How Does Telemedicine Compare to Conventional Follow-Up After General Surgery?

Cremades M, Ferret G, Parés D, et al. Telemedicine to follow patients in a general surgery department: A randomized controlled trial. Am J Surg. 2020 March 26;S0002-9610(20)30179-3.

Study Overview

Objective. To compare the impact of conventional versus telemedicine follow-up of general surgery patients in outpatient clinics.

Design. Prospective randomized clinical trial.

Setting and participants. Participants were recruited from Hospital Germans Trias i Pujol, a tertiary care university hospital located in the outskirts of Barcelona (Catalonia, Spain). To be included in this study, participants had to have been treated in the general surgery department, have basic computer knowledge (ability to use e-mail or a social network), have a computer with webcam, and be 18 to 75 years of age, or they had to have a partner who met these criteria. Exclusion criteria included any disability making telemedicine follow-up impossible (eg, blindness, deafness, or mental disability; proctologic treatment; difficulty describing and/or showing complications in the surgical area; and clinical complications before discharge more severe than Clavien Dindo II), as well as withdrawal of consent. Patients who met the criteria and had just been discharged from the hospital were offered the opportunity to enroll by the surgeon in charge. Patients who agreed to participate provided informed consent and were assigned using a computerized block randomization list (allocation ratio 1:1).

Intervention. Time to visit was generally between 2 and 4 weeks after discharge (the interval to the follow-up visit was determined at the discretion of the treating surgeon, but always followed the usual schedule). To conduct the telemedicine follow-up through a video call, a medical cloud-based program fulfilling all European Union security and privacy policies was used. Four surgeons were assigned to perform the telemedicine visits and were trained on how to use the program before the study started. Visit format was the same in both groups: clinical and wound condition were assessed and pathology was discussed (the one difference was that physical exploration was not performed in the telemedicine group).

Main outcome measures. The primary outcome was the feasibility of telemedicine follow-up, and this was measured as the percentage of participants who completed follow-up in their corresponding group by the date scheduled at hospital discharge. Secondary outcomes included a comparison of clinical results and patient satisfaction. To assess the clinical results, extra visits to an outpatient clinic and/or the emergency department during the first 30 days after the follow-up visit were collected.

To evaluate patient satisfaction, a questionnaire was sent via email to the participants after the visit and, if they did not respond, a telephone survey was carried out (if there was no contact after 2 telephone calls,

the participants was considered a missing value). The questionnaire was informed by the United Kingdom National Health Service outpatients questionnaire and the Telehealth Usability Questionnaire. It included 27 general questions asked of participants in both groups, plus 8 specific questions for participants in the conventional follow-up group and 14 specific questions for participants in the telemedicine group. To summarize all the included fields in the questionnaires (time to visit and visit length, comfort, tests and procedures performed before and during the visit, transport, waiting time, privacy, dealings with staff, platform usability, telemedicine, and satisfaction), participants were asked to provide a global satisfaction score on a scale from 1 to 5.

Analysis. To compare the groups in terms of proportion of outcomes, a chi-square test was used to analyze categorical variables. To compare medians between the groups, ordinal variables were analyzed using the Mann-Whitney U test. Statistical significance was set at $P < 0.05$.

Main results. Two-hundred patients were randomly allocated to 1 of the 2 groups, with 100 patients in each group. The groups did not differ significantly based on age ($P = 0.836$), gender ($P = 0.393$), or American Society of Anesthesiologists (ASA) score ($P = 0.232$). Time to visit did not differ significantly between the groups ($P = 0.169$), and while visits were generally shorter in the telemedicine group, the difference was not significant ($P = 0.153$). Diagnoses and treatments did not differ significantly between the groups ($P = 0.853$ and $P = 0.461$, respectively).

The primary outcome (follow-up feasibility) was achieved in 90% of the conventional follow-up group and in 74% of the telemedicine group ($P = 0.003$). Of the 10 patients in the conventional follow-up group who did not complete the follow-up, 8 did not attend the visit on the scheduled day and 2 were hospitalized for reasons not related to the study. In the telemedicine group, the 2 main reasons for failure to follow-up were technical difficulties (n = 10) and requests by patients to attend a conventional visit after being allocated to the telemedicine group (n = 10). Among the remaining 6 patients in the

telemedicine group who did not attend a visit, 3 visited the outpatient clinic because of a known surgical wound infection before the visit, 2 did not respond to the video call and could not be contacted by other means, and 1 had other face-to-face visits scheduled in different departments of the hospital the same day as the telemedicine appointment.

There were no statistically significant differences in the clinical results of the 164 patients meeting the primary endpoint ($P = 0.832$). Twelve of the 90 (13.3%) patients in the conventional group attended extra visits after the follow-up, while 9 of the 74 patients (12.1%) in the telemedicine group ($P = 0.823$) attended extra visits after follow-up. The median global patient satisfaction score was 5 in both the conventional group (range, 2-5) and the telemedicine group (range, 1-5), with no statistically significant differences ($P = 0.099$). When patients in the telemedicine group were asked if they would accept the use of telemedicine as part of their medical treatment on an ongoing basis, they rated the proposition with a median score of 5 (range, 1-5).

Conclusion. Telemedicine is a feasible and acceptable complementary service to facilitate postoperative management in selected general surgery patients. This option produces good satisfaction rates and maintains clinical outcomes.

Commentary

In recent years, telemedicine has gained increased popularity in both medicine and surgery, affording surgeons greater opportunities for patient care, mentoring, collaboration, and teaching, without the limits of geographic boundaries. Telemedicine can be broadly described as a health care service utilizing telecommunication technologies for the purpose of communicating with and diagnosing and treating patients remotely.[1-4] To date, literature on telemedicine in surgical care has been limited.

In their systematic review, published in 2018, Asiri et al identified 24 studies published between 1998 and 2018, which included 3 randomized controlled trials, 3 pilot studies, 4 retrospective studies, and 14 prospective observational studies. In these studies, telemedicine protocols were used for preoperative assessment, diagnostic

purposes, or consultation with another surgical department (10 studies); postoperative wound assessment (9 studies); and follow-up in place of conventional clinic visits (5 studies).[3] In a 2017 systematic review of telemedicine for post-discharge surgical care, Gunter et al identified 21 studies, which included 3 randomized controlled trials, 6 pilot or feasibility studies, 4 retrospective record reviews, 2 case series, and 6 surveys.[4] In these studies, telemedicine protocols were used for scheduled follow-up (10 studies), routine and ongoing monitoring (5 studies), or management of issues that arose after surgery (2 studies). These 2 reviews found telemedicine to be feasible, useful, and acceptable for postoperative evaluation and follow-up among both providers and patients.

Additional benefits noted in these studies included savings in patient travel, time, and cost. Perspectives on savings to the health system were mixed—while clinic time slots may open as a result of follow-up visits being done via telemedicine (resulting in potential improvements in access to surgical services and decreased wait times), there are still significant direct costs for purchasing necessary equipment and for educating and training providers on the use of the equipment. Other published reviews have discussed in greater detail the application, benefits, limitations, and barriers to telemedicine and provided insight from the perspectives of patients, providers, and health care systems.[1,2]

Because studies on the use of telemedicine are limited, particularly in general surgery, and few of these studies have used a randomized clinical trial design, the present study is an important contribution to the literature. The authors found a significant difference between groups in terms of percentage of completed follow-up visits—90% of conventional follow-up group participants completed their visit versus 74% of telemedicine group participants. However, these differences were primarily attributed to technical difficulties experienced by telemedicine group participants, as well requests to have a conventional follow-up visit. In addition, telemedicine capabilities were limited to video calls via computers and webcams, and it is likely that successful completion of the follow-up visit would have been higher in the telemedicine group had the use of video calls via tablets or smartphones been an option. Perhaps

more important, no significant differences were found in clinical outcomes (extra visits within 30 days after the follow-up visit) or patient satisfaction.

A key strength of this study is the use of a randomized clinical trial design to evaluate telemedicine as an alternative method for conducting patient visits following general surgery. Inclusion and exclusion criteria did not impose strict limitations on potential participants. Also, the authors evaluated differences in time to visit, length of visit, clinical results, and patient satisfaction between groups, in addition to the primary measure of completion of the follow-up visit.

This study has important limitations that should be noted as well, particularly related to the study design, some of which are acknowledged by the authors. Because this study was implemented in only 1 hospital, specifically, a tertiary care university hospital on the outskirts of an urban European city, the generalizability of the findings is limited. Also, the likelihood of selection bias is high, as enrollment was not offered to all patients who were discharged from the hospital and met inclusion criteria (limited by patient workload). The comparison of clinical results was limited, as the selected measure focused only on extra visits to an outpatient clinic and/or the emergency department during the first 30 days after the follow-up visit. This chosen measure does not account for less severe clinical results that did not require an additional visit, and does not represent a nuanced comparison of specific clinical indicators. In addition, this measure does not account for clinical complications that may have occurred beyond the 30-day period. Recall bias also was likely, given that the patient satisfaction questionnaire was delivered via email to patients at a later time after the follow-up visit, instead of being administered immediately after the visit. Last, group differences at baseline were assessed based only on age, gender, and ASA score, which does not preclude potential differences related to other factors, such as race/ethnicity, household income, comorbidities, insurance, and zip code. Future research with a similar objective would benefit from a randomized clinical trial design that recruits a wider diversity of patients across different clinic settings and incorporates more nuanced measures of primary and secondary outcomes.

Applications for Clinical Practice

With the ongoing COVID-19 pandemic, the integration of telemedicine capabilities into hospital systems is becoming more widespread and is proceeding at an accelerated pace. This study provides evidence that telemedicine is a feasible and acceptable complementary service to facilitate postoperative management in selected general surgery patients. Assuming that the needed technology and appropriate program training are available, telemedicine should be offered to patients, especially to maximize savings in terms of travel, time, and cost. However, the option for conventional (in-person) follow-up should remain, particularly in cases where there may be barriers to successful follow-up visits via telemedicine, including limited digital literacy, lack of access to necessary equipment, language/communication barriers, complex follow-up treatment, and difficulties in describing or showing complications in the surgical area.

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References

1. Williams AM, Bhatti UF, Alam HB, Nikolian VC. The role of telemedicine in postoperative care. *mHealth.* 2018 May;4:11-11.
2. Huang EY, Knight S, Guetter CR et al. Telemedicine and telementoring in the surgical specialties: A narrative review. *Am J Surg.* 2019;218:760-766.
3. Asiri A, AlBishi S, AlMadani W, et al. The use of telemedicine in surgical care: A systematic review. *Acta Informatica Medica.* 2018;26:201-206.
4. Gunter RL, Chouinard S, Fernandes-Taylor S, et al. Current use of telemedicine for post-discharge surgical care: a systematic review. *J Am College Surg.* 2016;222:915-927.

Remdesivir in Hospitalized Adults With Severe COVID-19: Lessons Learned From the First Randomized Trial

Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial [published online April 29, 2020]. Lancet. doi:10.1016/S0140-6736(20)31022-9

Study Overview

Objective. To assess the efficacy, safety, and clinical benefit of remdesivir in hospitalized adults with confirmed pneumonia due to severe SARS-CoV-2 infection.

Design. Randomized, investigator-initiated, placebo-controlled, double-blind, multicenter trial.

Setting and participants. The trial took place between February 6, 2020 and March 12, 2020, at 10 hospitals in Wuhan, China. Study participants included adult patients (aged ≥ 18 years) admitted to hospital who tested positive for SARS-CoV-2 by reverse transcription polymerase chain reaction assay and had the following clinical characteristics: radiographic evidence of pneumonia; hypoxia with oxygen saturation ≤ 94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen ≤ 300 mm Hg; and symptom onset to enrollment ≤ 12 days. Some of the exclusion criteria for participation in the study were pregnancy or breast feeding, liver cirrhosis, abnormal liver enzymes ≥ 5 times the upper limit of normal, severe renal impairment or receipt of renal replacement therapy, plan for transfer to a non-study hospital, and enrollment in a trial for COVID-19 within the previous month.

Intervention. Participants were randomized in a 2:1 ratio to the remdesivir group or the placebo group and were administered either intravenous infusions of remdesivir (200 mg on day 1 followed by 100 mg daily on days 2-10) or the same volume of placebo for 10 days. Clinical and safety data assessed included laboratory testing, electrocardiogram, and medication adverse effects. Testing of oropharyngeal and nasopharyngeal swab samples, anal swab samples, sputum, and stool was performed

for viral RNA detection and quantification on days 1, 3, 5, 7, 10, 14, 21, and 28.

Main outcome measures. The primary endpoint of this study was time to clinical improvement within 28 days after randomization. Clinical improvement was defined as a 2-point reduction in participants' admission status on a 6-point ordinal scale (1 = discharged or clinical recovery, 6 = death) or live discharge from hospital, whichever came first. Secondary outcomes included all-cause mortality at day 28 and duration of hospital admission, oxygen support, and invasive mechanical ventilation. Virological measures and safety outcomes ascertained included treatment-emergent adverse events, serious adverse events, and premature discontinuation of remdesivir.

The sample size estimate for the original study design was a total of 453 patients (302 in the remdesivir group and 151 in the placebo group). This sample size would provide 80% power, assuming a hazard ratio (HR) of 1.4 comparing remdesivir to placebo, and corresponding to a change in time to clinical improvement of 6 days. The analysis of primary outcome was performed on an intention-to-treat basis. Time to clinical improvement within 28 days was assessed with Kaplan-Meier plots.

Main results. A total of 255 patients were screened, of whom 237 were enrolled and randomized to remdesivir (158) or placebo (79) group. Of the participants in the remdesivir group, 155 started study treatment and 150 completed treatment per protocol. For the participants in the placebo group, 78 started study treatment and 76 completed treatment per-protocol. Study enrollment was terminated after March 12, 2020, before attaining the prespecified sample size, because no additional patients met study eligibility criteria due to various public health measures implemented in Wuhan. The median age of participants was 65 years (IQR, 56-71), the majority were men (56% in remdesivir group vs 65% in placebo group), and the most common comorbidities included hypertension, diabetes, and coronary artery disease. Median time from symptom onset to study enrollment was 10 days (IQR, 9-12). The time to clinical improvement between treatments (21 days for remdesivir group vs 23 days for placebo group) was not significantly different (HR, 1.23; 95% confidence interval [CI], 0.87-1.75). In addi-

tion, in participants who received treatment within 10 days of symptom onset, those who were administered remdesivir had a nonsignificant (HR, 1.52; 95% CI, 0.95-2.43) but faster time (18 days) to clinical improvement, compared to those administered placebo (23 days). Moreover, treatment with remdesivir versus placebo did not lead to differences in secondary outcomes (eg, 28-day mortality and duration of hospital stay, oxygen support, and invasive mechanical ventilation), changes in viral load over time, or adverse events between the groups.

Conclusion. This study found that, compared with placebo, intravenous remdesivir did not significantly improve the time to clinical improvement, mortality, or time to clearance of SARS-CoV-2 in hospitalized adults with severe COVID-19. A numeric reduction in time to clinical improvement with early remdesivir treatment (ie, within 10 days of symptom onset) that approached statistical significance was observed in this underpowered study.

Commentary

Within a few short months since its emergence. SARS-CoV-2 infection has caused a global pandemic, posing a dire threat to public health due to its adverse effects on morbidity (eg, respiratory failure, thromboembolic diseases, multiorgan failure) and mortality. To date, no pharmacologic treatment has been shown to effectively improve clinical outcomes in patients with COVID-19. Multiple ongoing clinical trials are being conducted globally to determine potential therapeutic treatments for severe COVID-19. The first clinical trials of hydroxychloroquine and lopinavir-ritonavir, agents traditionally used for other indications, such as malaria and HIV, did not show a clear benefit in COVID-19.[1,2] Remdesivir, a nucleoside analogue prodrug, is a broad-spectrum antiviral agent that was previously used for treatment of Ebola and has been shown to have inhibitory effects on pathogenic coronaviruses. The study reported by Wang and colleagues was the first randomized controlled trial (RCT) aimed at evaluating whether remdesivir improves outcomes in patients with severe COVID-19. Thus, the worsening COVID-19 pandemic, coupled with the absence of a curative treatment, underscore the urgency of this trial.

The study was grounded on observational data from several recent case reports and case series centering on the potential efficacy of remdesivir in treating COVID-19.[3] The study itself was designed well (ie, randomized, placebo-controlled, double-blind, multicenter) and carefully implemented (ie, high protocol adherence to treatments, no loss to follow-up). The principal limitation of this study was its inability to reach the estimated statistical power of study. Due to successful epidemic control in Wuhan, which led to marked reductions in hospital admission of patients with COVID-19, and implementation of stringent termination criteria per the study protocol, only 237 participants were enrolled, instead of the 453, as specified by the sample estimate. This corresponded to a reduction of statistical power from 80% to 58%. Due to this limitation, the study was underpowered, rendering its findings inconclusive.

Despite this limitation, the study found that those treated with remdesivir within 10 days of symptom onset had a numerically faster time (although not statistically significant) to clinical improvement. This leads to an interesting question: whether remdesivir administration early in COVID-19 course could improve clinical outcomes, a question that warrants further investigation by an adequately powered trial. Also, data from this study provided evidence that intravenous remdesivir administration is likely safe in adults during the treatment period, although the long-term drug effects, as well as the safety profile in pediatric patients, remain unknown at this time.

While the study reported by Wang and colleagues was underpowered and is thus inconclusive, several other ongoing RCTs are evaluating the potential clinical benefit of remdesivir treatment in patients hospitalized with COVID-19. On the date of online publication of this report in *The Lancet*, the National Institutes of Health (NIH) published a news release summarizing preliminary findings from the Adaptive COVID-19 Treatment Trial (ACTT), which showed positive effects of remdesivir on clinical recovery from advanced COVID-19.[4] The ACTT, the first RCT launched in the United States to evaluate experimental treatment for COVID-19, included 1063 hospitalized participants with advanced COVID-19 and lung involvement. Participants who were administered remdesivir had a 31% faster time to recovery compared to those in the placebo group (median

time to recovery, 11 days vs 15 days, respectively; $P < 0.001$), and had near statistically significant improved survival (mortality rate, 8.0% vs 11.6%, respectively; $P = 0.059$). In response to these findings, the US Food and Drug Administration (FDA) issued an emergency use authorization for remdesivir on May 1, 2020, for the treatment of suspected or laboratory-confirmed COVID-19 in adults and children hospitalized with severe disease.[5] While the findings noted from the NIH news release are very encouraging and provide the first evidence of a potentially beneficial antiviral treatment for severe COVID-19 in humans, the scientific community awaits the peer-reviewed publication of the ACTT to better assess the safety and effectiveness of remdesivir therapy and determine the trial's implications in the management of COVID-19.

Applications for Clinical Practice

The discovery of an effective pharmacologic intervention for COVID-19 is of utmost urgency. While the present study was unable to answer the question of whether remdesivir is effective in improving clinical outcomes in patients with severe COVID-19, other ongoing or completed (ie, ACTT) studies will likely address this knowledge gap in the coming months. The FDA's emergency use authorization for remdesivir provides a glimpse into this possibility.

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References

1. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial [published online April 14, 2020]. medRxiv.org. doi:10.1101/2020.04.10.20060558.
2. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. *N Engl J Med.* 2020;382:1787-1799.
3. Grein J, Ohmagari N, Shin D, et al. Compassionate use of remdesivir for patients with severe COVID-19 [published online April 10, 2020]. *N Engl J Med.* doi:10.1056/NEJMoa2007016.
4. NIH clinical trial shows remdesivir accelerates recovery from advanced COVID-19. www.niaid.nih.gov/news-events/nih-clinical-trial-shows-remdesivir-accelerates-recovery-advanced-covid-19. Accessed May 9, 2020
5. Coronavirus (COVID-19) update: FDA issues Emergency Use Authorization for potential COVID-19 treatment. www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-issues-emergency-use-authorization-potential-covid-19-treatment. Accessed May 9, 2020.

Timing of Surgery in Patients With Asymptomatic Severe Aortic Stenosis

Kang D, Park S, Lee S, et al. Early surgery or conservative care for asymptomatic aortic stenosis. N Engl J Med. 2020;382:111-119.

Study Overview

Objective. To determine the timing of surgical intervention in asymptomatic patients with severe aortic stenosis.

Design. Open-label, multicenter, randomized controlled study.

Setting and participants. A total of 145 asymptomatic patients with very severe aortic stenosis were randomly assigned to early surgery or conservative care.

Main outcome measures. The primary endpoint was a composite of operative mortality or death from a cardiovascular cause during follow-up. The major secondary endpoint was death from any cause during follow-up.

Main results. The primary endpoint occurred in 1 of 73 patients (1%) in the early surgery group and 11 of 72 patients (15%) in the conservative care group (hazard ratio [HR], 0.09; 95% confidence interval [CI], 0.01-0.67, *P* = 0.003). The secondary endpoint occurred in 7% of patients in the early surgery group and 21% of patients in the conservative care group (HR, 0.33; 95% CI, 0.12-0.90).

Conclusion. Among asymptomatic patients with very severe aortic stenosis, the incidence of the composite of operative mortality or death from cardiovascular causes during follow-up was significantly lower among those who underwent early valve replacement surgery compared to those who received conservative care.

Commentary

Aortic stenosis is a progressive disease that can lead to angina, heart failure, and death.[1] A higher mortality rate is reported in patients with symptomatic aortic stenosis, as compared to patients with asymptomatic disease, and current guidelines require symptoms to be present in order to proceed with aortic valve replacement.[2]

Management of asymptomatic patients is often determined by the treating physician, with treatment decisions based on multiple factors, such as left ventricular function, stress test results, and the local level of expertise for surgery.[2]

In this context, the RECOVERY investigators report the findings of their well-designed randomized controlled study assessing patients with asymptomatic severe aortic stenosis, which was defined as aortic valve area ≤ 0.75 cm^2 and either transvalvular velocity > 4.5 m/s or a mean gradient ≥ 50 mm Hg. Compared to patients who received conservative care, patients who underwent early valve surgery had a significantly lower rate of a composite of operative mortality or death from any cardiovascular causes during follow-up. Notably, the number needed to treat to prevent 1 death from cardiovascular causes within 4 years was 20.

The strengths of this trial include complete long-term follow-up (> 4 years) and low cross-over rates. Furthermore, as the study targeted a previously under-studied population, there were a number of interesting observations, in addition to the primary endpoint. First, the risk of sudden death was high in patients who received conservative care, 4% at 4 years and 14% at 8 years, a finding contrary to the common belief that asymptomatic patients are at lower risk of sudden cardiac death. Second, 74% of patients assigned to initial conservative care required aortic valve replacement during the follow-up period. Furthermore, when the patients assigned to conservative care required surgery, it was often performed emergently (17%), which could have contributed to the higher mortality in this group of patients. Finally, hospitalization for heart failure was more common in patients randomized to conservative care compared to patients with early surgery. These findings will help physicians conduct detailed, informed discussions with their patients regarding the risks/benefits of early surgery versus conservative management.

There are a few limitations of the RECOVERY trial to consider. First, this study investigated the effect of surgical aortic valve replacement; whether its findings can be extended to transcatheter aortic valve replacement (TAVR) requires further investigation. Patients who were enrolled in this study were younger and had fewer comorbidities than typical patients referred for TAVR. Second, all patients included in this study had the most severe form of aortic stenosis (valve area $\leq$ 0.75 cm^2 with either a peak velocity of $\geq$ 4.5 m/s or mean gradient $\geq$ 50 mm Hg). Finally, the study was performed in highly experienced centers, as evidenced by a very low (0%) mortality rate after aortic valve replacement. Therefore, the finding may not be applicable to centers that have less experience with aortic valve replacement surgery.

Applications for Clinical Practice

The findings of the RECOVERY trial strongly suggest a mortality benefit of early surgery compared to conservative management in patients with asymptomatic severe aortic stenosis. Early surgery should be favored over conservative management in this patient population.

–Taishi Hirai, MD

References

1. Otto CM, Prendergast B. Aortic-valve stenosis--from patients at risk to severe valve obstruction. *N Engl J Med.* 2014;371:744-756.
2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation.* 2017;135: e1159-e1195.