



## Opinion Piece

## Palliative treatment of coronary “atherosclerotic cancer” by drug-eluting or bare-metal stents: From oculo-stenotic reflex period to age of precision medicine



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## ABSTRACT

Medications and treatments are said to have a palliative effect if they relieve symptoms without having a curative effect on the underlying disease such as atherosclerosis or cancer. Some authors speculated that atherosclerotic coronary artery disease (CAD) could be considered a “cancer of the coronary arterial wall”. Although the percutaneous coronary intervention (PCI) has proven to be effective in decreasing mortality rates among patients with acute coronary syndromes, the previous meta-analyses of PCI versus optimal medical therapy for stable CAD have not been able to demonstrate a reduction in major adverse cardiac outcomes. However, few cardiologists discussed the evidence-based benefits of angiogram and PCI for stable CAD, and some implicitly or explicitly overstated the benefits. Recently, the precision medicine is defined as an evidence-based approach that uses innovative tools and biological and data science to customize disease prevention, detection, and treatment, and improve the effectiveness and quality of patient care. Providing patients with accurate and complete information appears to be an effective way to combat the reliance on the oculostenotic reflex. The foundation of precision medicine is the ability to tailor therapy based upon the expected risks and benefits of treatment for each individual patient. As said by Doctor William Osler, “The good physician treats the disease; the great physician treats the patient who has the disease.”

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Medications and treatments are said to have a palliative effect if they relieve symptoms without having a curative effect on the underlying disease or cause. Some authors speculated that atherosclerotic coronary artery disease (CAD) could be considered a “cancer of the coronary arterial wall” :<sup>1–3</sup> a stable coronary arterial disease as a “benign” and acute myocardial infarction syndromes as a “malign” form. The choice of treatment of coronary atherosclerotic cancer is considered important since it could lead to differences in long-term outcomes. The development of bare metal stents (BMS) was a major advance relative to balloon angioplasty in the management of symptomatic CAD.<sup>4</sup> Although BMSs were first underestimated due to the fact that they were generally used in bailout situations, then they were overused quite uncritically rather to the detriment of the patient.<sup>5</sup> In the early 2000s, first-generation DES (1st-DES) have been widely used

because of the dramatic decrease in-stent restenosis and the need for target lesion revascularization. However, concern was raised about an increased risk of late stent thrombosis after 1st-DES implantation,<sup>6,7</sup> and then the 2nd-generation DES (2nd-DES) has been designed with the goal of improving safety, efficacy, and device performance. These new-generation 2nd-DES have exceedingly low rates of very late stent thrombosis, significantly improving on 1st-DES and similar to BMS.<sup>8</sup> Moreover, newer generation DESs with shorter durations of dual antiplatelet therapy (3 months to 6 months) were non-inferior to 12 months or 24 months of treatment with regard to either a composite of cardiovascular events or cardiovascular events plus major bleeding.<sup>9</sup> Therefore, the DES use trends indicate rapid and broad initial use followed by a sharp decline in 2007 and a progressive rise in 2011.<sup>10</sup> Although the PCI has proven to be effective in decreasing mortality rates among patients with acute coronary syndromes, the previous meta-analyses of PCI versus optimal medical therapy for stable CAD have not been able to demonstrate a reduction in major adverse cardiac outcomes, even when trying to limit the analysis to patients with documented ischemia.<sup>11</sup> The COURAGE

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trial<sup>12</sup> suggest PCI is associated with only a modest improvement in quality of life, which actually dissipated over time. These studies consistently indicated no risk reduction in the incidence of myocardial infarction or death associated with PCI, except for high risk stable CAD (defined as >3% annual death or myocardial infarction risk) patients with significant left main coronary artery disease, ostial left anterior descending artery, multivessel disease, severe resting LV dysfunction not readily explained by non-coronary causes or resting perfusion abnormalities  $\geq 10\%$  of the myocardium).<sup>13</sup> On the other side, clinicians are being challenged to understand why a divergence exists between recent evidence and the conventional wisdom that PCI is associated with a large benefit in symptom relief without altering overall prognosis.<sup>14</sup> Recently, the NORSTENT trial, was the largest stent trial ever conducted, showed that patients receiving 2nd-DES have similar rates of death or spontaneous myocardial infarction than those receiving contemporary BMS, but the rate of repeat revascularization is lower with the use of DESs.<sup>15</sup> After a median of 5 years of follow-up, no significant differences were found between the two groups for the primary composite outcome of death from any cause or nonfatal spontaneous myocardial infarction, with a cumulative rate of 16.6% in the 2nd-DES group versus 17.1% in the BMS group (HR 0.98, 95% CI 0.88–1.09; P=0.66).<sup>15</sup> This was relatively disappointing results for 2nd-DESs but not BMSs. Both types of stents have pros and cons; decisions should be based on what is considered appropriate for a patient since the choice of stent type may have an impact on long-term outcomes.<sup>16</sup> The use of BMSs remains an important option for PCI in some patients, including those with a large vessel diameter in whom restenosis rates are low, those who cannot complete the longer duration of dual-antiplatelet therapy recommended for DESs because of noncompliance or need for noncardiac surgery, those who cannot pay for DESs or a longer duration of dual-antiplatelet therapy because of increased cost, and those at increased risk for bleeding (e.g. recent bleeding or concomitant anticoagulation use).<sup>5,16,17</sup> While patients generally appear to receive the most optimal stent given their clinical characteristics (demographic and anatomical factors), however, stent choice seems partially determined by the treating physician and hospital, which may lead to differences in long-term outcomes.<sup>18,19</sup> Fortunately, in field of cardiology, innovations, research and clinical trials are conducted widely all around the world and clinical practice guidelines are updated very regularly.<sup>13,20</sup> However, physician adherence to guidelines is often poor.<sup>21</sup> Although the fractional flow reserve measurement of intermediate coronary stenoses is recommended by guidelines when demonstration of ischemia by noninvasive testing is unavailable, the visual estimation continues to dominate the treatment decisions for intermediate stenosis, indicative of a worrisome disconnect between recommendations and current practice.<sup>22,23</sup> In some cases, experts say, doctors are motivated to use stents for financial reasons, because of the large revenue streams that stent procedures can bring hospitals. In transitioning health systems, some patients develop mistrust for physicians' motives as inequalities in health care expand and close ties between pharmaceutical companies and physicians are revealed.<sup>24</sup> In a study published in *The Archives of Internal Medicine*, Dr. Lin found that some doctors performed elective angioplasty procedures because they believed it would alleviate a patient's anxiety. Others felt that new and better stents would make a difference, or they worried they would feel guilty if they did not operate and a patient had a heart attack down the line.<sup>25</sup> In a small study in *The Annals of Internal Medicine*, Dr. Rothberg reported that patients with stable CAD who are told they have a blockage naturally assume that angioplasty must be lifesaving, unless their doctor explains to them otherwise.<sup>26</sup>

Patient-centered care has been identified as 1 of the 6 aims for the 21st-century health care system and aims to engage patients as active partners in their care and treatment to improve the management of their illness.<sup>27</sup> Recently, the precision medicine is defined as an evidence-based approach that uses innovative tools and biological and data science to customize disease prevention, detection, and treatment, and improve the effectiveness and quality of patient care.<sup>28</sup> The foundation of precision medicine is the ability to tailor therapy based upon the expected risks and benefits of treatment for each individual patient.<sup>28–30</sup> It is in contrast to a “one-size-fits-all” approach, in which disease treatment and prevention strategies are developed for the average person, with less consideration for the differences between individuals. Indeed, it is well known that the effective doctor-patient communication is a central clinical function in building a therapeutic doctor-patient relationship, which is the heart and art of medicine.<sup>31–34</sup> In general almost all patients want to know their diagnosis and most patients also want to be informed about the chance that they will be cured.<sup>35</sup> This does not imply that these patients want to hear the really bad news about their condition. Many patients, when they fear that their prognosis is rather poor, do not ask for precise information and do not hear it if it is provided by the doctor.<sup>36,37</sup> This can lead to collusion between the doctor and the patient where the true poor prognosis will tend to be hidden during the doctor-patient communication about the illness.<sup>37</sup> A similar situation has also been reported in daily PCI decision-making practice. Few cardiologists discussed the evidence-based benefits of angiogram and PCI for stable CAD, and some implicitly or explicitly overstated the benefits.<sup>26,38</sup> In the real-life practice, even in developed countries with prevalent medical malpractice suits; almost half of PCIs done in patients with stable angina are inappropriate or of uncertain appropriateness.<sup>23,39</sup> Although the clinical guidelines emphasize medical therapy as the initial approach to the management of patients with stable CAD, among patients with stable CAD undergoing PCI, less than half were receiving optimal medical therapy before PCI and approximately two-thirds were receiving optimal medical therapy at discharge following PCI, with relatively little change in these practice patterns after publication of the COURAGE trial.<sup>40</sup> Moreover, for some cardiologists the oculostenotic reflex is already potentiated leading to iatrogenesis fulminans.<sup>41</sup> Providing patients with accurate and complete information appears to be an effective way to combat the reliance on the oculostenotic reflex, which is a term to describe doctors who act on the belief, “any blockage you see is a blockage you treat, even if evidence suggests no benefit”.<sup>42</sup> However, the most patients with stable CAD do not know the PCI procedure is not related mortality benefit and receive unbiased information about the risks and benefits of each procedure and the alternatives.<sup>26,43,44</sup> Although a personalized consent form that enables patient engagement and individualized risk modeling allow for a greater understanding of the procedure and a more interactive process for subjects prior to PCI,<sup>19</sup> most operators shy away from using precision medicine in their PCI decision-making process.<sup>44</sup> In the age of precision medicine, even if it is under the shade of some ethical problems with pay performance system<sup>45–48</sup> and defensive medicine due to medico-legal fears,<sup>49,50</sup> physicians must first and foremost always remain patient advocates and continue to act independently.<sup>51,52</sup>

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