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Death, coronary revascularization choices, and chronic kidney disease

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Medical decision-making is a give and take, an assessment of risks versus benefits of any action. Palliative medicine's growth is a reflection of the application of this approach at the end of one's life. Other examples include decisions around chemotherapy in the field of oncology and arguably termination of pregnancy for medical reasons. In each of these examples, the decision-making sits at the level of the individual. It takes into account a whole host of variables that embrace the spiritual, psychological, and physical realms of the individual affected by the decision-making.

In contrast to these very personal examples, the medical community embraces guidelines based upon 'evidence'. In some ways, this is the other end of the decision-making spectrum. It is an impersonal approach in which the choice among alternative approaches is determined by the average response of average patients in the same situation.

Somewhere between these two poles lies a 'sweet spot' in which there is a merger of personalized decision-making that is also informed by evidence-based medicine. We have less understanding of how individuals approach this interaction between their personal wishes and the evidence from average patients to make a specific decision. This becomes relevant to how we, as medical providers, use evidence-based data to provide informed consent for many procedures.

In this issue of *Coronary Artery Disease* data from two registries in British Columbia, Canada were combined to assess the mortality and renal outcomes of individuals with baseline chronic kidney disease [estimated glomerular filtration rate (eGFR) < 60 ml/min

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Conflicts of interest

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and referred to a nephrologist] and who underwent coronary artery bypass grafting (CABG), coronary angiography and percutaneous coronary interventions (PCIs), or medical therapy for coronary artery disease between 2003 and 2009. There are likely to be vast differences between these three groups of patients on objective variables such as demographics, baseline comorbidities, and therapeutics as well as unknown differences related to those spiritual, psychological and physical realms. In an effort to compare ‘oranges with oranges’, the authors used propensity matching in these three groups to compare outcomes. The variables used to match patients included: age at index, sex, BMI at index, smoking status, duration of care by nephrologists, mean eGFR within 1 year before index (also accounting for the number of eGFRs available), eGFR at index, index year, emergency status of procedure, diabetes, history of cerebrovascular disease, congestive heart failure, peripheral vascular disease, dyslipidemia, history of PCI or CABG, and number of diseased coronary vessels. The outcomes were death, dialysis, or 30% reduction in kidney function at 3 and 24 months.

It is appreciated that patients with chronic kidney disease are more likely to develop acute kidney disease and/or worsening kidney function following either PCI or CABG. Some of this association may be causal. The hemodynamic consequences of cardiopulmonary bypass, the nephrotoxic effects of iodinated contrast media, or the occurrence of cholesterol emboli may all lead to acute kidney injury (AKI) with incomplete recovery of function and a further decrease in kidney function in the long term. Some of the association however represents an ascertainment bias. That is, a much smaller loss of glomerular filtration rate (GFR) is necessary to raise the serum creatinine to the threshold for AKI definition when GFR is already low [1]. This is based partly on mathematics. Serum creatinine does not change linearly with GFR. To achieve a 0.3 mg/dl increase in creatinine (the threshold for AKI based upon the KDIGO criteria) requires a greater reduction in absolute GFR when you start with a creatinine of 1.0 mg/dl than when you start with a creatinine of 2.0 mg/dl. Furthermore, the amount of ‘renal reserve’ is greatly diminished in patients with a creatinine of 2.0 mg/dl. Renal reserve, which is the amount of additional GFR that can be generated by each nephron, is decreased when there is a reduction in nephron number because the remaining nephrons are using their reserve in an effort to maintain GFR. When loss of nephrons occurs in patients with normal kidney function, there is usually enough renal reserve in the unaffected nephrons to maintain GFR even though there is a reduction in the number of functioning nephrons. This obscures the extent of the injury. Thus a much greater injury is needed in those with normal kidney function to achieve the definition of AKI compared with patients who at baseline have a decrease in GFR. So the data from this study appropriately addresses a group of patients who are more likely to experience the outcomes of interest. This should not be taken as a reason not to worry about all the other patients not included in the analysis.

What question(s) are the authors of this study trying to address? One obvious question is whether one or more of these therapies is associated with a worse prognosis, as reflected in 3- and 24-month mortality, progression of chronic kidney disease, or need for renal replacement therapy. This is an important issue as the specific endpoints are all very clinically significant and contribute substantially to a patient’s quality of life. Are the authors also asking the complementary question: is one of these therapies associated with a better prognosis. This is not just the absence of one of the primary endpoints, but also

includes functional status, reduced hospital admissions and frequency of office visits, and number of medications, etc. These are quantifiable outcomes and perhaps as important to the individual as mortality, progression of chronic kidney disease, and need for renal replacement therapy.

The basic finding of their analyses is that survival is better with CABG compared with PCI or medical therapy. This is supported by other retrospective cohort studies in New York [2]. However, a formal systematic review of CABG versus stenting finds no significant difference [3]. In the current study, mortality is reduced significantly without a significant difference in how many patients have worsening of kidney function at 24 months. Interpreting these observations requires more than simply looking at the index procedure. All of the subsequent events during the 24-month follow-up period including differences in the processes of care among these three groups could influence the primary outcomes. For example, how many patients in each group underwent cardiac rehabilitation? How well were blood pressures and blood sugars controlled? What medications were prescribed in the three groups?

An interesting observation is that the incidence of dialysis dependency at 24 months was markedly different between the CABG and PCI patients (10%) and those getting medical therapy (20%). This could mean that there were significant differences between the CABG and PCI patients and the medical therapy group that are not captured in the propensity-matching algorithm. For instance, patients matched through the propensity algorithm are likely more representative of patients at too high risk to undergo CABG in the providence. Although estimated GFR's were similar at the index procedure, we do not know anything about the trajectory of renal function. For example, was kidney function declining in those who received medical therapy versus stable in those who underwent CABG or PCI? An alternative explanation is that improving cardiac function following CABG may have an effect on the trajectory of kidney function. For example, did kidney function improve in patients who underwent revascularization? This might be a type of cardiorenal syndrome in which improvement in one organ leads to improvement in another. This is an interesting hypothesis and further work in this area is clearly needed.

There are notable limitations to the propensity-matching approach undertaken by the investigators. Even though propensity matching was conducted to help to control for confounding, the propensity matching does not remove the strong actor of selection bias in the providential medical system. By propensity matching on prior cardiac procedures (CABG or PCI) and number of diseased vessels, a more rigorous approach to build upon prior research in this area would be to do exact matching to these risk factors: for instance, the patient population could have been limited to patients with significant (>70% stenosis) in two or three coronary artery vessels with exact matches in each procedural arm for the number of diseased vessels; and KDIGO eGFR categories could have precise matches in each arm.

In summary, the evidence presented in this work will help guide medical decision-making but it will not be used *in vacuo* – that is, without a lot of additional factors that reflect the individual patient. This personalized decision-making embraces the ‘art’ of medicine,

something more encompassing than ‘evidence-based medicine’. It would be foolish to conclude from this data that all patients with both chronic kidney disease and coronary artery disease should undergo CABG; for that we will have to wait for findings from ISCHEMIA-CKD (<https://clinicaltrials.gov/ct2/show/NCT01985360>). What is really needed is more data that gets at the underlying factors that prompted CABG, PCI, or medical therapy in these patients.

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