

Valvular Heart Diseases Surveillance: A Commanding Necessity



See also page 2633

THE EPIDEMIC OF VALVULAR HEART DISEASES, FOREMOST MITRAL REGURGITATION

Until the twentieth century, valvular heart disease (VHD) was a scourge of humanity, because young patients affected by rheumatic heart disease succumbed after few years of severe functional impairment. During the twentieth century, the advent of improved hygiene and running water and the discovery of penicillin yielded progressive decline of rheumatic heart disease prevalence. Subsequent invention of cardiopulmonary bypass, surgical valve replacement, and then repair culminated in a sense of victory over VHD. The resulting impression of a resolved medical problem (despite continuing affliction in poorer countries) led to limited research interest in VHD and infrequent grant funding from national agencies, including the National Institutes of Health.

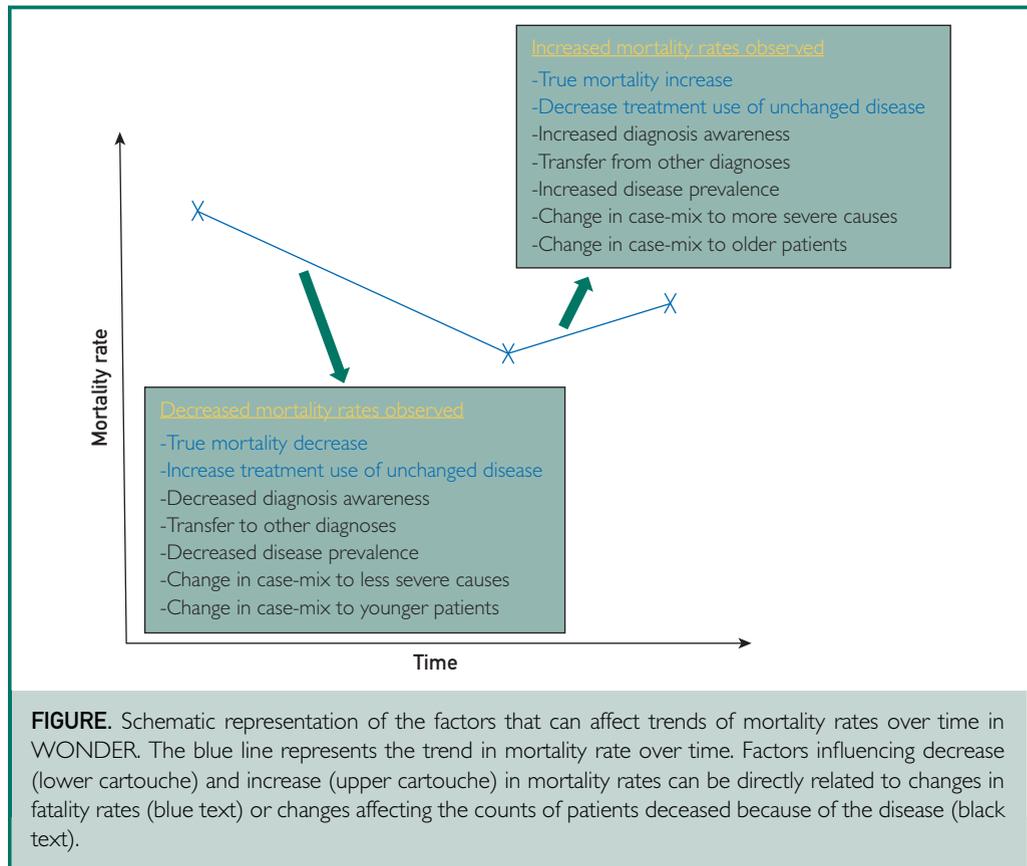
However, with an increase in average life expectancy, VHD (now mostly of degenerative etiology) has returned to the forefront.¹ What do we know of the prevalence of VHD? Unfortunately, VHD clinical diagnosis is at best mediocre and insensitive, requiring echocardiographic imaging for accurate diagnosis.² Population studies using systematic imaging are rare, but they suggest an overall adjusted prevalence in the adult US population of left-sided hemodynamically significant (moderate or severe) VHD of 2.5% with a strong link to aging.¹ Similar findings were reported by limited Doppler echocardiographic studies in the developing world² and the OxVALVE study in the United Kingdom.³ The ongoing Heart of New Ulm study, (New Ulm, Minnesota) scanning specifically for detecting VHD has the potential to provide refined US prevalence estimates. Regardless, these worldwide studies indicate

that mitral valve disease (dominated by mitral regurgitation [MR]) is the most frequent left-sided VHD. Noteworthy is the high frequency (at least one third of all cases) of undiagnosed significant left-sided valve disease.^{1,3} To these one needs to add mitral valve prolapse (estimated prevalence 2.4%),⁴ vastly predominant in the adult and overlapping with significant MR in only 15%.⁵ Hemodynamically significant right-sided VHD—mostly tricuspid regurgitation, prevalent in 0.55% of adult population—dominates in older subjects.⁶ Finally, bicuspid aortic valve, a congenital VHD with clinical case-burden low in infancy, inconsistently diagnosed, mostly reveals itself during adulthood,⁷ with prevalence estimated at 1.3% of live births.⁸

Overall, one can estimate US prevalence of VHD to be 15 to 18 million adults. A similar proportion of the population is affected in Western Europe, and worldwide VHD burden is estimated at hundreds of millions, which will grow with the aging of the population. Despite this considerable burden, efforts directed at VHD epidemiology and surveillance are minimal. This vacuum is shocking because the VHD community studies have emphasized considerable excess mortality and undertreatment.^{1,9} Therefore, many questions regarding VHD epidemiology remain unanswered, and all efforts at VHD surveillance are essential and laudable.

ASSESSING CHANGES IN VHD MORTALITY USING THE WONDER DATABASE

In the current issue of *Mayo Clinic Proceedings*, Parcha et al¹⁰ present an analysis of the WONDER detailed mortality database to assess trends in mortality related to MR. WONDER is an acronym for Wide-ranging ONline Data for Epidemiology Research, and it gathers more than 20 collections of databases accessible online and to all,



including the public under coordination by the Centers for Disease Control Prevention. These collections include US births, deaths, cancer diagnoses, and environmental data. The detailed mortality is accessible by International Classification of Disease [ICD] diagnosis codes from 1999, and it can be stratified by many criteria, including age, sex, race, location, and calendar year. Calculation of mortality rates is based on the count of deaths linked to a given ICD diagnosis (the numerator) and its ratio to the population count with the same selection characteristics (the denominator); this can be adjusted for overall US population characteristics. With this open-source methodology, Parcha et al¹⁰ calculated mortality rates for the ICD codes applicable to MR and analyzed trends over time, observing that MR-linked mortality rates in persons age 45 years and older showed a decline, particularly in the 2000s, followed in 2012 by a slight mortality increase. This change in

trend was significant and observed in both sexes, in all US regions, and across most age ranges. Sensitivity analysis expanding potential ICD diagnoses led to similar conclusions, although the trend inflection appeared more as a flattening of mortality rates. We congratulate the authors for conducting one of the few studies of VHD surveillance in the United States.

What conclusions can be drawn from these data? At face value, these results suggest that we can congratulate ourselves for successfully reducing MR-related mortality, albeit with a slight worry regarding the resurgence inflection. Although it would be uplifting to consider that the efforts of the cardiovascular community to increase the uptake of early valve repair are in part responsible for the decline in MR-linked mortality, there are considerable limitations to VHD surveillance using the WONDER database. Whoever has worked with certificates of death understands the terrible imprecision of the diagnoses listed

and their potential to change. This imprecision is compounded by the vagaries of ICD codes. Indeed, there is no unique code for MR, and two items are often mixed in the same code (e.g., 105-1 rheumatic mitral insufficiency or 105-2 rheumatic mitral stenosis with insufficiency). There is no etiologic qualification, and one can understand why the authors tried to mix MR with heart failure to impute a cause. However, whether MR is caused by ventricular failure (functional MR) or degenerative MR is complicated by heart failure remains uncertain. In the VHD world, ICD codes have remained mostly unchanged, and they fail to reflect the progress in our understanding of VHD causes and mechanisms that imaging provided.

Independent of the authors' excellent work, these methodologic issues might explain the oddities of the dataset. Indeed, although the population prevalence of MR is similar in men and women, two thirds of the deaths counted are in women. The differences in mortality rates between ethnicities are also puzzling.

Furthermore, the interpretation of mortality-rates changes is difficult because (1) MR diagnosis is clinically unreliable and requires imaging (imaging rates changes?), (2) mention on a death certificate implies awareness of MR diagnosis and of its link to the patient's demise, and (3) MR mortality rate changes could reflect subtle changes in population characteristics (Figure). Changes in observed mortality rates based on WONDER might reflect true change in MR mortality (in blue), but many other factors could spuriously affect the observed mortality rates (in black). Hence, while it is important and simple to follow mortality rates using WONDER, it is also essential to develop plans for VHD surveillance using new approaches.

VHD SURVEILLANCE: THE WAY FORWARD

Sparse epidemiologic data demonstrated the large burden of VHD, frequent underdiagnosis, marked excess-mortality, high heart failure incidence, and massive undertreatment.^{1,3,6,9} Though crucial, these limited data cannot be the end of the story, and the possible increase

in MR mortality reported by Parcha et al¹⁰ using the WONDER database adds to the need for a call to action in regard to VHD epidemiology and surveillance.

Which Direction Should Research Take?

Echocardiography is of prime importance in establishing VHD presence and severity, but imaging an entire nation is impossible. Well-designed programs of systematic imaging in communities or populations such as the OxVALVE or Heart-of-New-Ulm programs are essential to maintain and expand. These programs will provide clinical contexts, ethnic and social determinants of undiagnosed VHD and their consequences. Such programs and family studies will also provide new insights into mechanisms of degenerative VHD and future perspectives for prevention.

VHD surveillance must go beyond subjects enrolled in prospective imaging cohorts that are representative but limited in span. Taking advantage of current widespread availability of electronic medical record and clinical imaging data repositories, we believe that a new era of VHD surveillance is possible. VHD surveillance will require intensive data scientists' involvement to provide complete and epidemiologic sound information. The collaboration of providers allowing entire communities to be evaluated is crucial to understanding VHD clinical prevalence and management in a variety of geographic and social circumstances. Partial data on VHD management in entire countries are already available in Europe.¹¹ This indispensable endeavor requires considerable resources only available to national health research agencies such as the National Heart, Lung, and Blood Institute in the United States. As national funding for VHD research has remained nominal, effective VHD surveillance will require awareness within institutes' leadership and establishing resources for effective epidemiologic surveillance. Such programs are not only possible, from scientific and financial perspectives; they are also crucial in treating patients with VHD and restoring their life expectancy.

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