Economics and Quality of Care for Patients with Acute Coronary Syndromes: The Impending Crisis

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Summary: Several factors are placing significant financial burdens on the health care system today. These include the growing older population, the obesity and type II diabetes epidemics, and the attendant increased prevalence of heart disease, which remains the leading cause of death in the United States. In response, cardiovascular medicine is undergoing sweeping change in the use of advanced technology and interventions. In addition, biomarkers, such as troponin, are emerging as critical predictors of responses to therapy, particularly for coronary stenting. Future trends in the treatment of acute coronary syndromes (ACS) will embrace the use of genomic solutions, such as gene expression profiling, to predict therapeutic outcomes. Careful consideration will need to be given to these innovative approaches to ensure they are cost effective.

Key words: acute coronary syndrome, angiography, C-reactive protein, genomics, interleukin-6, myocardial infarction, stents, troponin

Introduction

The American health care system is in crisis. In a recent article in the *Archives of Internal Medicine*, this situation was described as “the chassis is broken, and the wheels are coming off.”¹ This crisis in health care comes at a time when the popu-

lation is getting older and degenerating more quickly. Over the next 10 to 20 years, the Institute for the Future predicts a rapid rise in the number of elderly.² Coupled with this is the increasing prevalence of obesity and diabetes in the United States. Currently, one in four Americans now qualifies as being obese, with diabetes increasing in proportion.³

Despite considerable interest in cancer, neurological disorders, and other diseases, heart disease remains the leading cause of death in the United States. Even with better therapies, the cardiology community is losing ground due to poor lifestyle choices and the aging population. According to the Centers for Disease Control and Prevention (CDC),⁴ a person's odds of dying from heart disease in the next year is 1 in 388, worse odds than dying in a motor vehicle accident or from bad medical care. Given these grim statistics, this is where society should be putting its national health care resources.

The Rise in Health Care Spending

Health care spending in the United States continues to take on exponential growth (Fig. 1). In the past 5 years, the biggest jump has occurred in prescription drug costs, up 17% in 2000.⁵ Health care now comprises 13.2% of the gross national product (GNP). Total health care expenditures are projected to increase 101%, with prescription drug costs projected to increase 213%.⁶

The field of cardiovascular medicine is also experiencing a surge in expensive, medical technology. This includes such things as the artificial heart, automatic implantable cardioversion defibrillators (AICD), biventricular pacemakers, and coated stents. Practically every part of the human body is being studied to see how it can be replicated artificially.

What has been the potential impact of these new cardiovascular medical devices? As can be seen in Table I, four of these devices have been analyzed in terms of cost per patient and their cost to the health care system: defibrillator, left ventricular assist device (LVAD), coated stent, and biventricular pacing (Bi-Vp). For example, only 60,000 patients currently receive a defibrillator every year. The new clinical trial data from the

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FIG. 1 Health care spending in the United States. Reprinted from the U.S. Department of Health and Human Services with permission. GNP = Gross National Product.

Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II), however, support their use in more than 600,000 patients, a > 10-fold increase.⁷ Yet, the estimated number of people who have a $\leq 30\%$ ejection fraction post MI is more than 2 million.

Biomarkers

All of these factors are currently affecting the way cardiologists treat acute coronary syndromes (ACS). Change is required if a crisis is to be averted. A good solution to the impending crisis in ACS care is to develop smarter therapeutic strategies.

Biomarkers are a good illustration of a better strategy. In just the last 3 to 5 years, troponin has evolved as a critical component of assessing patients with ACS. Over time, this importance will extend to inflammation, thrombosis, embolization, and hemodynamic considerations. In the Thrombolysis in Myocardial Infarction (TIMI) 11B trial, elevations of cardiac troponin I (cTnI) and negative levels of creatine kinase (CK)-

MB among patients with non-ST segment elevation, ACS predicted those who were at higher risk for very early adverse outcomes, including recurrent ischemia.⁸ Patients who were cTnI positive had better response to enoxaparin than those patients who were cTnI negative (Fig. 2). Troponin-positive patients also respond well to glycoprotein IIb/IIIa inhibitors, which reduce the occurrence of death or myocardial infarction (MI).⁹ In a study of tirofiban, troponin I and troponin T were reliable markers for identifying high-risk patients with ACS.¹⁰

Coronary Stenting

Another novel therapeutic approach in patients with ACS is coronary stenting. There has been some analysis to see whether conservative management of ACS is more cost effective.¹¹ In the Veterans Affairs Non-Q-Wave Infarction Strategies In-Hospital (VANQWISH) trial, a more conservative, ischemia-guided strategy of selective coronary angiography and revascularization was found to be more cost effective when compared with routine coronary angiography in patients with uncomplicated non-Q-wave MI.¹²

The case for invasive strategies, however, has been made in the Thrombolysis and Counterpulsation to Improve Cardiogenic Shock Survival (TACTICS) trial. Minor elevations of troponins I and T predicted the benefits from early, invasive strategies in patients with unstable angina and non-ST elevation MI.¹³ Patients randomized to the invasive approach, consisting of coronary angiography and revascularization, experienced a significant reduction in the trial's primary endpoint of death, MI, or rehospitalization for ACS at 6 months. Those patients with cTnT levels of ≥ 0.1 ng/ml had the greatest reduction in primary endpoint of death or MI (Fig. 3). A later cost analysis showed that the overall increase in cost for initial hospitalization in the patients receiving invasive therapy was \$2,000.¹⁴ However, when it came to follow up costs, those in the conservative treatment group showed an increase in cost of \$1,000 compared with the invasive group.

TABLE I Approximate costs of recent evidence-based cardiovascular medical devices. Costs are extrapolated from The Cleveland Clinic

Trial	Tech	↑N	↑Cost/patient	U.S. cost
MADIT-II ⁷ (Mortality 20 → 14%)	ICD	600,000	\$25 K	15 Billion
REMATCH ²⁹ (Mortality 52 → 25%)	LVAD	100,000	\$160 K	16 Billion
RAVEL and SIRIUS ^{30,31}	Coated stent	600,000	\$4 K	2.5 Billion
MIRACLE ³²	Bi-Vp	1,000,000	\$60 K	60 Billion

Abbreviations: ICD = implantable cardioverter-defibrillator, LVAD = left ventricular assist device, Bi-Vp = biventricular pacing, MADIT II = Multicenter Automatic Defibrillator Trial, REMATCH = Randomized Evaluation of Mechanical Assistance for Treatment of Congestive Heart failure, RAVEL = Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions, SIRIUS = A Multicenter Randomized, Double-Blind Study of the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions, MIRACLE = Multicenter INSYNC Randomized Clinical Evaluation.

FIG. 2 Response to enoxaparin as predicted by troponin elevations in the TIMI 11B trial (n = 359). CK = creatine kinase, Neg. = negative, Pts. = patients, cTnI = cardiac troponin I, D = death, MI = myocardial infarction, UR = urgent revascularization. Adapted from Ref. No. 8 with permission.

Aggressive Angiography

Aggressive first-day angiography has also been compared to conservative treatment in the Value of first day coronary angiography/angioplasty In Evolving Non-ST-segment elevation myocardial infarction: An Open multicenter randomized trial (VINO) study.¹⁵ This randomized trial examined the value of first-day angiography and angioplasty in patients with evolving MI without persistent ST-elevation. After 6 months, the mortality in the first-day angiography/angioplasty group was 3.1 versus 13.4% in the conservative group. The rate of nonfatal reinfarction was 3.1% in the aggressive therapy group versus 14.9% in the conservative group.

FIG. 3 Impact of coronary angiography and revascularization on death or myocardial infarction (MI) in patients with elevated troponin levels (cTnT). Adapted from Ref. No. 13 with permission.

C-Reactive Protein

Another smarter approach to treating patients with ACS is to identify those who have increased levels of high-sensitivity C-reactive protein (CRP). High CRP levels are predictive of lower event-free survival rates among patients with stable and unstable angina (Fig. 4).¹⁶ Such low-grade inflammation is an independent predictor of adverse outcomes after coronary stent implantation and is associated with proliferative responses inside implanted stents.¹⁷ As such, preprocedural levels of CRP predict early complications and clinical restenosis.¹⁸ Therefore, it may be wiser to get a patient's inflammation under control before these procedures are performed.

FIG. 4 Ability of C-reactive protein (CRP) to predict risk of death or myocardial infarction in patients with stable and unstable angina. CI = confidence interval. Adapted from Ref. No. 16 with permission.

FIG. 5 The association between mortality and interleukin 6 (IL-6) levels in the FRISC II trial. RR = relative risk. Adapted from Ref. No. 19 with permission.

Interleukin 6

The relationship between inflammation and invasive versus conservative strategies has also been investigated with interleukin 6 (IL-6) in the Fragmin during Instability in Coronary Artery Disease (FRISC) II trial.¹⁹ Higher levels of IL-6 (> 5 ng/l) were associated with a greater increased mortality in the noninvasive group (Fig. 5). Early aggressive treatment, however, significantly lowered the 12-month mortality in those patients with elevated IL-6.

Smarter Prescribing of Cardiovascular Drugs

Even in the case of cardiovascular drugs, clinicians need to be smarter in prescribing them. When the major trials of these drugs were reviewed, the number of patients benefiting from them was approximately 9 out of 100 (Table II).²⁰ This shows a lack of benefit overall. It may not be necessary to give the same drugs to 100 patients if only 9 benefit from them. This is where a case can be made for pharmacogenomics.

TABLE II Benefit versus lack of benefit for several popular cardiovascular drugs.

Trial	Drug	Event rates (%)		Lack of	
		Placebo	Treated	benefit/100	Benefit/100
HOPE ³³	Ramipril	17.8	14.0	3.8	96.2
APTC ³⁴	Aspirin	14.0	10.0	4.0	96.0
FTT ³⁵	Thrombolytics	11.5	9.6	1.9	98.1
4S ³⁶	Simvastatin	28.0	19.0	9.0	91.0
EPIC ³⁷	Abciximab	12.8	8.3	4.5	95.5
CURE ³⁸	Clopidogrel	11.5	9.3	2.2	97.8

Abbreviations: HOPE = Heart Outcomes Prevention Evaluation, APTC = AntiPlatelet Trialists' Collaboration, FTT = Fibrinolytic Therapy Trialists' Collaborative Group, 4S = Scandinavian Simvastatin Survival Study, EPIC = Evaluation of c7E3 Fab for the Prevention of Ischemic Complications, CURE = Clopidogrel in Unstable angina to prevent Recurrent Events. Adapted from Ref. No. 20 with permission.

Genomic Solutions in Cardiac Care

The treatment of ACS will benefit from genomic solutions in the near future. Already, leukemia has provided an example to the field of cardiology for how targeted therapies can change the course of treatment. Imatinib mesylate, a new oral targeted therapy for leukemia, works specifically at the genomic basis of tyrosine kinase that occurs as a result of translocation.²¹ This tyrosine kinase (BCR-ABL) gene mutation is the oncogene that causes Philadelphia-chromosome-positive leukemia.²² Based on DNA microarray analysis, gene expression data can have clinical relevance for the pretreatment assessment of leukemia by predicting drug resistance prior to therapy.²³

Gene expression profiling is also now being used to predict clinical outcomes in breast cancer.²⁴ By using DNA microarray analysis and applied supervised classification to identify gene expression signature, oncologists are now able to predict which patients will have a short interval to distant metastases.²⁵

Microarray expression profiles are also being used to finally identify indistinguishable disease states in diffuse large B-cell lymphoma. By using a gene expression model, two categories of patients have been identified with different 5-year overall survival rates (70 vs. 12%).²⁶ In addition, this model is also able to delineate patients within specific International Prognostic Index (IPI) risk categories who are most likely to be cured or die from their disease.

These advances are beginning to be transferred over to the field of cardiovascular medicine. Figure 6 depicts a self-organizing map analysis of 72 experiments that reveal approximately 1,700 platelet-selective genes.²⁷ It is also now known that susceptibility genes form the basis for a family history of cardiovascular disease. In one study, the whole genome was scanned in 513 families to identify chromosomal regions linked to MI and other risk factors known to be under genetic control.²⁸ The risk of MI was mapped to a single region on chromosome 14 with a significant lod score of 3.9 (Fig. 7). This provided evidence for a principal MI locus. Linkages were found for various risk factors, such as lipoprotein (a) (chromosome 1), diabetes mellitus (chromosome 6), hypertension (chromosomes 1 and 6), high-density and low-density lipoprotein cholesterol (chromosomes 1 and 17), and triglyceride concentrations (chromosome 9).

Conclusion

As cardiologists continue to use emerging technology, cost considerations will become an issue of increasing interest, not only for third-party payers but for patients as well. The drive for evidence-based medicine will require cardiologists to utilize the most clinically effective and cost effective strategies in the treatment of patients with ACS. Various clinical trials have demonstrated the benefit as well as the cost savings of several interventions, including coronary stenting, the use of troponin in assessing patients with ACS, aggressive angiography, and the use of C-reactive protein and interleukin-6. Cardiologists

FIG. 6 Self-organizing map analysis of 72 experiments revealing approximately 1,700 platelet-selective genes. Reprinted from author with permission.

will also be required to limit their use of pharmacologic therapies, as not all drugs will benefit all patients. Finally, advances in the field of genomics are expected to revolutionize the field of cardiology.

Discussion

Califf: I agree with Eric except that I do not feel optimistic about genes being the key in coronary disease. I think it is very different than cancer, where it tends to be a fairly specific reproducible mutation, for example, that may create the problem. Do you really think that coronary disease genetics are as simple as cancer genetics?

Topol: They could turn out to be simpler, but we are way behind. We got to catch up.

Ferguson: But the issue is you talk about the guidelines. The guidelines may be all well and good, but they lag behind the clinical trial data, and they do not always provide us with guidance as to the true selectivity of which patients may ultimately benefit. This seems to be the Achilles heel of that approach. The problem that you run into as you talk about these so-called smarter strategies is what if you get into the scenario of identifying candidate genes in a population that may be at risk. You cannot guarantee that if I treat this patient, they are going to get better. But what if, in fact, you unmask this whole hitherto unidentified population of patients? The example that I would point to is the new ATP-3 guidelines. As we talk about the coronary heart disease equivalents and about people who are candidates for statin therapy on the basis of good evidence-based medicine, in fact we are talking about five to six times more people being candidates for statin therapy. Yes, we may find candidate genes, but they may be more prevalent in the population than we may have hoped entirely.

Topol: Unfortunately, the cardiology community has already turned its back on some of the pharmacogenetic data for statins. But again, I will emphasize that all the data we have to date from the statin trials, even new trials that show benefits in PCI patients, none of the trials show benefits above 9 patients per 100 patients treated, not one. That means that 90 patients out of 100, at least for the duration of the trial, and sometimes these trials go on for many years, have never been shown to have any benefit. It is time to wake up to this and not to give patients five, six drugs. For example, we know at least 10 percent of patients have no response to aspirin, insofar as platelet function. Why are we giving everybody aspirin? Well, because it is so inexpensive. Okay. But a lot of the other choices we have are expensive and they have risk. Obviously, it becomes a big issue when you talk about big-ticket items like these very ex-

FIG. 7 Mapping of a single region on chromosome 14 responsible for myocardial infarction (MI) by using genome-wide scanning in 513 German families. Adapted from Ref. No. 28.

pensive devices. I really think that biomarkers are in a transitional state. All these years we take a history, listen to the patient, look at the cardiogram and the labs, and figure out what to do with the patients with an acute coronary syndrome. Now with troponins, that has totally been revamped by various studies and various strategies. And I think that is just the way medicine is going to go over the next several years.

Califf: Do you not think it is potentially self-defeating, because as Terry said, we are getting so good at figuring out what works, that you may find a smaller group that benefits from an individual treatment. The sum total would be higher. I do want to take disagreement with the comment made about oncologists. They are ahead in a few selective diseases; however, show me the data that a specific rate of death from cancer is declining. It is not.

Topol: Well, they have the same problem we have.

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