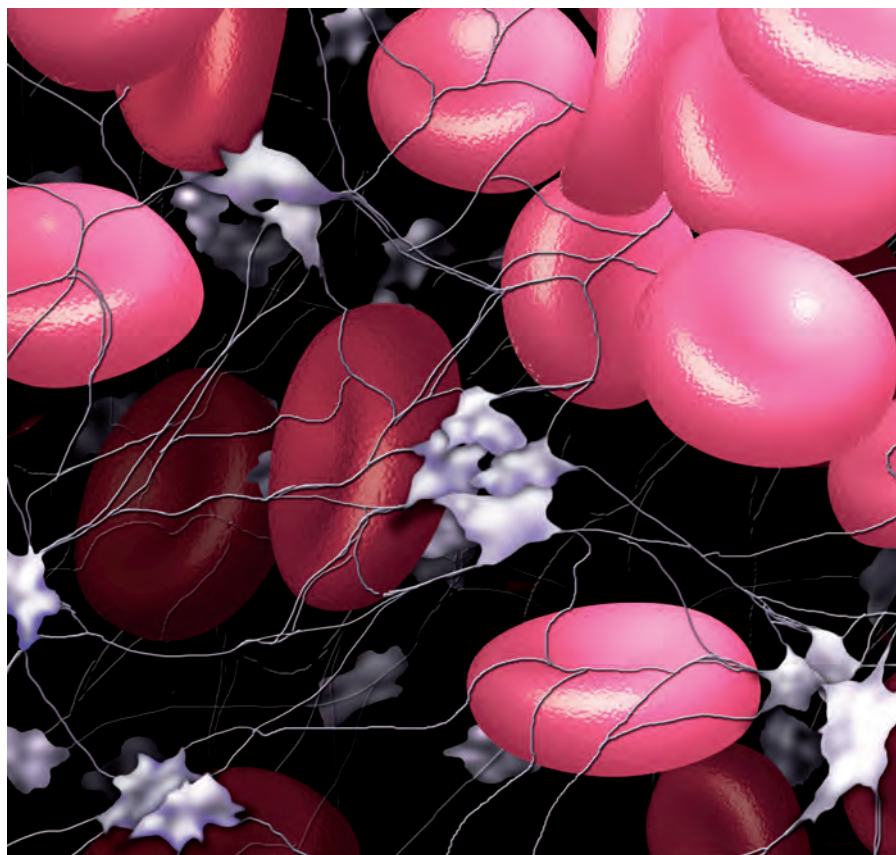
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A recent Phase II trial undertaken by Thomas Povsic and colleagues at Duke University (NC, USA) has revealed that the novel anticoagulation system, REG1, which acts by inhibiting the factor IX molecule for a 24-h duration through binding of its active component pegnivacogin (an RNA aptamer which binds and inhibits factor IX), followed by the administration of anivamersen (which binds to and inactivates pegnivacogin) convey total ACUITY bleeding similar to that of heparin, whilst decreasing major bleeds and the time required before sheath removal.

The results of this study were presented at the American College of Cardiology 2011 Scientific Sessions, where the

application of this novel anticoagulant system was explained by Povsic: "The system allows very high levels of anticoagulation for a short period, and then, on administration of the reversal agent, coagulation levels go back to normal quickly, so it is ideal for use in procedures such as percutaneous coronary intervention (PCI), where you just need high levels of anticoagulation during the procedure itself. We found that because we can normalize anticoagulation levels more quickly with the REG1 system, this allows faster removal of the sheath." It is believed that REG1 may also demonstrate potential anticoagulation benefits in other percutaneous procedures.

The RADAR trial was partially blinded, whereby 640 acute coronary syndrome patients scheduled for catheterization were given in open-label fashion either 1 mg/kg pegnivacogin (n = 479) or heparin (n = 161), before PCI was performed. Following PCI, patients who had received pegnivacogin were blindly administered with anivamersen at four different doses, corresponding to 25, 50, 75 and 100% reversal. Such a high bleeding rate was observed in the 25% reversal group that it was discontinued in the trial – this low dose of anivamersen was not high enough to reverse the pegnivacogin initially administered. Encouraging results were seen in the other three dose groups, with a rate of total ACUITY bleeding similar to that seen in the heparin group. However, it was hard to compare the overall bleeding rates in the REG1 and heparin groups owing to the open nature of the pegnivacogin administration. Povsic commented that "Less severe bleeding is quite a subjective measure, and operators may be more sensitive to minor bleeding with a new investigational agent".





In REG1 patients, sheaths could be removed on average 24 min after PCI, whereas in the heparin group it was only removed after 3 h. A reduced rate of ischemic events was observed in the REG1 group (3.0% compared with 5.7% in the heparin group), however, as the trial was relatively small, and only a total of 23 events were observed, no definite conclusions can be made at this point.

Three allergic reactions were observed following the administration of pegnivacogin towards the end of this trial in Europe: a mild dermal reaction in a single patient, to another patient who required hemodynamic support. It is not thought that these are related to drug stability or contamination and investigations are still continuing.

Commenting for *Interventional Cardiology*, Povsic said “The REG1 system offers a new paradigm for antithrombotic therapy with control, allowing one to

actively modulate the degree of anticoagulation to which a patient is exposed at any given time. RADAR suggests that reversal may mitigate bleeding. More importantly, the availability of reversal allows one to target short term high intensity anticoagulation, which may translate into lower ischemic rates. Thus, while not definitive, RADAR suggests that high level FIX inhibition with active control may be an attractive strategy to favorably impact both ischemic and bleeding endpoints”. Povsic and colleagues are now working on the design of a Phase III trial which is thought to be a PCI study based on both acute coronary syndromes and elective patients.

Source: Povsic TJ, Cohen MG, Chan MY et al.: Dose selection for a direct and selective factor IXa inhibitor and its complementary reversal agent: translating pharmacokinetic and pharmacodynamic properties of the REG1 system to clinical trial design. *J. Throm. Thrombolysis* 32(1), 21–31 (2011).

Obesity may lower the risk of mortality following percutaneous coronary intervention

The association between BMI and percutaneous coronary intervention outcome has recently been investigated by Michael Farkouh and colleagues at the Mount Sinai Medical Center (NY, USA). The researchers studied patients undergoing elective percutaneous coronary intervention between October 2003 and December 2006 and examined the prevalence of metabolic abnormality clustering and its relation to mortality in 9673 obese and normal-weight patients, who were split into the following groups based on their BMI: 18.5–24.9, 25.0–29.9, 30.0–34.9 and 35 kg/m² or more. The average age in the study group was 65.9 years and 66% were men.

In the lowest BMI category, 18.5–24.9 kg/m², the highest mortality rate was observed, regardless of their number of metabolic abnormalities. All-cause mortality for this low BMI group amounted to 55.5 per 1000 person-years, however, in the 25.0–29.9 kg/m² group this was 33.7, 28.3 in the 30.0–34.9 kg/m² group and 33.8 in the group with a BMI greater than 35 kg/m².

In the higher BMI categories, metabolic abnormalities such as hypertension, impaired fasting glucose/diabetes, triglycerides >150 mg/dl, HDL cholesterol <40 mg/dl and CRP >2.0 mg/l, were more widely observed. Also, as BMI increased it was seen that the chance of having four or five metabolic abnormalities increased proportionally (at 18.5–24.9 kg/m² there was a 12% chance of having four to five metabolic abnormalities, an 18% chance at 25.0–29.9 kg/m², a 24% chance at 30.0–34.9 kg/m² and with a BMI over 35 kg/m², a 31% chance of having four to five metabolic abnormalities). When these results are compared with patients who had zero to one metabolic abnormalities, those with two to five had increased hazard ratios for mortality.

It is somewhat counterintuitive that patients with a high BMI and high number of metabolic abnormalities should have a lower mortality rate. Farkouh and colleagues believe this could be due to higher screening in obese patients, based on their higher BMI increasing their chances of

developing metabolic abnormalities, which is likely to lead to earlier recognition of diseases in these patients. In addition, in some patients with higher BMI, it may be suggestive of higher lean body mass, rather than a measurement of excess fat, therefore, it may be more accurate to measure waist circumference or waist-to-hip ratio to assess adiposity. Finally, patients with low BMI may also be suffering from comorbidities, such as hemodynamic instability or chronic obstructive pulmonary disease, which may result in a poorer long-term mortality rate, not related to cardiovascular risk. The author's believe that “consequently, patients with lower BMI may not be as robust as those with higher BMI in possessing the metabolic reserve required to effectively deal with the stress of revascularization.”

Source: Bashey S, Muntner P, Kini AS et al. Clustering of metabolic abnormalities among obese patients and mortality after percutaneous coronary intervention. *Am. J. Cardiol.* 107(10), 1415–1420 (2011).



US FDA approves ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System

Boston Scientific Corporation (MA, USA) has announced the approval by the US FDA of the ION™ Paclitaxel-Eluting Platinum Chromium Coronary Stent System, their third-generation drug-eluting stent technology. The new stent is currently known outside the USA as the TAXUS® Element™ Paclitaxel-Eluting Coronary Stent System.

A unique platinum chromium alloy has been incorporated into this new stent system, designed specifically for coronary stenting and it is hoped that it will advance coronary stent implantation in the treatment of coronary artery disease, through greater strength, improved deliverability and outstanding visibility. The new stent provides physicians the broadest size matrix on the market, ranging from a diameter of 2.25–4.00 mm and a length of 8–38 mm.

The ION stent was examined in the PERSEUS trial, a study of 1600 patients in 90 centers worldwide, where it successfully demonstrated safety and efficacy outcomes in workhouse lesions compared with the TAXUS® Express2® Stent System and previous generation Boston Scientific stents. The data from PERSEUS was

pooled in April 2011 with the TAXUS ATLAS clinical trial, encompassing a total of 2298 patients worldwide, where it was found that the ION stent, compared with the TAXUS® Liberte® Paclitaxel-Eluting Stent System, resulted in significantly lower rates of major adverse cardiac events, target lesion failure and myocardial infarction.

Hank Kucheman, the Executive Vice President and Group President, Cardiology, Rhythm and Vascular for Boston Scientific believes that “the platinum chromium platform sets a new standard for drug-eluting stent performance and represents the future of coronary stenting.”

Louis Cannon, Heart and Vascular Institute Program Director at Northern Michigan Regional Hospital (MI, USA) believes “The platinum chromium alloy represents a leap forward in materials technology and will address many of the limitations found in older stent alloys. Exceptional stent deliverability offers cardiologists the potential to treat patients with difficult-to-reach lesions.”

Source: Boston Scientific News Release: bostonscientific.mediaroom.com/index.php?s=43&item=1003

Transcatheter-valve implantation for severe aortic stenosis is noninferior to the surgical procedure

Results from the PARTNER cohort A trial were presented at the American College of Cardiology 2011 Scientific Session/i2 Summit by the principal investigator, Craig Smith (Columbia University, NY, USA). The results suggested, in terms of all-cause mortality, that in high-risk aortic-stenosis patients considered appropriate for the surgical technique, the transcatheter aortic valve implantation (TAVI) procedure was just as efficient as traditional aortic valve replacement. Smith believes “These results indicate that [transcatheter aortic-valve replacement] TAVR is an acceptable

alternative to AVR in selected high-risk operable patients,” and concluded that “Future randomized studies should focus on lower-risk patients who are candidates for operation.”

The trial included 699 elderly patients with an average age of 84.1 years with severe aortic stenosis. These patients were randomized to either the conventional surgical procedure or TAVI at one of 26 participating centers in the USA, Canada and Germany. The TAVI procedure was carried out via both the fully transfemoral route (in 244 patients) or the transapical

route (in 104 patients), the latter which is used when the femoral artery is considered unsuited to the TAVI catheters. At 30 days post-treatment, the number of deaths was lower in the TAVI group compared with the surgical group, but the values were not significantly different at this point (3.4% 30-day mortality in the TAVI group, compared with 6.5% mortality in the surgery groups). However, at 1 year post-treatment, the deaths in both groups were almost identical, with 24.2% mortality in the TAVI groups compared with 26.8% in the surgical group.



However, the risk of major stroke in the TAVI group was significantly higher than the surgical group following treatment (5.1% compared with 2.4% at 1 year), as was the risk of vascular complications (11% in the TAVI group compared with 3.2% in the surgical group). However, unsurprisingly the risk of major bleeding was twice as likely in the surgically treated patients (19.5% compared with 9.3%). The investigators believe it is the risk of stroke that may put patients off the treatment: “It’s almost like the primary focus got lost because of the stroke issue,” Mack comments.

Robert Bonow (Northwestern University, IL, USA) told *Interventional Cardiology* that “the major concern is the risk of vascular injury and stroke, which is higher with TAVR than with surgical AVR, and the risk of stroke appears to increase over the course of time after TAVR. One hopes that the stroke risk will decrease with further advances in technology and newer delivery systems”. A number of experts did

comment that the stroke rate in cohort A is lower than that of cohort B (a previous study comparing TAVI with best medical therapy), suggesting that the stroke rates were already declining as operators gained greater experience.

Whilst this research is exciting for the field, Mack does point out that “as great as the results for cohort B were, and as great as these results are from cohort A, you still have a therapy in which between 25 and 35% of patients are dead at 1 year. So you have to ask, is that an appropriate use of expensive technology?” Mack believes it is the work of both the surgeons and interventionalists together, to recognize when comorbid diseases are too advanced to make treatment worthwhile. Mack commented that he “would be disappointed if, in the next series, the 1-year survival doesn’t climb up to 80, 85 and 90%.”

Source: *Heartwire: PARTNER cohort A: transcatheter valves noninferior to surgery*: www.theheart.org/article/1204701.do

Higher rates of access site complications are observed with antegrade access in peripheral interventions

A recent study conducted by Ashraf Mansour and colleagues at Spectrum Health (MI, USA) evaluated 5918 cases of peripheral vascular intervention carried out between January 2007 and December 2008 at 13 Michigan hospitals. The data was provided by the Blue Cross Blue Shield of Michigan Cardiovascular Consortium Peripheral Vascular Intervention Quality Improvement Initiative (BMC2PVI) registry.

In both the antegrade and retrograde groups, approximately 76% of indications for intervention were due to severe lower extremity claudication, whilst other indications included hybrid vascular surgery, limb salvage and rest pain. Angioplasty and stenting were the main interventional techniques used, yet intravascular ultrasound, lysis, laser and cryoablation therapies were also carried out. A total of 12.6% of the procedures carried out were via the antegrade access, whereas 87.4% were retrograde. The median procedure time in both groups was similar (80 min

for antegrade, 75 min for retrograde), however, the antegrade group was more likely to exceed the average time.

In the antegrade and retrograde groups, the rates of periprocedural mortality, myocardial infarction and stroke were similar, however, the occurrence of blood transfusion, vascular access complications and subsequent amputation were all higher in the antegrade group. For example, in the antegrade group, 11.5% of patients had transfusions compared with 5.6% in the retrograde group and 5.9% of patients in the antegrade group had vascular access site complications, compared with just 3.2% in the retrograde group.

Whilst the implications of carrying out antegrade access can be observed, the author’s explained that “In many cases, retrograde access may not be possible for anatomic or technical reasons, such as vessel occlusion or calcification,” and that “in diabetic patients who present predominantly with infrapopliteal occlusive

disease, reaching the target may not be possible from a contralateral approach, leaving [antegrade access] as the only option. Furthermore, in some cases, catheter and wire manipulation is more easily accomplished using [antegrade access].”

Mansour suggests that to ensure a positive outcome with antegrade access, patients should be selected with great care, anticoagulation and technique should be paid great attention and clinicians should use ultrasound if they need to guide the puncture. He also commented that “in certain patients complication rates are going to be higher, so be prepared for that” yet commented to *Interventional Cardiology* that “still this approach is very valuable in certain situations, especially when interventions are planned in the distal leg”.

Source: *Wheatley BJ, Mansour MA, Grossman PM et al.: Complication rates for percutaneous lower extremity arterial antegrade access. Arch. Surg. 146(4), 432–435 (2011).*