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CARDIOLOGY

Yearbook of Cardiology 2017



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Akshay Mehta

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SECTION 1

Coronary Heart Disease

Critical Journal Review

1. Impact of the Timing of Metoprolol Administration During ST-segment Elevation Myocardial Infarction on Infarct Size and Ventricular Function

Dev B Pahlajani

Ref: García-Ruiz JM, Fernández-Jiménez R, García-Alvarez A, et al. Impact of the timing of metoprolol administration during STEMI on infarct size and ventricular function. J Am Coll Cardiol. 2016;67(18):2093-104.

KEY POINTS

1. ST-segment elevation myocardial infarction patients who undergo primary percutaneous coronary intervention and receive intravenous metoprolol have greater salvage of myocardium than placebo treated patients
2. Earlier the administration, greater the salvage of myocardium
3. Patients receiving earlier administration of intravenous metoprolol have smaller myocardial infarctions and higher left ventricular ejection fraction compared to those who receive delayed intravenous metoprolol.

CRITICAL APPRAISAL

Beta-blockers have been long tried to salvage myocardium following myocardial infarction (MI). Various drugs like propranolol, timolol, and metoprolol have been administered with conflicting reports. In the earlier studies by Braunwald et al., Maroko et al. demonstrated that early intravenous treatment with β-blockers reduces the myocardial infarct size. While the β-blockers have no effect on the necrotic myocardium, ischemic

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cells at the risk of death could be salvaged so as to reduce the size of MI. The concept was the result of pharmacologic actions of blockers since they reduce myocardial oxygen consumption by reducing heart rate, blood pressure, and myocardial contractility.

However, results were conflicting which could be related to the fact that the timing and administration of β-blockers could have been different in different studies. With the advent of reperfusion of fibrinolytics and later primary PCI, the entire focus of salvage of MI was shifted towards achieving 'Thrombolysis In Myocardial Infarction (TIMI) III flow, myocardial blush grade III in achieving door to balloon time of less than 90 minutes so as to achieve maximum benefit of reperfusion. However, the interest in the β-blockers did not die down completely and in the TIMI II trial patients who received immediate intravenous metoprolol when compared to oral metoprolol and receiving fibrinolytic therapy had better outcomes compared to the patients who received oral metoprolol. Later on, the β-blockers have been prescribed as several physicians had discharged to reduce reinfarction and ischemic attacks. Later on, Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial enrolled 270 patients with acute anterior wall ST-segment elevation myocardial infarction (STEMI) and who were undergoing primary PCI administered 50 mg intravenous metoprolol and compared with those who received placebo. The trial assessed that by cardiac magnetic resonance (CMR) 5–7 days after STEMI which showed that infarct size was smaller in metoprolol patients (25.6 g compared with control 32 g, p = 0.012). The creatinine kinase results curve was also available in patients treated with intravenous metoprolol. These treated patients also had higher ejection fraction. The beneficial effect of metoprolol continued to be sustained with EF of 48.7% in the treated patients versus 45% in the placebo group (p = 0.025). In the current study, Garcia-Ruiz et al. performed *post hoc* analysis of METOCARD-CNIC trial. They studied the time interval between primary metoprolol bolus and reperfusion. They defined short interval metoprolol to time shorter than medial of 53 minutes and longer interval was defined as metoprolol to duration longer than the median. They performed the CMR 5–7 days post-infarction and at 6 months. There were 218 patients out of which 105 received intravenous metoprolol and the rest placebo. Compared with their interval group, those with longer metoprolol exposure had smaller infarcts (22.9 vs. 8.1 g; p = 0.06). Longer exposure to metoprolol also was associated with higher left ventricular ejection fraction (48.3% vs. 43.9%; p = 0.019) at 5 days. They simultaneously performed animal study to substantiate their evidence. The studied picks were in which 51 pigs were subjected to ischemic perfusion. Pigs were allocated intravenous metoprolol with longer or shorter reperfusion interval. Subsequently, CMR was performed in both clinical and experimental settings. In the animal study, the longer interval group had smaller infarcts with highest longer term indicating that the timing of the intravenous administration of metoprolol is important and should be administered at the earliest.

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2. Outcomes in Women Better with Newer Generation Drug-eluting Stents

Dev B Pahlajani

Ref: Giustino G, Baber U, Aquino M, et al. Safety and efficacy of new-generation drug-eluting stents in women undergoing complex percutaneous coronary artery revascularization: From the WIN-DES Collaborative Patient-Level Pooled Analysis. JACC Cardiovasc Interv. 2016;9(7):674-84.

KEY POINTS

1. Women undergoing noncomplex percutaneous coronary intervention (NCPCI) have lower major adverse cardiac events (MACE) compared to those who undergo complex PCI (CPCI) at 3 years
2. Women with CPCI who received newer generation drug-eluting stents (DES) had significantly lower 3 year risk of MACE
3. The benefit of new generation DES as regards to efficacy and safety is similar between CPCI and NCPCI
4. New generation DES carry low risk of very late stent thrombosis irrespective of procedural complexity.

CRITICAL APPRAISAL

Women constitute a substantial component of patients who undergo percutaneous coronary intervention (PCI) irrespective of the fact that in many trials, the proportion of females is smaller than the males. Registry data from National Interventional Council of India indicated that of over 350,000 patients in 2015, there were 28% females who underwent PCI. The number has remained more or less static since last 4 years. Females generally have higher rates of comorbidities like obesity, diabetic, hypertension, and renal dysfunction. They also have greater tendency to excessive bleeding despite radial access and use of vascular closure devices. Their outcomes are unfavorable following PCI since many of them have complex coronary artery anatomy like diffuse disease, long lesions, tortuosity, calcified vessels, and lower ejection fraction. Whether the new generation drug-eluting stents (DES) with thin struts, and biocompatible or bioabsorbable polymer will improve outcomes compared to older generation stents has not been studied in great detail except for small registries.

In this analysis of 1,024 patients from pooled data based on 26 randomized control trials of DES, Gennaro Giustino et al., identified 11,577 (26.3%) women who were enrolled in the trials and published their data in Journal of the American College of Cardiology Cardiovascular Intervention Vol 9, No. 7, 2016. After excluding patients who received bare-metal stents, there were 10,241 women who underwent DES PCI. Out of them, 45% had complex PCI which is defined as composite of total stent length more than 30 mm, 2 or more stents, 2 or more lesions treated, or bifurcation lesions as the target vessel. The primary endpoint was major adverse cardiac events (MACE)

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defined as composite of all-cause mortality, myocardial infarction, and target lesion revascularization at 3 years of follow-up.

At 3 years follow-up, the risk of MACE was higher in complex PCI versus noncomplex PCI ($p \leq 0.0001$). Women with complex PCI who received new generation DES had significantly lower 3 year risk of MACE (adjusted hazard ratio 0.81), lower target lesion revascularization, and lower rates of definite or probable late stent thrombosis. The incidence of very late stent thrombosis was less than 0.4% irrespective of procedural complexity.

Thus, the current study indicates significant benefit of new generation DES in women compared to older generation DES irrespective of the complexity of the lesion and comorbid conditions.

Compared to coronary artery bypass grafting (CABG), the procedural outcomes of PCI are unfavorable in patients with intermediate or high SYNTAX (The SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) score was shown in the SYNTAX trial. The stent used in the SYNTAX trial was TAXUS—a first generation DES. The current study not only shows beneficial effect of the new generation DES in women but it can be expected that they would be associated with better outcomes even in complex PCI across board and comparable to CABG.

The trial has certain limitations. It is not a randomized control trial but rather an analysis of the data from the patients pooled from earlier randomized control trials. Many women with more complex patients might have been already omitted and, therefore, may not be comparable to the population of women in general. Nonetheless, the results of favorable outcomes with new generation stents is encouraging since many more women whether with favorable or complex anatomy or comorbid conditions could be subjected to PCI with favorable outcomes.

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3. When is Rotational Angiography Superior to Conventional Single-plane Angiography for Planning Coronary Angioplasty?

Akshay Mehta

Ref: Morris PD, Taylor J, Boutong S, et al. When is rotational angiography superior to conventional single-plane angiography for planning coronary angioplasty? Catheter Cardiovasc Interv. 2016;87(4):E104-12.

KEY POINTS

1. To assess the usefulness of rotational coronary angiography (RoCA) in planning percutaneous coronary intervention (PCI), 127 stable CAD patients underwent either RoCA or conventional coronary angiography (CA) before PCI and these were compared with the referral CA (all conventional) in terms of quantitative lesion assessment and operator confidence. An independent panel reanalyzed all parameters
2. RoCA was associated with a reduction in the number of lesions judged to involve a bifurcation (23 vs. 30 lesions, $p < 0.05$), reduction in the assessment of vessel caliber (2.8 vs. 3.0 mm, $p < 0.05$) and improved confidence assessing lesion length ($p = 0.01$), percentage stenosis ($p = 0.02$), tortuosity ($p < 0.04$), and proximity to a bifurcation ($p = 0.03$), particularly in left coronary artery cases
3. Compared with conventional CA, RoCA augments quantitative lesion assessment, confidence in the assessment of coronary artery disease and the precise details of the proposed procedure without affecting X-ray dose, contrast agent volume, or procedure duration.

SUMMARY

Six operators performed 127 procedures [60 rotational coronary angiography (RoCA), 60 conventional coronary angiography (CA), and 7 crossed-over] and assessed 212 lesions. Patients were selected for standard CA or RoCA planning according to operator choice, keeping a balance between the two techniques. After the referral CAs (all conventional) were evaluated, by the operator, these assessments were compared with referral CAs, to evaluate any added value associated with the different techniques in terms of planning percutaneous coronary intervention (PCI). X-ray dosage, contrast usage, and procedure time were recorded as well as level of operator confidence associated with each angiographic method in terms of lesion assessment and PCI planning.

Conventional multiple, single-plane CA was performed according to standard practice. Rotational coronary angiography was performed after iso-centering in posteroanterior, and lateral planes on a breath hold, with a single hand injection of 15–20 mL contrast. Right coronary artery (RCA) target vessels underwent a single RoCA with 25° cranial tilt, and left coronary

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artery (LCA) cases underwent two RoCAs, one with 25° cranial tilt and one with 25° caudal tilt.

Paired comparison analysis of lesion characteristics revealed that using RoCA to plan PCI resulted in reduction in the assessment of vessel caliber (2.8 mm vs. 3.0 mm, $p < 0.05$) and a reduction in the number of lesions deemed to involve a bifurcation (23 vs. 30 lesions, significantly greater operator confidence (confidence level on a scale of 0–10 was 8.9 vs. 8.2, respectively; $p < 0.05$), especially for lesion length, % stenosis, tortuosity, and angulation.

There were no statistically significant differences in total procedure time, X-ray dose, screening time, cine runs, or contrast usage between PCIs guided by the two techniques, although all trends favored conventional CA over RoCA.

Interestingly, RoCA use did not confer much advantage as compared to conventional CA when used in the RCA. However, advantage of RoCA vs. conventional CA was particularly observed in assessment of the LCA.

CRITICAL APPRAISAL

This is the first study comparing RoCA against conventional single-plane CA for immediate pre-PCI planning. Rotational coronary angiography improved the operator's understanding of the target lesions and the proposed procedure compared with the knowledge gained from the conventional CA. Rotational coronary angiography resulted in a better evaluation of lesion characteristics and operator confidence which may directly influence PCI strategy.

Advantages of a RoCA technique are:

1. Reduction in the volume of contrast agent used and the total radiation dose–of special use in patients with renal insufficiency
2. Availability of 121 separate views and, therefore, more anatomical detail than conventional CA
3. Possibility of generating a 3-D reconstruction of vessel geometry, which can aid planning of percutaneous coronary intervention as well as for computing intracoronary physiological parameters such as fractional flow reserve.

On the downside, there could be increased procedure time with RoCA, which may occur because of the requirement for careful iso-centering and a "dummy run" with adjustments to drapes, patient position, and table height before restarting the whole process. In addition, errors in iso-centering (cutting off a vessel), insufficient contrast in the syringe, or disengagement of the catheter requires RoCA to be repeated. Even good-quality RoCAs may have to be supplemented with conventional runs (52% in this study). Besides, RoCA is impossible in very obese patients.

Limitations of the study were that it was an observational, single center study with relatively small number and without clinical outcomes as an endpoint. Also, the modality selection was self-determined and non-rando-

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mized introducing the possibility of bias. Additional usefulness for RCA evaluation was limited.

CONCLUSION

For PCI planning, RoCA may offer advantages of better appreciation of lesions than conventional CA, particularly in LCA cases. In contrast to purely diagnostic RoCA, it does not reduce the volume of contrast used, the X-ray exposure, or the procedure time. Whether this technique should be routinely preferred in all patients undergoing diagnostic angiogram is open to question.

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4. Effects of Optimism and Gratitude on Physical Activity, Biomarkers, and Readmissions After an Acute Coronary Syndrome: The Gratitude Research in Acute Coronary Events Study (GRACE Study)

Akshay Mehta

Ref: Huffman JC, Beale EE, Celano CM, et al. Effects of optimism and gratitude on physical activity, biomarkers, and readmissions after an acute coronary syndrome: The Gratitude Research in Acute Coronary Events Study. Circ Cardiovasc Qual Outcomes. 2016 Jan;9(1):55-63.

KEY POINTS

1. To investigate associations of baseline optimism and gratitude with subsequent physical activity, prognostic biomarkers, and cardiac rehospitalizations in post-acute coronary syndromes (ACS) patients, 164 participants were enrolled during admission for ACS and underwent assessments at baseline (2 weeks post-ACS) and follow-up (6 months later)
2. Post-ACS optimism, but not gratitude, was prospectively and independently associated with superior physical activity and fewer cardiac readmissions. There were no significant relationships between optimism and biomarkers. Gratitude was minimally associated with post-ACS outcomes.

CRITICAL APPRAISAL

Negative psychological traits, such as depression and anxiety, are known to be independently associated with worse prognosis after an acute coronary syndrome. But the prospective relationship between positive psychological outlook (such as optimism and gratitude) and cardiac health after an acute coronary syndrome is not well studied.

This is the first study to concurrently examine the effects of these specific positive psychological constructs on outcomes in patients with acute coronary syndromes (ACS), a population at substantial risk for rehospitalizations, and mortality. It is also the first to examine the prospective effects of these on health behaviors, prognostic biomarkers, and clinical outcomes within the same study to explore possible mechanisms by which these constructs may confer benefit.

The study found that optimism, measured 2 weeks after ACS, was associated with greater physical activity in mean steps per day at 6 months, controlling for pre-ACS physical activity and numerous baseline demographic and medical factors, and independent of depression and anxiety, suggesting a unique effect of positive psychological well-being on post-ACS physical activity.

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Thus, a sense of optimism may serve as a novel predictor of subsequent physical activity and fewer readmissions when measured shortly after an acute coronary syndrome.

In contrast, gratitude was not associated with physical activity, biomarkers, or readmissions during the same time period.

Why were the results of these two traits, optimism and gratitude, different?

Optimism is a general expectation that the future will be favorable. Believing that one's future (and future health) was likely to improve may play a substantial role in motivation and confidence to make change. The thought that one can do something to reach a goal, may promote beneficial changes in health behavior.

In contrast, gratitude (an attitude of appreciation and thankfulness for people, events, and experiences in one's life) is largely a current- or past-focused construct, in which people experience well-being by taking stock of their immediate and previous experiences. It may be less directly linked to making behavioral changes.

There were some limitations to the study. Firstly, it was conducted at a single academic site and enrolled a preponderance of white men, potentially limiting its generalizability. Secondly, it only measured number of steps per day rather than activity intensity. Finally, the 6-month period for assessing readmissions, could be relatively short and limited.

Despite these limitations, this study suggests a distinct contribution of optimism to increased physical activity and readmission reduction during the critical post-ACS period, and if measured shortly after an ACS, could be used as a novel predictor of reduced physical activity or readmissions.

Interestingly, the effects of optimism on physical activity were above and beyond the adverse effects of depression and anxiety, and were in contrast to gratitude, which was not linked to outcomes.

An important implication of the study for us as physicians is to examine and be watchful of our own demeanor and communication with patients as these aspects of treatment are known to positively (or negatively) affect their sense of optimism.

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5. Impact of Ivabradine on Central Aortic Blood Pressure and Myocardial Perfusion in Patients with Stable Coronary Artery Disease

Akshay Mehta

Ref: Dillinger JG, Maher V, Vitale C, et al. Impact of ivabradine on central aortic blood pressure and myocardial perfusion in patients with stable coronary artery disease. Hypertension. 2015; 66(6):1138-44.

KEY POINTS

1. The effect of β-blockers on central blood pressure with resultant increase in cardiovascular risk is well known
2. Whether ivabradine can also have this deleterious effect was studied in a randomized, double-blind trial of 12 normotensive or controlled hypertensive patients with stable coronary artery disease and heart rate more than or equal to 70 beats/min (sinus rhythm)
3. After 3 weeks, treatment with ivabradine was associated with a significant reduction in resting heart rate without any relevant between-group difference in change in central aortic systolic blood pressure or augmentation index. Ivabradine caused a modest increase in left ventricular ejection time and a prolongation of diastolic perfusion time. Thus, heart rate decrease with ivabradine was not associated with increase in central aortic blood pressure and was associated with improvement in myocardial perfusion index.

CRITICAL APPRAISAL

Studies have shown that β-blocker associated heart rate reduction is associated with increased risk for cardiovascular events in patients with hypertension. It was surmised that this could be related to a relative increase in central blood pressure with β-blockade versus other classes of antihypertensive agent. On the other hand, the rate reduction with ivabradine was associated with –4.0 mmHg reduction in central SBP and a +0.8% change in augmentation index.

Also, trained individuals with physiologically low heart rate have low central aortic pressure and augmentation index.

The deleterious effects of β-blockers, in contradistinction to the beneficial effects of ivabradine and athletic habits could be hypothesized to be due to two mechanisms:

1. Beta receptor blockade associated peripheral vasoconstriction, leading to an increase in augmentation index for high doses of β-blockers corresponding to the lower heart rate values
2. Impact of β-blockers on myocardial contractility, which reduces LV dP/dt, could delay the peak of the outgoing wave leading to a coincidence of

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the reflected wave with late systole, thereby increasing central systolic blood pressure.

Both these effects are not characteristic of ivabradine and athletic training.

Thus, the study suggests that the increased risk of cardiovascular events in hypertensive patients treated with β-blockers may not be because of an impact of pharmacological heart rate reduction on central aortic blood pressure but rather to side effect of β-blockers, which are not shared with ivabradine.

The main limitations of the study were the small number of patients two of whom had stable CAD without hypertension and the rest had controlled hypertension. Hence, one may not be easily able to extend these results to patients with uncontrolled hypertension.

The strength of the study was its randomized, double-blind, crossover design, which showed no change in parameters with placebo as compared to the beneficial effects with ivabradine.

Given the possible benefits, should ivabradine be used in preference to β-blockers in patients with hypertension and CAD, especially the elder ones? Future will tell.

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